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Haemostasis in Spine Surgery

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Research and evidence about blood sparing in spine surgery

Blood loss in spine surgery seems to be significant, not only for major surgery for deformity and tumors but also in more frequent and near-routine fusion procedures. In some deformity surgery, such as that for neuromuscular scoliosis, the problem is worsened by the probable coagulation troubles present in those patients.

However, while almost every hip- or knee-arthroplasty database contains information about blood loss and/or transfusion performed, this does not appear to be the case for spine surgery. The number of publications treating that subject is also much smaller in the case of spine surgery. Is the problem underestimated or understudied?

With a few exceptions (vasoconstrictor infiltration, epidural blockage) the techniques used for hemostasis and blood sparing in spine surgery are very similar to those widely used in other fields of surgery. Given the wide use of those methods and the large number of publications in multiple surgical fields, it is surprising to discover the lack of evidence regarding the efficacy of most of them. Most of the available evidence is for the field of cardiac surgery. Less is available for most other types of surgery, and very little is based on true evidence when it comes to spinal procedures. The widely varying methods for preventing excessive blood loss or transfusion requirements concern both the surgeon and the anesthetist, and the results demand a close and efficient collaboration.

Classical hemodynamic methods show the highest levels of evidence, although conflicting reports are common. Planned autologous donation is also efficient for reducing the need for homologous transfusions. However, there are some reports of overcollection and under-use as frequent and important waste factors contributing to high price [4], which may lead to declining use [1]. Likewise, while usually considered efficacious, hypotensive anesthesia and acute normovolemic dilution are also the subject of inconclusive reports in spine surgery.

It is also surprising to see that some very widely used techniques are based solely on some common knowledge and feeling, but no evidence. A good example is the infiltration with vasoconstrictor agents of the paraspinal muscles. The use of antifibrinolytic drugs, some of them quite expensive, only showed evidence in cardiac surgery and in patients with bleeding disorders and for a limited number of those agents [2]. In other fields, including spine, the reported studies show conflicting results. It appears that the efficacy of these agents is procedure-specific, and evidence should be demonstrated in each case. RCT trials should be conducted in spine surgery to demonstrate unequivocal evidence.

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The routine, daily use of all those techniques is also quite limited at the present time. Several surveys have shown that, outside of cardiac surgery, the regular use of any blood-sparing method is infrequent [3]. Lack of familiarity is the first reason given for their infrequent use.

True evidence must be gathered for blood-sparing strategies in the field of spinal procedures, and popularization with those techniques that show efficacy should be promoted. In this way, blood sparing will have the same place and importance in the armamentarium of spine surgeons and anesthetists that it has in that of other surgical specialties.

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Blood loss in adult spinal surgery

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Abstract Spinal surgery in adults can vary from simple to complex and can also have variable anticipated surgical blood loss. There are several factors that can put patients at increased risk for greater intraoperative blood loss. These factors, including a review of the literature, will be discussed.

Keywords Adult · Blood loss

With an increasing number of spinal operations – more and more complex – being performed, there is mounting awareness of the effects of blood loss on the patients' outcomes. From the most simplistic standpoint, greater blood loss means greater transfusion needs, exposure to more blood products and the potential for disease transmission or transfusion reactions. Significant blood loss also results in greater fluid shifts, which can affect cardiac, pulmonary and renal status, or even, in the extreme example, lead to transfusion-related acute lung injury (TRALI) [25]. Increasing data suggests that blood products may impair the immune system and, therefore, increase the infection rate after surgery [5, 19, 28]. A significant blood loss can lead to coagulopathy or even disseminated intravascular coagulation (DIC), which may lead to postoperative hematoma and potential neurologic compromise or increase the risk of infection.

There are a number of reasons, certainly known to most spine surgeons, that can cause surgical blood loss that can be considerable even in routine cases. The exposure of the spine, with stripping of muscle off bone, leaves exposed surfaces of muscle and bone that can bleed, unless they are coagulated. While young patients usually have thick periosteum and have less bleeding during exposure, older patients can have thin periosteum, and osteoporotic bone with wider vascular channels. Patients with neuromuscular scoliosis – children, and adults with their osteoporotic bone – also have increased blood loss. When a patient needs decompression, laminectomy can result in epidural bleeding.

Adult patients have stiffer spines than children and adolescents, and they can have arthritic facet joints that may require osteotomy. These osteotomies will increase the bleeding from exposed bone. Adults are more likely to need more vertebral segments fused, especially in deformity surgery, since their compensatory curves may have become structural and may require inclusion to maintain truncal balance. Adult spine patients also have a higher rate of revision surgery, which has a greater risk of increased bleeding [31].

Intraoperative management from the anesthesiologist's standpoint can be challenging. While controlled hypotension can be used in many pediatric cases, adults with medical comorbidities such as hypertension, cardiac or carotid disease often cannot tolerate decreased perfusion to critical organs. Some patients have taken analgesics such as non-steroidal antiinflammatories, which can decrease platelet function if not discontinued a week or two prior to surgery. Herbal or naturalistic supplements, notably ginseng, ginkgo, and vitamin E among others, can also increase bleeding. Oftentimes, patients do not think to tell their physicians about their non-prescription medications.

In general, most spine surgeons have found a low likelihood of needing transfusions for patients undergoing laminectomy alone [6], with patients who auto-donate

blood prior to laminectomy not using their donated blood in 80% of cases. By comparison, patients who had fusions who pre-donated decreased their risk of receiving allogeneic blood by 75% for non-instrumented fusions, and 50% for instrumented fusions. The estimated blood loss (EBL) for these two groups was 674 ml (+/-443 ml) and 1,257 ml (+/-793 ml), respectively. Surgeons fused up to three levels in this patient population, although most of their patients only had one level fused.

Surgical blood loss for lumbar fusion surgery can vary, averaging over 800 ml (range 100–3,100 ml) for non-instrumented fusions to 1,517 ml (range 360–7,000 ml) for instrumented fusions in one study [18]. Other studies have shown comparable findings [2, 4, 7]. Hur et al. [13] looked at a wide range of spinal fusion surgeries and found the average total blood loss to be 1,122 ml, but had one patient whose total blood loss was 3,000 ml for a two-stage surgery.

With increasing numbers of adult deformity surgery being performed, and with greater numbers of levels of fusion required, reports of blood loss in the literature have ranged from less than 1 liter to 3 liters [1, 3, 12, 24, 27, 30] for posterior procedures, with similar results with anterior instrumented procedures [16, 23], but greater blood loss when osteotomies through prior fusions are performed, ranging from 325 to 4,700 ml [8, 14, 17].

Autologous blood donation has become increasingly common for elective spine surgery patients and can lead to a decrease in the likelihood of homologous blood exposure [10]. Use of erythropoietin in patients auto-donating for elective orthopedic surgery, in conjunction with iron sulfate supplements, can increase the number of autologous units the patients are able to donate [11]. This study had one patient who was randomized to receive erythropoietin and who developed a peripheral arterial thrombosis. The safety of use of erythropoietin in elective spine patients, particularly if they are to undergo anterior spinal surgery that incurs a higher risk of thromboembolic disease, is not yet established.

Intraoperative blood salvage is another method of decreasing use of homologous blood transfusion during surgery. Simpson et al. [26] found that, for their pediatric and young adult population who also donated autologous blood prior to surgery, this method was efficacious only if the estimated blood loss was greater than 2,000 cc. This group only represented about 10% of their patient population. They did not analyze their patients for risk factors for this greater blood loss.

Nuttall et al. [21] reviewed their experience in adult patients, including an average of over four levels fused (SD+/-4) and found several factors that resulted in a greater risk of allogeneic blood transfusion, including low preoperative hemoglobin, tumor surgery, increased number of posterior levels fused, history of pulmonary disease, and decreased amount of autologous blood available. In an accompanying article [22], they applied a "surgical blood order equation" to help the surgical team decide how much blood to order preoperatively. This was an attempt to decrease an excessive setting aside of blood for an individual patient's surgery. They found that the most important preoperative variables were preoperative hemoglobin and whether the patient had had a surgical diagnosis of a tumor.

Zheng et al. [31] looked at revision lumbar spinal fusions and found that intraoperative blood loss rose statistically in proportion to increasing fusion levels, preoperative hemoglobin, and body weight. They also found male gender, higher body mass index and the presence of degenerative scoliosis to correlate with greater blood loss. Johnson et al. found that instrumentation, multilevel fusion, and combined approaches increased the intraoperative blood loss for lumbar fusions [15].

Looking at complex adult reconstructive surgery that requires sequential anterior and posterior spinal fusion, Urban et al. [29] found an average intraoperative EBL of 3,556 ml, although he did not give ranges. The average number of levels fused in this study was seven anteriorly and 13 posteriorly. This prospective, randomized study specifically looked at efficacy of the antifibrinolytics Amicar (epsilon-aminocaproic acid [EACA], Lederle, Philadelphia) versus aprotinin (Transylol, Bayer, West Haven, CT, USA) on perioperative blood loss. Although both study groups had less perioperative blood loss than the control group, only in patients receiving aprotinin did this reach statistical significance. Duration of surgery was also correlated with blood loss. Murray, in an accompanying point of view, noted that this decrease was only 20% overall, and the cost of Aprotinin for an 8-h infusion would be $1,000. In addition, aprotinin has been associated with sensitization and anaphylaxis after exposure [9].

The issues of exposure to allogeneic blood products are certainly a reason to strive to decrease perioperative blood loss. However, there are other consequences of greater surgical blood loss that raise the impact of decreasing EBL. Nahtoma-Shick et al. [20] demonstrated that higher EBL, increased crystalloid administration and total blood administration were all factors that led to increased crystalloid infusion and increased length of stay in the ICU in their patient populations. Additional predictors were age, ASA physical status, surgical procedure (decompression alone, decompression and fusion, complex procedures, and combined anterior/posterior procedures), and total intraoperative crystalloid/platelet administration. Their EBL for patients who stayed in the ICU more than 1 day was 2,702+/-1,771 ml compared with 612+/-480 ml for those who did not require ICU stay.

In summary, spinal fusion surgery can result in significant intraoperative blood loss, with some risk factors predicable and others not. With increasing magnitude and complexity of spinal surgery, surgeons and anesthesiologists should anticipate greater potential blood loss. Although the risks of disease transmission with transfusion

have decreased with better testing, greater exposure to homologous blood may increase the length of ICU care. The risk of increased infection, immune system compromise or of transfusion-related acute lung injury may be relatively small, but should be considered important in these patients.

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Blood loss in pediatric spine surgery

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Abstract This article reviews the extent of blood loss in spine surgery for scoliosis corrections in the pediatric age group. An extensive literature review presents blood loss values in surgery for adolescent idiopathic scoliosis, cerebral palsy, Duchenne muscular dystrophy, spinal muscular atrophy, and myelomeningocoele. The underlying disorder plays a major role in determining the extent of blood loss. Blood loss is considerably higher in those patients with a neuromuscular scoliosis compared with adolescent idiopathic scoliosis. Within the neuromuscular group those with Duchenne muscular dystrophy demonstrate the highest mean levels of blood loss. Blood loss is also shown to be progressively greater with increasing numbers of vertebral levels incorporated into the fusion, with posterior fusions compared to anterior fusions, and in those patients having both anterior and posterior fusions.

Keywords Scoliosis surgery · Pediatric age group · Blood loss

Introduction

Blood loss is an important concern in performance of spinal surgery. This article will review the extent of blood loss in spine surgery for scoliosis and kyphoscoliosis corrections in the pediatric age group since these are the procedures which are most extensive and subject to the greatest amounts of loss.

The pediatric age group refers to the first two decades of life, with the majority of spinal surgical procedures done in the second decade. Distinction must be made between studies in pediatric and adult patients, since blood loss in the adult patient can be proportionately greater than in the pediatric age group for the same procedure. The modern era of scoliosis surgery will be reviewed involving procedures performed from the early 1960s onward using spinal instrumentation and spine fusion for correction and stabilization of deformity.

The underlying disorder plays a major role in determining the extent of blood loss. Blood loss is considerably higher in those patients whose scoliosis is associated with a neuromuscular disease compared with those in the idiopathic category. Blood loss is also shown to be progressively greater with increasing numbers of vertebral levels incorporated into the fusion and with posterior fusions compared to anterior fusions.

Considerations regarding literature reports of blood loss in scoliosis surgery

Blood loss determinations

Limitations must be recognized in the accuracy of intra-operative blood loss determinations and, therefore, in the value of comparing studies from one center to another. Blood loss is reported as "estimated blood loss" (EBL) since this represents the only practical way that operating room determinations can be made. Since these are estimates they are not rigidly accurate or reproducible as they are dependent on a combination of numbers including: volume of blood suctioned from the operative field (from which irrigating fluid must be subtracted), determination of blood loss collected on sponges (as determined by weighing by the operating room nurses), and estimates of blood loss on drapes, gowns, and floor (which is educated guesswork at best). To a great extent the value determined is dependent on the degree of rigor used by the operating room team in making the determination.

Measurement values used to present information

Different ways of presenting blood loss information are used in different papers reporting on scoliosis surgery. In almost all studies the extent of blood loss is reported in total milliliters (mL or ml) or cubic centimeters (cc). A second way is by determination of blood loss per vertebral level included in the fusion (total blood loss divided by number of vertebral levels in the fusion). A third way calculates the blood loss as a percentage in relation to the patient's estimated blood volume (EBV). The EBV is generally calculated to be 70 ml/kg (weight) [21]. For a 50 kg patient the EBV is 70×50=3,500 ml. A blood loss of 1,000 ml in that patient would represent a 28.6% loss. Wider presentation of blood loss as percent EBV would be helpful since this value provides the most physiologic indicator by taking patient size into account.

Diagnostic category of scoliosis

Awareness of the disorder associated with the scoliosis is essential since distinction must be made between idiopathic scoliosis and secondary scoliosis, which usually refers to neuromuscular disorders causing the scoliosis. Some reviews lump all types of neuromuscular deformity together but in many reports they are subdivided into the common variants of neuromuscular scoliosis which are cerebral palsy, myelomenigocoele, and Duchenne muscular dystrophy (DMD). Each of these disorders has differing responses regarding blood loss during surgery as well as differing needs for spinal correction and stabilization.

Types of surgical procedure

Distinction is made regarding blood loss in surgery between solitary posterior spinal fusions, solitary anterior spinal fusions, and combined anterior and posterior spinal fusions (including consideration of whether the anterior-posterior procedures are done as a single operation or separately with 1–2 weeks between stages).

Primary reason for the report from which blood loss information is abstracted

A few papers in this review were directed specifically to determining blood loss, usually comparing one anesthetic method to another or the use of a particular blood loss reducing agent. Since this article provides an overview of the problem of blood loss in pediatric spine fusion surgery, we have used the control group values from such studies but have usually also presented findings with the particular modification used.

Since limiting intra-operative blood loss is universally recognized as highly important, essentially all procedures done since the 1970s have incorporated several control mechanisms without necessarily indicating so in reports. These include: minimizing abdominal pressure with positioning, some form of hypotensive anesthesia, blood transfusion at pre-determined levels of hemoglobin, early replacement of platelets and fibrinogen, and surgical techniques stressing rigorous mechanical wound hemostasis [21, 26, 47, 57, 67]. For these reasons, most comparative studies relating to methods diminishing intra-operative blood loss are not scientifically controlled.

The large majority of papers in this review addressed problems relating to surgical technique, stabilization systems, and concerns specific to particular disorders and types of scoliosis. We have abstracted blood loss data as presented in each paper and derived EBL/vertebral segment and percent EBV numbers if sufficient information was provided.

The paper is designed to review intra-operative blood loss data. Some reports also assess post-operative blood loss but usually as separate determinations. In the few instances where combined data only were provided we have indicated that fact, and have used such studies only if the author indicated that post-operative loss was negligible.

Review of blood loss data from the literature

Blood loss data from the literature are presented in Tables 1, 2, 3, 4, 5 and 6. In each table we have listed the study (article) with year of publication and year(s) when surgery was performed, estimated mean blood loss (ml or cc) with ranges and/or standard deviations, the number of operative procedures in the study, surgical technique with bone

Table 1 Blood loss data from studies on posterior spinal fusions for AIS. *C-D* Cotrel-Dubousset (instrumentation), *H-rod* Harrington rod, *TSRH* Texas Scottish Rite Hospital (instrumentation), *L-rod* Luque rod

Study [reference] (date of publication)/ (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss/ individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss/ total estimated blood volume (EBL/EBV)	Comments
Shufflebarger et al. [62] (2004)/(1998)	500 (200–800)	55 (Lenke5)	Posterior shortening, posterior segmental pedicle screws with 5 mm rods (Moss-Miami)	-	-	No iliac crest graft
	627 (350–1500)	7 (Lenke 6)		-	-	
	675 (500–750)	3 (Lenke 3c)		-	-	
DuToit et al. [18] (1978)/	567	27	Harrington rod	-	-	Use of acute hemodilutional autotransfusion intraoperatively
Copley et al. [16] (1999)/(1995–1997)	608 (hemodilution)	43	Posterior fusions, systems not described	608/10.7=57	608/3780=16%	Comparison of hemodilution technique to control group, iliac crest bone graft, multicenter
	672 (control)	43		672/10.2=66	672/3774=18%	
Guidera et al. [32] (1993)/	660	-	-	660/7=94	-	Smaller curves <60º, levels=7
	1696	34		1696/8.8=193	-	Larger curves >60º, levels=8.8 [numbers per group not listed]
Erwin et al. [20] (1976)/(1966–1972)	743	187	Harrington-rod, no iliac crest bone graft	-	-	-
	840	177	Harrington rod, iliac crest bone graft	-	-	
Harrington and Dickson [33] (1973)/(1961–1972)	748 (110–3480)	578	Harrington rod, iliac crest bone graft	748/10=75	-	Hypotensive anesthesia, systolic 85–95 mmHg
Youngman and Edgar [71] (1985)/ (1974–1982)	779 (<200–>1400)	319	Harrington rod, iliac crest bone graft, multiple ancillary procedures (operation in cast, sublaminar wires, etc)	779/11.9=65	-	Induced hypotension, systolic 60–65 mmHg
Lawhon et al. [39] (1984)/(1972–1978)	801	120	Harrington rod technique	-	-	Induced hypotension, mean arterial pressure (diastolic pressure + 1/3 of pulse pressure) less than 90mmHg
	1583	31	Harrington rod technique	-	-	Normotensive anesthesia
Siller et al. [63] (1996)/(1991)	823 (186–1587)	55	C-D, iliac crest bone graft	1084/11.1=98	-	Hypotensive anesthesia
Florentino-Pineda et al. [26] (2004)/ (1999–2001)	893 +/– 220	19	Posterior spinal fusion with segmental instrumentation; allograft only	893/12=74	893/3095=29%	ε-aminocaproic acid group
	952 +/– 372	17		952/12=79	952/3153=30%	Control group

Table 1 (continued)

Study [reference] (date of publication)/ (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss/ individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss/ total estimated blood volume (EBL/EBV)	Comments
Florentino-Pineda et al. [25] (2001)/ (1996–1998)	988 (+/– 411)	29	Multiple instrumentations	988/12=82	988/2973=33%	Pre-operative autologous blood and controlled hypotension (systolic 20% less than pre-induction value) ε-aminocaproic acid (EACA)
	1405 (+/– 671)	31		1405/12= 117	1405/3188= 44%	No EACA
Patel et al. [56] (1985)/(1977–1980)	1102 (+/– 72)	27	H-rod, autologous iliac crest bone grafts	46	1102/3836= 29%	Induced moderate hypotensive anesthesia (Systolic blood pressure 20–30 mmHg < preoperative systolic pressure)
	1541 (+/– 156)	22		84	1541/4186= 37%	
Moran et al. [48] (1995)/(1989–1993)	1113	84	C-D, iliac crest bone graft	-	-	Preoperative autologous blood donation
Richards et al. [59] (1994)/(1988–1991)	1122 (350–4000)	95	TSRH	-	-	-
Guadagni et al. [30] (1984)/(1979–1982)	1187	30	H-rod, L-rod with spinous process wiring H-rod	1187/11=108	-	-
	1543	31		1543/10=154		
McMaster [46] (1991)/(1975–1987)	1200 [a] (500–2458)	156	H-rod	1200/11+109 [a]	-	Same surgeon all cases, Autogenous iliac crest grafts
	1490 [a] (695–2945)	152	L-rod	1490/10.9= 137 [a]	-	
Lenke et al. [40] (1992)/(1985–1988)	1211 (300–3000)	95	C-D, autogenous bone graft iliac crest (occasional ribs)	1211/11=110	-	-
Albers et al. [1] (2000)/(1991–1995)	1421 (+/– 881)	21	Single rod TSRH, 11 iliac crest bone graft	-	-	-
	1801 (+/– 1201)	24	Dual rods (TSRH, C-D or Paragon) 17 iliac crest bone graft	-	-	
Lovallo et al. [42] (1986)/(1978–1982)	1500 (300–4000)	133	H-rod, autogenous iliac crest bone graft	1500/10=150	-	-
Barr et al. [3] (1997)/	1571 (550–3300)	39	C-D (thoracic) but lumbar pedicle hooks/ screws 20 and lumbar hooks only 19	1571/~10=157	-	Double major curves; blood loss same in two approaches
Guay et al. [31] (1994)/	1971 (+/– 831)	30	C-D, autogenous iliac crest bone graft	1971/9.3=212	61.5%	Low normotensive anesthesia

[a]Blood loss during and after surgery (post surgery loss negligible)

Table 2 Blood loss data from studies on anterior spinal fusions for AIS. *TSHR* Texas Scottish Rite Hospital (instrumentation), *C-D* Cotrel-Duboussett

Study [reference] (date of publication) / (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss / individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss/ total blood volume	Comments
Moskowitz, Trommanhauser [49] (1993)/(1983–1989)	330	13	Zielke, rib graft	330/4.4=75	-	-
Bernstein, Hall [9] (1998)/(1990–1993)	344	17	TSRH (anterior)	344/3.4=101	-	-
Turi et al. [69] (1993)/	401 (100–800)	14	TSRH (anterior), rib graft	401/5=80	-	-
Newton et al. [52] (2003)/(1991–2001)	424 (+/– 302)	38	Thoracoscopic anterior instrumentation Isolated structural thoracic curves-Lenke IA, IB, IC	424/7=61	-	An earlier study compared thorascopic anterior release and fusion (EBL 235 ml) with fusion by open thoracotomy (EBL 270 ml) (reference 53)
	551 (+/- 363)	68	Anterior open instrumentation (Depuy-Acro Med Harms Study group)	-	-	
Bullman et al. [14] 2003/	437 (+/– 221; 100–1000)	45	Anterior dual rod Halm-Zielke	437/4.7=93	-	-
Bitan et al. [11] 2003/	505 (150–1000)	24	TSRH, Moss-Miami and C-D Horizon rib graft	505/2.9=174	-	-
Majad et al. [44] (2000)/	590 (250–950)	22	TSRH, Moss-Miami, Isola/ rod (3–11 levels fused)	-	-	-
Lowe, Peters [43] 1993/	610	36	Zielke, rib graft	610/4.5=136	-	-
Hopf et al. [35] 1997/(1992–1994)	630 (400–1200)	16	C+D - Hopf anterior system	-	-	-
Kaneda et al. [37] 1997/(1992–1994)	650	20	Kaneda anterior spinal system	650/7.5=87	-	-
Betz et al. [10] (1999)/(1991–)	956 (+/– 857)	78	Flexible rods (Harms-Moss, DuPuy-Motech-Acromed)	-	-	-
Hsu et al. [36] (1982)/	1645 (440–3400)	28	Dwyer	1645/4.7=350	-	-

graft information, mean EBL per individual vertebral level in fusion, mean EBL as a percentage of total EBV, and additional comments. In each table the studies are listed in order of mean EBL, beginning with those with the least loss reported to those with the highest amounts.

Table 1 reviews posterior spinal fusions for adolescent idiopathic scoliosis (AIS), Table 2 reviews anterior spinal fusions for AIS, Table 3 reviews spinal fusions for cerebral palsy, Table 4 reviews posterior spinal fusions for DMD, Table 5 reviews spinal fusions for pooled neuromuscular disorders (both anterior and posterior approaches), and Table 6 reviews spinal fusions for other neuromuscular disorders including spinal muscular atrophy and myelomeningocoele.

Blood loss in scoliosis surgery assessed by underlying disorder

Awareness of potential blood loss problem with any spinal fusion surgery

The operating team must have a high degree of preparation for blood loss in any spinal surgery for scoliosis in the pediatric age group, regardless of etiology and surgical approach to correction. Although AIS treated by spinal fusion has the lowest mean values for blood loss in scoliosis procedures, the ranges of blood loss measurements in all studies are wide, and amounts necessitating blood transfusion are often noted for both anterior and posterior approaches (Tables 1 and 2).

Table 3 Blood loss data from studies on spinal fusions for cerebral palsy. *P* posterior spinal fusion, *A* anterior spinal fusion, *P/a* posterior spinal fusion with some cases having anterior spinal fusion, *H-rod* Harrington rod system, *L-rod* Luque rod system, *DDAVP* desmopressin acetate

Study [reference] (date of publication) / (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss / individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss / total blood volume	Comments
Bulman et al. [15] 1996/(1988–1993)	P/a 1325 (350–4000)	15	Luque-Galveston (15) plus anterior release, disk excision, arthrodesis (7)	1325/14.5=91	-	Same day procedures; blood loss for total approach
	P/a 1240 (300–3400)	15	Unit rod (15) plus anterior release, disk excision, arthrodesis (4)	1240/15=83	-	
Sponseller et al. [64] 1986/1982–1984	P 1681 (hypotensive anesthesia)	20	H-rod/L-rod, 1 or 2 with spinous process wiring, iliac crest bone graft; anterior release 2 weeks pre posterior fusion in 21–13 with Dwyer instrumentation	1681/15=112	-	Blood loss only for posterior procedures
	P 2200 (normotensive anesthesia)	14		2200/15=147	-	
Swank et al. [66] 1989/(1981–1985)	P 1760 (600–3000)	10	Luque or Luque-Galveston, autogenous iliac crest bone graft	1760/12=147	-	
	A 906 (200–3600)	21	Anterior fusion, Zielke system	906/5=181	-	Two week interval between anterior and posterior stages
	P 2040 (600–6490)	-	Posterior fusion, Luque system, autogenous iliac crest bone graft	2040/14=146	-	
Allen, Ferguson [2] 1982/(1977–1980)	P 2086 (550–3900, both)	7	Luque rods to L5 or above	2086/10.7=195	-	-
	2267	3	Luque rods to pelvis. Both with iliac crest autografts	2267/14.7=154	-	
Gersoff, Renshaw [28] 1988/ (1979–1983)	P 2125	33	Luque rod, bone bank bone graft	2125/14=152	-	Hypotensive anesthesia not used. No anterior approaches
Lonstein, Akbarnia [41] 1983/ (1948–1979)	I: A 1919	3		1919/7=274	58% EB volume	Group I - double balances curves
	P 2215	41	Harrington system, autogenous iliac crest bone graft	2215/13=170	79% EB volume	
	II: A 1803	>25	Dwyer or Zielke systems	1803/7=258	54% EB volume	Group II - large unbalanced thoraco-lumbra or lumbar curves
	P 2629	99	Harrington system, multiple other methods	2629/15=175	84% EB volume	Some posterior fusions without instrumentation
Bonnett et al. [13] (1976)/(1960–1972)	P 2230	10	Harrington rod system	2230/7.4=301	-	Many revisions subsequently needed with both approaches. Eventually recommended both anterior and posterior – improved results.
	A 1500	18	Dwyer anterior fusion system only	1500/5.5=273	-	

Table 3 (continued)

Study [reference] (date of publication) / (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss / individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss / total blood volume	Comments
Dias et al. [17] (1996)/(1988–1991)	P 2149	31	Unit rod to pelvis local autogenous bone graft plus bone back allograft. T1 to sacrum	2149/17=126	-	7 patients had anterior release with rib graft 1 week before posterior fusion
Theroux et al. [68] (1997)/	Not reported	21	Unit rod fusion T1 to sacrum	-	DDAVP group Median loss 148% (range 57–425) EBV Placebo group Median loss 111% (range 65–240) EBV	-

Adolescent idiopathic scoliosis

AIS patients have the lowest amount of mean blood loss per procedure of all operative scoliosis groups. In the group treated by posterior spinal fusion (Table 1) in several studies the mean EBL ranges between 600 and 1,000 ml, and most studies document mean ranges between 750 and 1,500 ml. Treatment of AIS by anterior spinal fusion (Table 2) yields even lower mean EBL values, with most studies ranging between 350 and 650 ml and almost all less than 1,000 ml.

While the ranges of EBL per vertebral level included in the fusion in AIS are similar for posterior approaches (65–150 ml) and anterior approaches (60–135 ml), the overall blood loss is considerably less in the anterior group because fewer levels need to be fused to gain acceptable correction. The number of levels fused in the anterior surgery group is usually between 4 and 7 while the posterior group involves 9 to 12 (Tables 1 and 2).

Cerebral palsy

Blood loss is considerably higher in cerebral palsy patients undergoing scoliosis correction compared to patients with AIS (Table 3). The mean blood loss ranges in posterior approaches are concentrated between 1,300 and 2,200 ml, while many in the anterior group range from 900 to 1,800 ml. Blood loss per vertebral level fused is approximately similar for anterior and posterior approaches, although greater than AIS amounts, with most studies reporting losses between 100 and 190 ml per level. Blood loss amounts are much greater in posterior approaches primarily because of the larger number of vertebral levels involved; 13–15 with posterior procedures and 5–7 with anterior procedures.

Duchenne muscular dystrophy

Blood loss in DMD patients is even higher in most series than amounts reported for cerebral palsy patients. Several large studies have reported mean blood loss amounts from 2,500 ml to 4,000 ml+ (Table 4). Other studies have reported lower mean values of 930–1,680 ml but even these reports show some patients at the 3,000, 4,000 ml levels. The blood loss amounts are further magnified in effect since many DMD patients are small in stature with low body weight. Fusion is invariably performed from the upper thoracic region to the sacrum encompassing 13–16 levels. Mean values of EBL per vertebral level are in the 200–280 ml range, although more recent studies with less blood loss are being reported.

Studies on pooled neuromuscular disorders

Many studies on scoliosis surgery pool data from patients with neuromuscular disorders and do not distinguish between cerebral palsy, DMD, etc. Much valuable information is still provided, especially concerning blood loss with varying approaches. Most of these papers involve complex, severe deformities in which individual patients are treated by both anterior and posterior approaches. Mean EBL levels for anterior procedures are around 1,000 ml but posterior approaches range from 2,000 to 3,500 ml. The EBL per individual vertebral level in the fusion is correspondingly high as well.

Table 4 Blood loss data from studies on posterior spinal fusion for DMD. *CDI* Cotrel-Dubousset instrumentation, *TSRH* Texas Scottish Rite Hospital (instrumentation), *ISOLA* ISOLA instrumentation (Acromed)

Study [reference] (date of publication) / (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss / individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss / total blood volume	Comments
Marchesi et al. [45] (1997)/(1988–1993)	930 (750–1500)	25	Luque-Galveston with sacral screws, local bone graft plus allogeneic bone	-	-	-
Fox et al. [27] (1997)/(1989–1994)	1028 (400–3000)	19	Hartshill rectangle, allograft bone graft	1028/12.5=82	30%	Hypotensive anesthesia
Mubarak et al. [50] (1993)/(1980–1987)	1680 (250–4000)	22	Luque system (10), Luque-Galveston (to pelvis, 12) autogenous iliac crest	168/15.5=108	-	-
Ramirez et al. [58] (1997)/(1980–1993)	2500 (1000–4500)	30	Luque or Luque-Galveston (23), CDI 6, TSRH1; half autograft and half allograft	-	-	-
Bellen et al. [6] (1993)/(1984–)	2633 (+/– 1100)	47	Luque (12), Luque-Galveston (22), Hartshill (13), fusion to pelvis 38 of 47, local bone graft and allograft	2633/136=194	84.5%	-
Noordeen et al. [54] (1999)/(1983–1993)	2977	48	Harrington system and Harrington-Luque system	2977/13=229	87%	-
Bentley et al. [8] (2001)/(1983–1996)	3034 (500–8700)	64	Luque, Harrington-Luque, or Luque-Galveston, local bone graft only	3034/13=233	-	-
Weimann et al. [70] (1983)/(1974–1978)	3067 (1830–4400)	24	2 Harrington distraction rods; autogenous iliac crest bone grafts	3067/12.8=240	-	-
Gibson et al. [29] (1978)	3132	10	Harrington rod	-	-	-
Heller et al. [34] (2001)/(1992–1998)	3373 (800–8500)	31	ISOLA system	3373/16=211	-	-
Shapiro et al. [61] (1992)/(1980–1990)	3640 (+/– 1905)	27	Luque or Harrington-Luque, iliac crest autograft (7), allograft (20)	3640/13=280	-	-
Swank et al. [65] (1982)/(1967–1979)	4064 (3300–6200)	13	7/11 with 2 distraction Harrington rods	4064/15=271	-	-
Sakai et al. [60] (1977)/(1972–1979)	4400	6	-	-	-	-

Information concerning entities such as spinal muscular atrophy, myelomeningocoele, and anterior approaches alone for selected neuromuscular disorders

Table 6 provides information from smaller numbers of studies. Blood loss in spinal muscular atrophy surgery is considerable but distinctly less than in DMD. In one group of 26 the mean EBL was 1,437 ml with EBL/vertebral level 103 ml. Most reports on spinal fusion in myelomeningocoele have been pooled with other neuromuscular disorders and reported in the studies listed in Table 5. One study on this entity showed mean EBL levels of 1,960 ml for posterior fusion without instrumentation, 1,729 ml for posterior fusion with Harrington rod stabilization, and 1,841 and 2,134 ml for combined anterior fusion and posterior fusion with instrumentation. The use of improved anterior instrumentation for myelomenigocoele is shown by two studies using the Cotrel-Dubousset-Hopf instrumentation with a mean EBL of 800 ml in 16 cases in

Table 5 Blood loss data from studies on pooled neuromuscular disorders (anterior and posterior approaches). *A* anterior approach, *P* posterior approach, *AP* anterior and posterior approach, *CDI* Cotrel-Dubousset instrumentation

Study [reference] (date of publication) / (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss / individual vertebral level in fusion (ml) (EBL/# levels=)	Estimated blood loss / total blood volume	Comments
Floman et al. [24] (1982)/(1972–1977)	A 1033 P 2200	73 -	Multiple techniques. Posterior procedure performed 2 weeks after anterior procedure	- -	- -	EBL in Dwyer procedures 1250
Neustadt et al. [51] (1992)/(1985–1988)	P 1945 (450–4500)	18	Posterior fusion to pelvis with CDI	-	-	-
Benson et al. [7] (1998)/(1990–1994)	P 1684 (450–4000) AP 2329 (550–6000)	P 38 AP 12	Luque-Galveston and 39/50 Anterior discectomy and fusion without instrumentation	- -	- -	43 with allograft only; hypotensive anesthesia and autologous blood retrieval
Boachie-Adjei et al. [12] (1989)/ (1979–1984)	A 1100 (300–2225) P 2639 (270–8000)	AP 11 P 35	Luque-Galveston. Anterior fusion without instrumentation; local bone graft with allograft	A 100/7.4=149 P 2639/15=176	- -	-
Ferguson et al. [22] (1996)/(1977–1991)	1. A 896 P 3360	1. 29 -	1. Two stages (anterior discectomy and fusion) rib with no instrumentation. Posterior Luque-Galveston	1. A 896/8=112 P 3360/15= 224	1. A 28% P 100.9%	-
	2. AP 2058	2. 16	2. Both procedures same day	2. 2058/14.9= 138	2. 83%	
Bell et al. [5] (1989)/(1983–1986)	P 3500 (800–11000)	34	Unit rod system T2-pelvis. Local bone graft only	-	-	-

one report and a value of only 539 ml in 21 neuromuscular patients, 12 of whom had myelomeningocoele, in another.

Key factors determining amount of blood loss during scoliosis surgery

The material presented above clearly documents the extent of intra-operative blood loss during scoliosis surgery in both AIS and secondary scoliosis in patients with an underlying neuromuscular disorder. It is evident that blood loss is increased in patients with a neuromuscular diagnosis and an increasingly large number of vertebral levels included in the fusion. Studies assessing patients by the specific neuromuscular disorder demonstrate increasing losses as one moves from the cerebral palsy group, to spinal muscular atrophy and myelomenigocoele, and then to DMD which has the highest mean blood loss values. Posterior spine fusion procedures tend to lose more blood than anterior procedures, although most of this loss is due to the considerably larger number of vertebral levels fused in posterior approaches.

Several detailed papers have quantified the blood loss differences with statistical validation in relation to these matters. In one study neuromuscular patients had an almost seven times higher risk of losing greater than 50% of their estimated total blood volume during scoliosis surgery compared to idiopathic scoliosis patients when the extent of surgery (number of segments fused), age, weight, and pre-operative coagulation profile were controlled for statistically [19]. Another study showed that an underlying neuromuscular disease, lower body weight, and a higher number of vertebrae fused independently predicted a greater number of allogeneic red blood cell transfusions [47].

A large study of 319 patients operated between 1984 and 1993 clearly correlated the amount of bleeding with the disorder causing the scoliosis. The mean peri-operative bleeding was 9.8 ml/kg for idiopathic scoliosis (159 patients), 14.1 ml/kg for secondary scoliosis [including cerebral palsy (22 patients), myelomeningocoele (spina bifida)

Table 6 Blood loss data from studies on spinal muscular atrophy and myelomeningocoele. *C-D-Hopf* Cotrel-Dubousset-Hopf instrumentation, *H-rod* Harrington rod

Study [reference] (date of publication)/ (date(s) of surgery)	Estimated blood loss (EBL) (ml) [mean (range)]	Number of procedures	Technique	Estimated blood loss / individual vertebral level in fusion (ml) (EBL/#levels=)	Estimated blood loss/ total blood volume	Comments
Noordeen et al. [54] (1999)/(1983–1993)	1437 (350–3500)	26	Luque and Harrington-Luque	1437/14=103	-	Spinal muscular atrophy cases
Basobas et al. [4] (2003)/(1988–)	539 (175–1000)	21	Moss-Miami (15), Zielke (4), others (2)	539/5.5=98	-	12/21 myelomeningocoele
Hopf et al. [35] (1997)/(1992–1994)	800 (350–2500)	16	C-D-Hopf	800/4.7=170	-	Posterior fusion also done in all myelomeningoceole patients
Osebold et al. [55] (1982)/(1960–1979)	1960 (550–3250)	13	Posterior fusion without instrumentation	1960/9=218	-	
	1729 (50–6500)	13 Patients (27 procedures)	Posterior fusion with H-rod instrumentation; 22/27 autogenous bone	1729/10=173	-	
	2134 (245–4500)	3	Anterior fusion without instrumentation and posterior H-rod fusion; 2 allograft, 1 autograft	-	-	Blood loss levels for combined surgery, not separated by site
	1841 (100–5200)	17 Patients (40 procedures)	Anterior fusion with Dwyer or Zielke; posterior H-rod fusion; 10 allograft, 7 autograft	-	-	

(18 patients) and vertebral malformations (18 patients)], and 29.3 ml/kg for muscular dystrophy and spinal muscular atrophy (31 patients) [23].

Other factors increasing blood loss are the length of time for the surgery to be done and the extra loss associated with harvesting autogenous iliac crest blood. In one study involving 145 patients undergoing Cotrel-Dubousset posterior fusions mean blood loss was 500 ml at 2 h, 1,500 ml at 3 h, and 2,400 ml at 4.5 h. The same study documented 1,828 ml blood loss with autogenous iliac crest grafts and 1,120 ml when autogenous bone was not used [57].

There are several reasons why blood loss is greater in the neuromuscular patients. Some are easy to understand and include: a larger number of vertebral levels fused, more frequent resort to both anterior and posterior procedures and the fact that the patients are often younger and of less weight than patients with idiopathic scoliosis. A recent study also documented a prolonged prothrombin time and decrease in factor VII activity greater than seen in idiopathic patients intra-operatively. The authors suggested that consumption of clotting factors during spinal surgery along with dilution of clotting factors further enhanced blood loss [38]. In addition, many neuromuscular patients are poorly nourished and have been on seizure medications, some of which can affect coagulation.

Awareness of the extent of blood loss with scoliosis surgery helps with pre-operative preparation and intra-operative management and should enhance the study and development of methods to decrease its occurrence.

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An overview of blood-sparing techniques used in spine surgery during the perioperative period

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Abstract The problems linked to blood loss and blood-sparing techniques in spine surgery have been less studied than in other fields of orthopedics, such as joint-replacement procedures. Decreasing bleeding is not only important for keeping the patient's hemodynamic equilibrium but also for allowing a better view of the surgical field. In spine surgery the latter aspect is especially important because of the vicinity of major and highly fragile neurologic structures. The techniques and agents used for hemostasis and blood sparing in spinal procedures are mostly similar to those used elsewhere in surgery. Their use is modulated by the specific aspects of spinal approach and its relation to the contents of the spinal canal. Blood-sparing techniques can be divided into two categories based on their goals: either they are aimed at decreasing the bleeding itself, or they are aimed at decreasing the need for homologous transfusion. Various hemodynamic techniques, as well as systemic and local drugs and agents, can be used separately or in combination, and their use in the field of spine surgery is reported. The level of evidence for the efficacy of many of those methods in surgery as a whole is limited, and there is a lack of evidence for most of them in spine surgery. However, several blood-saving procedures and drugs, as well as promising new agents, appear to be efficient, although their efficacy has yet to be assessed by proper randomized controlled trials.

Keywords Hemostasis · Spine surgery · Bleeding · Blood sparing · Prevention

Introduction

Blood loss in spine surgery is an important issue, even though it appears underestimated, or at least understudied, compared to hip and knee arthroplasty surgery. Blood loss, however, may be an acute problem not only in major deformity surgery but also in less extensive fusion procedures. Decreasing bleeding is important for maintaining a patient's hemodynamic equilibrium and allowing a better view of the surgical field. In spine surgery, the latter aspect is especially important because of the vicinity of major and highly fragile neurologic structures. The surgeon's comfort shortens surgery time, which further decreases bleeding.

In this article we will summarize the main techniques used to spare blood in spine surgery during the perioperative period: from the immediate pre-op to the post-op period. Most of those modalities will be described in greater detail elsewhere in this issue.

Blood-sparing techniques

Blood-sparing techniques can be divided into two groups based on their goals: they are aimed either at decreasing the bleeding itself, or at decreasing the need for homologous transfusion.

Methods aimed at decreasing bleeding

Hemodynamic:

- Controlled hypotension
- Local vasoconstrictors
- Epidural blockade

Chemical/biological:

- Systemic:
  - Desmopressin
  - Aprotinin
  - Tranexamic acid
  - Epsilon-aminocaproic acid
  - Oestrogens
  - Other
- Local:
  - Bone wax
  - Hemostatic "sponges" (gelatin, collagen, cellulose)
  - Fibrin sealants
  - Other

Methods aimed at decreasing homologous transfusion needs

Hemodynamic:

- Acute hemodilution
- Planned autologous transfusion
- Blood saving:
  - Perioperative: cell saving systems
  - Postoperative: drainage recovery systems or cell saving

Chemical/biologic:

- Erythropoietin (EPO)
- Substitutive oxygen carriers

Planned preoperative autologous donation and erythropoietin treatment will not be discussed here, as they take place many weeks prior to surgery and, therefore, are not truly perioperative. This paper will discuss all blood-sparing techniques reported in orthopedics, even if they have not (yet) been published in the context of spine surgery.

Controlled hypotensive anesthesia

Controlled hypotension has been used with success since the 1950s in orthopedic surgery [52]. It is widely applied to spine surgery, and good results have been published since the early 1970s [44, 66, 72, 84, 87, 91, 109].

However, Lennon et al. [77] report in a retrospective study that hypotensive anesthesia did not decrease transfusion requirements compared with normotensive narcosis in scoliosis surgery. The goal of hypotensive anesthesia is to reach a systolic blood pressure of around 60–80 mm Hg. Many different drugs have been used over time, such as anesthetic gases [13], Ca channel blockers [75], beta-blockers [80], nitroglycerin, nitroprusside [59, 50], opiates [21] and anesthetic drugs.

The mechanism by which controlled hypotension decreases blood loss is still unclear and goes beyond the simple explanation that lower blood pressure induces lower blood extravasation. Some authors have hypothesized the existence of an ischemic wound during hypotensive anesthesia, but few studies have really tried to measure blood flow through scientific measures such as flowmetry. Lee et al. measured blood flow in the paraspinal muscles during spine surgery with two different hypotensive drugs, reaching a similar degree of hypotension. They found widely different values for local blood flow [73], although the blood losses were not very different. This indicates that the effect on local blood flow is not the only factor involved. The effect on blood flow in the epidural venous plexuses has also been hypothesized [74], and blood pressure by itself seems to be an important variable influencing blood loss [100].

In the context of spinal fusions, some authors report that, since bleeding is mainly linked to bone decortication and is, therefore, essentially venous, blood loss will not be influenced by a decrease in arterial pressure [15]. In their series of Jehovah's Witnesses, Brodsky et al. [15] found that blood flow was correlated to surgery duration more than to blood pressure. Kakiushi [62] measured intraosseous pressure in thoracic vertebral bodies during surgery and found that the intraoperative blood loss correlated with intraosseous pressure but that the latter was not correlated to the arterial pressure.

Hypotensive anesthesia may lead to complications [81] and is contraindicated in some cases, mainly in patients with hypertension or ischemic disorders: coronary, cerebral or peripheric.

The possibility of neurological damage at the level of already compressed and compromised nerve roots, where hypotension could add to the suffering of the root, was raised by Krengel et al. [69]. The effect of hypotension on spinal cord function during scoliosis surgery has also been questioned [44]. However, although evoked potential monitoring may show temporary alterations, it does not appear that hypotensive anesthesia increases the risk of neurologic damage [45].

Acute normovolemic hemodilution

In this technique venous blood is collected at the beginning of the procedure, after the induction of anesthesia, in order to diminish hematocrit to a level around 30. In children even lower values can safely be attained (under 20) [33, 101]. The lost volume is compensated with synthetic colloids. Hemodilution can be combined with hypotensive anesthesia.

Despite the hemoglobin loss, tissue oxygenation is maintained through increased cardiac output and better venous return due to reduced viscosity, shear and sludge effect. Furthermore, the loss of red blood cells is decreased, as the blood volume lost during surgery will contain fewer cells. The collected blood can then be retransfused according to need.

Acute normovolemic hemodilution is widely used in spine surgery with good results in fusion [55, 60, 88], as well as in scoliosis surgery [11, 24, 30]. The patient can be kept in hemodilution beyond the surgical-procedure duration by delaying transfusion until the next day, with transfusion then being performed based on clinical judgment [55]. The main contraindications to this technique are ischemic disorders and hemoglobinopathies.

Local vasoconstrictors

Local infiltration of paraspinal muscles with vasoconstrictors (epinephrine, ornipressin) is widely used in spine surgery. This is based on the common belief that vasoconstriction will decrease blood loss. However, the literature is very scarce, and there is little evidence of true efficacy [11]. Also, blood loss does not appear to be related to the dose injected [47].

Epidural blockade

Epidural blockade with normotensive anesthesia has been described as reducing blood loss [61]. It induces vasodilatation in the pelvis and lower limbs with a reactive vasoconstriction above the blocked level and, therefore, can only be used at the lumbar level.

Postoperative wound instillation

Bianconi et al. [12] reported that postoperative wound instillation with ropivacaine was effective in controlling pain and decreasing postoperative blood loss.

Lost blood salvage

Perioperative

With this technique, blood lost during surgery is recuperated and processed through a pump system (Cell Saver, Haemonetics), then transfused back to the patient. In this case it is scavenged blood that returns to the patient. It does not contain platelets or coagulation factors. Therefore, in the case of significant loss and return, a supplementation with fresh-frozen plasma is required [70]. This means that the need for homologous blood products is not entirely eliminated in this method. It is estimated that about half of the lost red blood cells can be salvaged [37].

The main complication is that a dilutional or disseminated coagulopathy can occur, and there is also a question about the complete elimination of tissue residues. Cell saving is therefore contraindicated in the presence of coagulopathies. Other rare complications include pulmonary injuries probably linked to leukoagglutinins [113] and transient hemoglobinuria [37]. This technique has been reported to be effective in spine surgery [10, 77, 84]. However, Copley et al. [24] did not show an efficacy in cell saving in conjunction with hypotensive anesthesia or with hemodilution in adolescents undergoing surgery for idiopathic scoliosis, and concludes that, in these cases, the cost exceeds the benefit. Shulman et al. compared acute normovolemic hemodilution and hemapheresis for blood-component sequestration with salvage alone. They found that the first technique was more cost effective, decreasing allogeneic as well as autologous blood need [99]. In a meta-analysis, Huet et al. [53] conclude that cell salvage in orthopedic surgery decreases the frequency of allogeneic transfusions, and a recent Cochrane review on cell salvage in surgery suggests that it is efficient in reducing need for allogeneic transfusion, despite the poor methodological quality of most studies [18, 19].

Postoperative

Postoperative collection and transfusion of either washed (cell saving) or unwashed blood has been described in many surgical fields. The most frequent technique consists of re-infusing filtered but unwashed blood from the wound-drainage systems. Many questions remain about the safety and real efficacy of this technique; e.g., the viability of the recovered erythrocytes is doubtful. The nephrotoxicity of free hemoglobin, originating from the hemolyzed red blood cells, poses a safety concern. Furthermore, the efficacy of the filtering system on all tissue residues and metabolites is not entirely clear. However, it seems that, although serum levels of fibrin-degradation products, free hemoglobin and some enzymes [97] increase, they return to previous levels after 24 h. Minor transient transfusion reactions may occur: chills, tachycardia and temperature-increase [103]. Infection and malignancy are contraindications.

This technique is very widely used in hip and knee arthroplasties. There are a few publications in the field of the spine, and these claim efficacy in reducing homologous transfusion requirements [10, 84]. Sebastian et al. [97] showed a reduction of 30% in transfusion needs after reinfusion of drainage-salvaged blood. A combination of intraoperative cell saving with the postoperative infusion of unwashed shed blood enabled Behrman to decrease transfusion requirements by 68% in spinal procedures [10].

Systemic drugs

Epsilon-aminocaproic acid (EACA):
Hemocaprol, Amicar (Lederle) and others

This is an antifibrinolytic agent that prevents plasmin from binding to fibrin. Some rare complications have been described: deep venous thrombosis, pulmonary embolism, renal failure and severe bradycardia.

In the field of spine surgery there are scarce and conflicting results published. In a controlled but not blinded study [35] and then in a proper randomized controlled study against placebo [36], Florentino-Pineda et al. showed a decrease in blood loss and transfusion requirements in patients undergoing idiopathic scoliosis surgery. In fusions in adults, Urban et al. showed limited effect, EACA being only marginally more effective than placebo but much less effective than aprotinin [110]. Amar et al. [5] used it in major orthopedic surgery (including spine) in patients with malignancy and found no efficacy. In a Cochrane review on antifibrinolytic drugs in surgery, Henry et al. [48] found a trend in favor of the use of EACA, but this was marred by poor methodology and biases in the reviewed articles. In other reviews Kovesi et al. [68] did not find any data to support routine use of EACA in orthopedic surgery, and Erstadt [32] came to the same conclusions concerning all types of surgery (including orthopedics).

Aprotinin: Trasylol (Bayer)

The complete mechanism of action of this substance remains unclear. It appears to decrease fibrinolysis by inhibiting plasmin, trypsin and kallikrein. It also avoids pathologic platelet activation by stabilizing the platelet membrane. Finally, it seems to decrease the inflammatory response by inhibiting bradykinin, interleukin and TNF.

Numerous problems are linked to its use: hypercoagulation, thrombus formation and effect on renal function. There also is a high risk of anaphylactic reaction after previous administration. This is especially important, as this drug is very widely used in cardiac surgery. This risk could preclude the drug's use in heart surgery in those patients having previously received it for other procedures such as spine surgery. In a multicenter randomized controlled trial, Samama et al. [94] have demonstrated a decrease of blood loss and transfusion with aprotinin in major orthopedic surgery. A Cochrane review [48] of antifibrinolytic drugs in surgery found existing evidence for the use of aprotinin, despite biases in some of the reviewed studies.

The use of aprotinin in spine surgery has been documented in a few controlled studies. Urban showed a decrease in blood loss and transfusion needs in adult fusion, and Cole et al. [23] showed similar results in deformity surgery on children and adolescents. Lentschener et al. [78] demonstrated dramatic reduction of intraoperative and 24-h blood loss but did not notice a significant reduction in homologous transfusion needs. This study demonstrated the decrease on intraoperative fibrinolysis through intraoperative dosage of D-dimmer. Amar et al. used aprotinin for major orthopedic surgery (including spine) in patients with malignancy and found no efficacy [5] in reducing blood loss. There are conflicting results as to the dose regimen to be used, with some reporting high dosage [78, 94] and others half-dosage efficacy [110].

Deamino-8-d-arginine-vasopressin
(DDVAP or desmopressin): Minirin (Ferring)

This is an analog to L-arginine-vasopressin or antidiuretic hormone (ADH). Its mechanism of action lies principally in an increase of the secretion of factor VIIIc. It also increases the secretion of von Willebrand factor (vWF) and has a paradoxical effect on the increase of plasminogen activator. There are conflicting reports about the use of desmopressin in scoliosis surgery. In a controlled trial, Kobrinsky et al. [67] found decrease in blood loss, transfusion requirements and use of analgesic agents in the postoperative period. The latter might be due to the decrease of bleeding in the wound. Other studies, however, do not confirm such findings. Alanay et al. [2] conducted a randomized trial against placebo and did not find any significant effect on blood loss in idiopathic or congenital scoliosis. Guay et al. [46] reached the same conclusion.

In neuromuscular scoliosis, where coagulation abnormalities are often present [63, 89], leading to severe blood loss [31], Theroux et al. [104], in a randomized controlled trial, showed that although administration of DDVAP significantly increased factor VIIIc and vWF, it didn't decrease blood loss compared to placebo. Similarly, Lett's et al. [79] conclude that DDVAP decreases bleeding in some patients while others show no response. They propose testing bleeding time after a test dose of DDAVP a few days before surgery.

Several reviews do not find arguments for a wide use of DDAVP in order to reduce surgical bleeding. Kovesi [68] concluded that it can be efficient in patients with a defect in platelet function but found no evidence for use in routine elective orthopedic surgery. A recent Cochrane review of DDAVP in surgery does not find any evidence for surgical use outside patients with congenital bleeding disorders [18]. Desmopressin might be well indicated in patients with von Willebrand disease, acquired platelet disorders, renal failure, cirrhosis or long-term salicylate treatment.

Oestrogens: estriol, conjugated oestrogens

Oestrogens have been widely used in the past for hemostasis. However, their apparent lack of efficacy has made

their use scarce [32]. The mode of action is unclear. It seems that they decrease the permeability and increase the resistance of capillary walls as well as improve the platelet/wall interaction. They also have an antifibrinolytic activity by altering levels of factor V and decreasing the antithrombin activity of plasma.

In a controlled study McCall et al. [86] have reported the efficacy of conjugated oestrogens (Premarin, Wyeth-Ayerst) in decreasing the postoperative drainage volume in adolescents having undergone deformity surgery. There were no side effects. In a review of systemic hemostatic drugs, Erstadt [32] found only limited efficacy of conjugated oestrogens in the reduction of blood loss in surgery.

Tranexamic acid: Exacyl (Sanofi-Synthelabo), Cyklokapron (Pfizer) and others

Tranexamic acid decreases fibrinolysis by inhibiting transformation of plasminogen into plasmin. Recent studies show efficacy in reduction of bleeding during hip- [76] and knee-replacement [56] procedures. Other studies, however, seem to show that tranexamic acid does not decrease hidden losses [40]. Meta-analysis of the use of tranexamic acid in surgery shows either specific efficacy in knee arthroplasty [32, 51] or a trend towards effectiveness in other procedures, but results are marred by methodological flaws in the existing publications [48]. In the field of spine surgery, only one double-blind, placebo-controlled study in children and adolescents undergoing scoliosis surgery showed a reduction in transfusion needs without added complications [90].

Recombinant factor VIIa/RhFVIIa (NovoSeven, Novo Nordisk)

This drug is an anti-hemophilic agent. Its efficacy on hemostasis in non-hemophilic subjects during surgery [4], neurosurgery [64] and trauma [43] has been reported. A double-blind randomized control trial has shown good results in prostatic surgery [39]. In spine surgery there are some anecdotal reports [106] but there is currently a lack of evidence, due to a paucity of available studies [68]. This agent seems promising but true evidence of its efficacy in reducing bleeding during spine surgery has yet to be collected.

Other systemic means

Amino-acid infusion that induces thermogenesis prevented a drop in body temperature and decreased blood loss in hip arthroplasty [114]. Likewise, aggressive warming to keep body temperature at 36.5°C appears to decrease blood loss in hip replacement [115]. There are no reports on the effect of warming during spine surgery. Etamsylate (Dycinone, Sanofi-Synthelabo), a drug marketed as hemostatic, was used without success in hip replacement [65], and no data on its use in spine surgery is available.

Substitutive hemoglobin carriers (hemoglobin raffimers)

Substitutive oxygen carriers are an elegant solution for the future [6]. They are often incorrectly called "artificial hemoglobins," whereas the products in clinical experimentation are made from human or animal stabilized acellular hemoglobin. Hemopure (Biopure) is already marketed in South Africa, although the ethical issues regarding the early commercial human use of such products are discussed [99]. It is a bovine stabilized hemoglobin for which an FDA regulatory filing phase III trial has been completed in orthopedic surgery (including spine). This study showed an important decrease in transfusion needs. There do not appear to be major safety issues [102].

Hemolink (Hemosol) is a similar product but based on human hemoglobin. Results of phase II trials in cardiac surgery have been published showing decreased allogeneic transfusion needs with good safety [20]. A clinical phase III study, along the same lines, shows a marked reduction in the need for transfusions [42]. Phase II trials in orthopedic surgery are on the way in Canada and the US.

Local agents

Bone wax

Bone wax is a mixture of beeswax (70%) and petroleum jelly (30%). It acts in a purely mechanical way, by covering and filling bleeding bone surfaces. Its best known use is probably the hemostasis of sternotomy surfaces. There have been few reports in the field of spine surgery. Abumi et al. [1] describe an injury of the vertebral artery during cervical pedicular-screw insertion that was subsequently stopped with bone wax. Use of bone wax to stop bleeding of the bony surface in the spine is hampered by the fear of leaving a foreign body that can intrude into the spinal canal. Indeed, Cirak and Unal describe a case of tetraplegia following use of bone wax [22].

Hemostatic "sponges"

Gelatin-based (Gelfoam (Pharmacia), Surgifoam (Johnson & Johnson), and others

Gelatin-based, local hemostatic agents have been used in surgery for decades. They can be of bovine, porcine or equine origin and are available in multiple presentations:

sheets, powder, foam, etc. They can be used alone or soaked with thrombin. Their mechanism of action is still not completely clear but appear to be more physical, by "surface effect", than through any action on the blood-clotting mechanism. Gelatin-based devices have been reported to induce a better quality clot than collagen-based products [28]. The substance has been widely used in spine surgery, as it is considered safe to leave in the canal because it does not swell. Some authors have even suggested that gelatin reduces scar adhesion [71].

However, several publications report severe neurological consequences including cauda equina syndromes linked to the use of gelatin products in the spinal canal [3, 9, 38, 49]. Allergic reaction to gelatin after spinal use has also been reported [92].

Collagen-based: Instat (Johnson & Johnson), Lyostypt (B-Braun), Hemocol (Pilling-Weck), and others

Collagen based hemostatic products are from bovine, porcine or equine origin, and also exist in different forms: sheets, powder, aggregates, etc. They act on platelet aggregation and activate Hageman factor (F XII). They should not be left in the spinal canal as they provoke adhesion formation and foreign body reactions.

A more elaborate product is Tachocomb (Nycomed). It consists of a patch of collagen coated with fibrinogen and thrombin. In contact with liquids the components dissolve and the last phase of coagulation is launched, resulting in a fibrin-clot formation. That mode of action is similar to that of the fibrin sealants reviewed later. It also contains aprotinin in order to inhibit clot fibrinolysis. It is mostly used in thoracic and abdominal surgery, but repair of lacerations to the dural sac with this product have been reported [58] and experimental models have shown effectiveness in avoiding epidural fibrosis [73]. The use in spine surgery appears to raise the potential danger of leaving collagen-based agents in the spinal canal.

Oxidized cellulose based: Surgicel (Johnson & Johnson), Curacel (Curaspon) and others

These products also exist in multiple forms, such as sheets, gauze and powder. Their action is essentially a surface effect, which activates the initial coagulation phase. They also induce a moderate acceleration of fibrinogen polymerization. They should not be left in the canal, as they swell and cause foreign-body reactions. Neurological complications have been widely reported [8, 14, 57, 82]. Epidural migration, causing severe, and sometimes permanent, neurological lesions after use of cellulose hemostatic agents for thoracotomy have also been reported [98, 112]. The foreign-body reactions provoked by cellulose may induce granulomas and pseudo tumors [16, 95]. These reactions may also result in misleading pseudo-compression images on MRI examinations [7].

Fibrin sealants

Fibrin sealants reproduce the last phase of coagulation: the formation of a fibrin clot. There are two main families of fibrin sealant. The first combines two components: a fibrinogen component and a thrombin solution. A more recent type of sealant uses the fibrinogen of the bleeding source itself.

Bi-component fibrin sealant: Tissucol/Tisseel (Baxter), Beriplast (Behring), Hemaseel (Haemacure), CoStasis (Cohesion Tech)

All the available sealants in this category are used by mixing a fibrinogen component with a thrombin solution to form a fibrin clot. They usually contain factor XII to speed the cross linking of the clot. Some may contain aprotinin to inhibit fibrinolysis and even plasminogen to control the reaction. They are applied with a syringe, but a sprayable form exists to cover larger surfaces. However, they adhere poorly on wet and bleeding surfaces. Content of the sealant solution is especially important in spine surgery because of possible contact with major neurological structures. Quixil (Omrix, Brussels, Belgium) contains tranexamic acid instead of aprotinin as antifibrinolytic adjuvant. It appears that tranexamic acid is neurotoxic. Fatal neurotoxic reactions have been reported after use in neurosurgery [85].

Fibrin sealants have been reported to be effective in spine surgery [107] and to diminish scar formation [111]. A Cochrane review on the use of fibrin sealants in surgery suggests efficacy, but this conclusion is hampered by the small number of trials and their mostly dubious methodology [17].

The use of bovine fibrinogen may pose a safety problem in the context of spongiform encephalitis and the marketing of one fibrin glue, Biocol, had to be stopped. CoStasis uses the patient's centrifuged plasma with bovine thrombin. It is useful for avoiding the need for bovine fibrinogen (although bovine thrombin remains), but it seems expensive, cumbersome and time consuming. It has been reported to be effective in spine surgery [29, 105].

Fibrin sealant using wound fibrinogen: FloSeal (Baxter, formerly Proceed, by Centerpulse)

This second family of sealants contains thrombin but relies on the wound's fibrinogen. The bi-component medium contains a collagen/thrombin component and a gelatin matrix. The swelling of the collagen granules will restrict bleeding through a tamponing mechanism, while the gelatin

matrix will provide structural integrity to remain in situ. The main advantage of that form is that it can more easily be used on wet and bleeding tissues. Good results have been reported in spinal procedures [93].

N-butyl-cyanoacrylate: Histoacryl (B-Braun)

Apart from its cutaneous applications, this acrylic glue is used classically in gastroenterology to control gastro-esophageal bleeding. In spine surgery it has been used for injection of vertebral hemangiomas or malignant tumors prior to surgery in order to reduce peroperative bleeding [25, 27, 108].

Conclusions: where is the evidence?

The range of techniques available for sparing blood in spine procedures, as in other areas of surgery, is very wide and the variety of concepts is large. However, the evidence, aside from the anecdotal, is often lacking or conflicting. Controlled studies are scarce, and we do not really know if we can adapt, to spinal surgery, conclusions stemming from other surgical fields, mainly cardiac surgery, as to the efficacy of hemostatic means.

There seems to be adequate evidence showing the efficacy of most hemodynamic methods, such as hypotensive anesthesia and normovolemic hemodilution. The systemic hemostatic agents show fragmented and conflicting evidence as to their effectiveness in spine surgery. A Cochrane review of antifibrinolytic drugs in elective surgery has found good evidence to support the use of aprotinin in cardiac surgery and found trends for the effectiveness of tranexamic acid and epsilon aminocaproic acid, without, however, finding conclusive evidence, due to the heterogeneity and biases of many studies [48]. In elective orthopedic surgery, some reviews state that no hard data exist to support use of any fibrinolytic or other systemic drug [68]. RhFVIIa seems promising in the field of spine surgery, in light of results in other fields, but conclusive evidence should be demonstrated in spine surgery by proper randomized controlled trials. Alternative hemoglobin carriers are undoubtedly experimental products. As far as the local agents are concerned, once again, conclusive evidence is scarce and reports are mainly anecdotal. However, the realization of true randomized trials for those kinds of techniques is very difficult.

The daily, routine use of all these methods is also quite limited at the present time. Several surveys have shown that, outside of cardiac surgery, regular use of any blood-sparing method is infrequent [41, 54]. Lack of familiarity is the first reason quoted for their infrequent use [54]. Techniques (hemodilution, cell salvage, etc.) are more frequently used than pharmaceuticals, and there is a considerable variation among different countries [34].

Blood sparing in spine surgery is important, and it clearly appears that, contrary to other orthopedic and surgical fields, it has been understudied, with the current practice being more based on beliefs than on evidence.

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What is the evidence for using hemostatic agents in surgery?

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Abstract The pharmacological methods used to achieve systemic hemostasis have generated much discussion due to concerns of serious adverse effects (e.g., thromboembolic complications) and costs of therapy in addition to efficacy considerations. There are a limited number of well-controlled trials involving pharmacological hemostasis for spine surgery. In the largest double-blinded randomized controlled trial to date involving spine surgery, there was a trend toward reduced homologous transfusion in patients receiving aprotinin, but the only statistically significant result ($p<0.001$) was a reduction in autologous red cell donations. The findings of this trial are important, since the investigators used a number of restrictive transfusion strategies (e.g., autologous donation, low hematocrit trigger for transfusion, blood-salvaging procedures with the exception of no cell saver) that were not always employed in earlier trials involving hemostatic agents. Smaller studies involving antifibrinolytic agents other than aprotinin have demonstrated reductions in blood loss and transfusion requirements in patients undergoing spine surgery, although the results were not always statistically significant. A very large randomized trial would be required to address comparative medication- and transfusion-related adverse events; such a trial involving patients undergoing cardiac surgery is currently being performed. Additionally, cost-effectiveness analyses are needed to help define the role of these agents based on the data that is available.

Keywords Hemostatics · Antifibrinolytic agents · Hemorrhage

Introduction

Topical, local, regional, and systemic routes of medication administration have been employed for preventing or reducing blood loss and associated transfusion requirements in patients with bleeding diatheses. Examples would include topical fibrin- or thrombin-based products for wound hemostasis, proton pump inhibitor therapy for preventing gastric rebleeding in patients with peptic ulceration, octreotide derivatives for reducing rebleeding in patients with variceal hemorrhage, and the antifibrinolytic agents and desmopressin for systemic hemostasis. The pharmacological methods used to achieve systemic hemostasis have generated much discussion due to concerns of serious adverse effects (e.g., thromboembolic complications) and costs of therapy in addition to efficacy considerations.

The studies that have been conducted have focused on the operating room, where substantial blood loss can often be anticipated. This paper is intended to provide an overview of the consequences and costs of medications used for systemic hemostasis during spine surgery in light of currently available evidence. Ideally, the efficacy and adverse effects of these agents would be defined by large, well-controlled studies restricted to spine surgery rather than by extrapolation from other surgical procedures. Unfortunately, there are a limited number of such trials involving pharmacological hemostasis in association with

spine surgery. Therefore, potentially applicable information from other investigations of systemic hemostatic agents in the perioperative setting will also be discussed with the caveat that the pathophysiology of bleeding and mechanisms of action of the hemostatic agents may vary depending on the type of surgical procedure being performed.

Evaluating the evidence

When evaluating the studies concerning the benefits and risk of systemic hemostatic agents in the perioperative period, it is important to recognize that there are no standardized levels of evidence or grades of recommendation for ranking the study designs [34]. However, one or more appropriately powered randomized controlled trials (RCTs) are typically considered level I evidence leading to a grade A recommendation using numeric and letter systems [32]. Such trials will be the focus of this review.

The ranking of meta-analyses in hierarchical systems is more controversial, since meta-analyses have been shown to be predictive of large RCT results only 35% of the time [19]. Furthermore, depending on the criteria used for study inclusion in a meta-analysis, the results and conclusions of more than one meta-analysis on a particular topic may conflict. More meta-analyses involving pharmacological forms of hemostasis have pertained to cardiac surgery than any other type of procedure, which is not surprising considering the large number of RCTs of medications that have been conducted in this area.

Sample-size considerations

The largest double-blinded RCT to date involving spine surgery was conducted by Lentschener et al. [21]. In that trial, only one patient in the placebo group (none in the aprotinin group) required more than 5 U of red blood cells (RBCs) [21]. Such patients, who lie in the upper tail of a transfusion curve, can hinder the detection of significant differences in bleeding and transfusion requirements between groups. This is illustrated by a multicenter, double-blind RCT involving patients undergoing repeat coronary artery bypass surgery [22]. The statistically significant difference in RBC requirements noted between high- and low-dose aprotinin regimens disappeared (1.6±0.2 U in high dose and 1.6±0.3 U in low dose) when one patient with extensive bleeding was eliminated from the statistical calculations. By assuming that such variation in RBC requirements will not occur, the estimated sample sizes for studies involving systemic hemostatic agents are substantially decreased. For example, in one double-blinded RCT investigating the usefulness of aprotinin for reducing blood loss in orthopedic surgery, it was estimated that only nine patients would be needed in each group to detect a significant difference with 90% power and a significance level of 0.05 [15].

Efficacy of systemic hemostatic agents in spine/orthopedic surgery

In the trial by Lentschener et al. [21], patients undergoing spine surgery were randomized to an aprotinin (2×10^6 KIU loading dose followed by 5×10^5 KIU/h infusion until skin closure) or placebo. This dose of aprotinin, which will be referred to as a high-dose regimen in this paper, has been called a high- or low-dose depending on the investigation, so the clinician needs to consider the actual units administered in any given trial [15, 30]. The sample size in the RCT by Lentschener et al. [21] was calculated from blood-loss data collected at their institution. It was estimated that 72 patients would be needed to find a 30% reduction (80% power, $p<0.05$) in the baseline transfusion requirement of 2,200±1,000 ml using a one-sided analysis. While there was a trend towards reduced RBC requirements in patients receiving homologous transfusions, the only statistically significant result ($p<0.001$) was a reduction in autologous RBC donations. No fresh frozen plasma was administered in either group. No adverse drug events were attributable to aprotinin. The findings in the trial by Lentschener et al. [21] are important, since the investigators used a number of restrictive transfusion strategies (e.g., autologous donation, low hematocrit trigger for transfusion, blood-salvaging procedures with the exception of no cell saver) that were not always employed in earlier trials involving hemostatic agents. The trial gives clinicians an estimate of the blood-sparing effects of aprotinin beyond these baseline restrictive strategies. Additionally, since the investigators provided a detailed breakdown of transfusion requirements, the data can be compared to that from other investigations that found reductions in allogeneic transfusion when autologous blood was administered.[6].

Assuming that the variation in transfusion requirements, and therefore sample size estimation, is similar to that calculated by Lentschener et al. [21], the number of adequately powered studies involving patients undergoing orthopedic and spine surgeries is quite limited (Table 1). [2, 14, 16, 21, 24, 31]. Based on the findings of two RCTs, desmopressin does not have significant hemostatic activity in association with hip or knee procedures. While it has been postulated that desmopressin may be more useful in patients with preexisting platelet dysfunction, controlled trials substantiating this claim are needed. The antifibrinolytic agent tranexamic acid appears to have some usefulness in reducing blood loss and transfusion requirements in knee arthroplasty, but there are no adequately powered RCTs involving this agent (or the related lysine analogue, aminocaproic acid) in spine surgery. Aprotinin appears to have efficacy in reducing blood loss and trans-

Table 1 Randomized, double-blinded, placebo-controlled trials involving hemostatic medications for orthopedic and spine surgeries[a]

Reference	Patients	Dosing regimen	Outcomes
Karnezis et al [16]	92 patients undergoing total hip or knee arthroplasty	Desmopressin 0.3 µg/kg IV during wound closure	No significant differences in blood loss or transfusion requirements
Schott et al [31]	79 patients undergoing total hip replacement	Desmopressin 0.3µg/kg IV immediately after spinal anesthesia and 6 h later	No significant differences in blood loss or transfusion requirements
Benoni and Fredin [2]	86 patients undergoing knee arthroplasty	Tranexamic acid 10 mg/kg IV before tourniquet deflation	Tranexamic acid significantly reduced total blood loss (730±280 ml versus 1410±480 ml, $p<0.001$) and number of patients receiving red blood cell transfusions (8 versus 24, $p<0.001$)
Hiippala et al [14]	77 patients undergoing knee arthroplasty	Tranexamic acid 15 mg/kg IV before tourniquet deflation plus two more doses of 10 mg/kg IV (one in recovery room and one on ward)	Tranexamic acid significantly reduced total blood loss (689±289 versus 1509±643 ml, $p<0.0001$) and red blood cell requirements (1.0±1.2 versus 3.1±1.6 U, $p<0.0001$)
Lentschener et al [21]	72 patients undergoing posterior lumbar spine fusion	Aprotinin 2×10^6 KIU IV then 5×10^5 KIU/h until skin closure; an additional bolus of 5×10^5 KIU was given for each 3 U of red blood cells administered	Aprotinin significantly reduced blood loss and red blood cell transfusion versus placebo (1935±873 versus 2839±993 ml, respectively, $p=0.007$ and 42 versus 95 U, respectively, $p=0.001$); significant reductions in transfusion limited to autologous (not homologous) donation
Murkin et al [24]	149 patients undergoing unilateral total hip replacement	Aprotinin 5×10^5 KIU IV (low dose); 1×10^6 KIU IV then 2.5×10^5 KIU/h (medium dose); 2×10^6 KIU IV then 5×10^5 KIU/h (high dose) until skin closure	Aprotinin significantly reduced blood loss (1169 ml low dose, 1090 ml medium dose, 1079 ml high dose versus 1408 ml placebo, $p=0.034$, $p=0.005$, $p=0.003$, respectively) and the number of patients transfused (6% with aprotinin versus 15% with placebo, $p=0.03$)

[a] Studies with enrollment of more than 70 subjects

fusion requirements when administered in association with hip replacement and spine surgery, particularly with higher-dose regimens, but only one RCT is available to substantiate each of these proposed uses.

There are three smaller prospective studies that have investigated the efficacy of antifibrinolytics in spine surgery. Two studies ($n=59$ and $n=40$) involving children undergoing posterior spinal fusion for scoliosis have demonstrated reductions in blood loss and transfusion requirements with either aminocaproic acid or tranexamic acid [10, 26]. In the other study involving 60 adult patients undergoing sequential anterior and posterior spine fusions were randomized (but not blinded) to receive either aprotinin, aminocaproic acid, or a control group [35]. Both aprotinin and aminocaproic acid led to reduced blood loss and transfusion requirements compared to the control group, but the reduction with aminocaproic acid was only statistically significant in the former study.

Efficacy of systemic hemostatic agents in other types of surgery

Although it is more problematic to extrapolate the efficacy of systemic hemostatic agents from hepatic or cardiac surgery to spine surgery, there are some general themes that are consistent across investigations. Of the larger studies involving hepatic resection or transplantation, two double-blinded RCTs ($n=97$ and $n=137$) involving aprotinin found statistically significant reductions in blood loss and transfusion requirements [20, 28], and a third RCT with a somewhat smaller sample size ($n=80$) found trends toward benefits with aprotinin [11]. A fourth double-blinded RCT ($n=132$) comparing tranexamic acid and aminocaproic acid to placebo found reductions in transfusion requirements with both lysine analogues compared to placebo, but the results were only statistically significant for tranexamic acid [7].

Numerous double-blinded RCTs, particularly with aprotinin, have been conducted in cardiac surgery. Several meta-analyses have also been conducted in attempt to compare the efficacy of desmopressin and the various antifibrinolytic agents [9]. While the *lack* of evidence supporting the use of desmopressin during cardiac surgery is quite consistent, possible efficacy differences between the antifibrinolytic agents is less apparent. Underlying the drive for the numerous RCTs and meta-analytic comparisons is the substantial cost differences between aprotinin and the other hemostatic agents. Given the increasing controversy concerning the place of meta-analysis in evidence-based classification systems, it is not surprising that the meta-analyses in the cardiac surgery area have not resolved the discussion of the preferred hemostatic agent. To the contrary, a 3-year multicenter RCT comparing antifibrinolytic

agents is currently being conducted in Canada with an anticipated enrollment of approximately 3,000 patients [29]. The desired enrollment indicates the perceived (as well as calculated) number of patients needed to definitively answer efficacy questions concerning the antifibrinolytic agents.

There have been four randomized trials (all conducted prior to 1987) involving the lysine analogues for preventing blood loss after prostatectomy or thyroid surgery. The first double-blinded RCT involving 92 patients undergoing transvesical prostatectomy found significant reductions ($p<0.02$) in blood loss in patients starting tranexamic acid the morning of surgery and continuing for 4 days [12]. A second unblinded RCT allocated 100 patients to receive tranexamic acid for 3 weeks after prostatectomy or endoscopic bladder tumor resection and also found significant reductions in blood loss in the tranexamic group ($p<0.01$).[23] Additionally, one of two small ($n=46$ and $n=54$) double-blinded RCTs involving aminocaproic acid in patients undergoing prostatectomy found a significant reduction in blood loss [18, 33]. A double-blinded RCT involving 76 patients undergoing thyroid surgery found no significant reduction in blood loss with tranexamic acid [1]. None of these trials involving the lysine analogues investigated reductions in transfusion requirements.

Adverse effects of systemic hemostatic agents

A major concern with all systemic hemostatic medications, and one of the reasons for increasing the sample size of clinical trials, is the possibility of adverse effects. Of concern with all systemic hemostatic medications is the potential for thrombotic complications, and isolated case reports of such complications exist [25, 37]. However, a cause-and-effect relationship based on isolated case reports is not possible, and for each of these reports, there are other large series of patients in which no thrombotic complications were found [3].

Aprotinin has the advantage in that it has been studied in a large number of RCTs in cardiac surgery, but other hemostatic medications such as the lysine analogues have been available for many years. For example, a double-blinded RCT evaluating the safety of aminocaproic acid in association with prostatectomy was published in 1966; no evidence of serious adverse effects such as thromboembolic complications were found in the 259 patients randomized to the treatment group [36].

Aprotinin has some unique concerns related to the bovine source of the product, in particular reports of anaphylaxis upon reexposure that have been documented in a multicenter, prospective, observational study [8]. Adverse-effect concerns with the use of systemic hemostatic medications must be balanced with possible transfusion-related reactions and infectious diseases that are avoided by reductions in blood requirements. A very large RCT would be required to address comparative medication, and transfusion-related adverse events considering safety concerns have not been resolved by previous investigations [17]. Hopefully, the Canadian trial that is in progress will address some of the adverse effects as well as efficacy concerns [29].

Economic considerations

Until the efficacy and adverse-effect concerns are resolved through further trials, clinicians must reconcile the costs and consequences of hemostatic medications and blood transfusion. This is where formal economic analyses have a role. Unfortunately, only one large multicenter, double-blinded study has compared antifibrinolytic agents with a prospectively implemented economic analysis [3]. In that trial, aprotinin was significantly more effective than aminocaproic acid in reducing blood loss, but transfusion rates between the two medications was similar. Therefore, aminocaproic acid was the less costly agent in the analysis that not only considered medication costs but transfusion and operating room costs as well.

Given the high cost of aprotinin, the other antifibrinolytic agents would always demonstrate economic superiority if transfusion requirements were similar and there were no significant differences in other efficacy or adverse effect measures. However, if aprotinin decreases transfusion requirements to a greater degree than other agents without a concomitant increase in adverse effects, as has been demonstrated in a number of trials discussed in this paper, economic analyses could define the relative cost-effectiveness of the agents. Similarly, a systematic review of the antifibrinolytic agents by the Cochrane collaboration found a reduced need for reoperation in patients receiving aprotinin compared to control (RR=0.4, 95% CI= 0.25–0.66) [13]. Again, this could have important implications in a cost-effectiveness analysis. Depending on the comparative decrease in transfused blood or reexploration rates, the analysis could define the point at which aprotinin might be a preferred product despite its higher purchase cost.

One way to improve the cost-effectiveness of all systemic hemostatic medications is to restrict their use to patients at high risk for bleeding and transfusion. Recent studies evaluating factors predictive of allogeneic transfusion in association with spine surgery have helped to define high-risk patient and institutional factors [5, 27, 38]. Some of the factors that have been significantly predictive increased allogeneic transfusion in at least two of these recent studies include increasing age, female gender, comorbidities or complications, and low preoperative hemoglobin concentrations. The cost-effectiveness of hemostatic medications can also be improved by knowledge of commercially available formulations. Such knowledge may allow for cost-reduction measures such as dose

rounding by product size when using weight-based dosing regimens or decreased product wastage associated with canceled procedures by diluting the agent in an intravenous solution immediately prior to use.

Conclusions

The vast majority of RCTs involving hemostatic agents have been conducted in the operating room, particularly in patients undergoing coronary artery bypass surgery. There is a limited amount of high-level evidence supporting the use of systemic hemostatic agents for noncardiac surgery. Large RCTs are needed to answer concerns not only related to efficacy but also toxicity. Additionally, cost-effectiveness analyses are needed to help define the role of these agents based on the data that is available.

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Predeposit autologous donation in spinal surgery: a multicentre study

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Abstract *Background.* Allogeneic blood transfusions (ABT) are often necessary in elective spine surgery because of perioperative blood loss. Preoperative autologous blood donation (PABD) has emerged as the principal means to avoid or reduce the need for ABT. Consequently, a multicentre study was conducted to determine the yield and efficacy of PABD in spine surgery and the possible role of recombinant human erythropoietin (EPO) in facilitating PABD.
Methods. We retrospectively reviewed the hospital charts and blood bank records from all consecutive spine surgery patients who were referred for PABD. Data were obtained from two A-category hospital blood banks and one general hospital. Although we collected data from 1994, the analytic study period was from the last quarter of 1995 to December 2003. Fifty-four (7%) out of 763 patients referred for PABD were rejected, and medical records were available for 680 patients who were grouped into spinal fusion (556; 82%) and scoliosis surgery (124;18%). EPO was administered to 120 patients (17.6%). From 1999 to 2003, PABD steadily increased from 60 to 209 patients per year.
Results. Overall, 92% of the patients were able to complete PABD, 71% were transfused, and almost 80% avoided ABT. PABD was more effective in fusions (86%) than in scoliosis (47%). Blood wastage was 38%, ranging from 18% for scoliosis to 42% for fusions. EPO allowed the results in the anaemic patients to be improved.
Conclusions. Therefore, despite the limitations of this retrospective study, we feel that PABD is an excellent alternative to ABT in spine surgery. However, the effectiveness of PABD may be enhanced if associated with other blood-saving techniques.

Keywords Autotransfusion · Predeposit autologous donation · Scoliosis · Spinal surgery · Erytropoeitin

Introduction

Allogeneic blood transfusions (ABT) are often necessary in elective spine surgery because of perioperative blood loss. However, ABTs are not a risk-free therapy as they carry the potential risk of viral disease transmission, bacterial contamination, incompatibility reactions or transfusion-related immunomodulation (TRIM) [4]. The TRIM effect has been particularly implicated in the increased postoperative infection rate observed in patients who received ABT [6, 25, 26, 27, 28].

Autologous blood transfusion (AUT) techniques have emerged as the principal means to avoid or reduce the need for ABT. These techniques involve the collection and reinfusion of the patient's own blood by using preoperative autologous blood donation (PABD), preoperative acute normovolaemic haemodilution, intraoperative sal-

vage of blood from the surgical field, or postoperative blood salvage, by which drained blood is collected and re-infused within the first 6–8 postoperative hours [18].

However, in order to minimise blood loss and further reduce the need for ABT, several other factors need to be considered, such as preoperative correction of anaemia and withdrawal of coagulation disturbing drugs, the use of controlled hypotensive anaesthesia, a meticulous surgical haemostasis and a sound clinical judgement in deciding when transfusion is required [18].

In addition to clearly reducing most of the ABT-related side effects, AUT has several other advantages; namely, it can be used for patients with rare blood groups, multiple allo-antibodies or religious objections to allogeneic transfusion [18], and helps to preserve the stocks of allogeneic blood, which are becoming increasingly scarce.

For all these reasons, AUT techniques are becoming popular, with PABD being the most used form of autologous blood replacement. Programmes for its use have become standard, especially in association with major orthopaedic procedures such as total joint replacement and spinal surgery. In Europe, the success of these programmes has been well documented in total joint replacement [19], but there is not much information regarding the use of PABD in spine surgery [18, 20].

Consequently, a retrospective multicentre study was conducted to determine: (1) the yield and efficacy [14] related to a PABD programme for patients (including children and teenagers) undergoing posterior spinal fusion or corrective surgery for scoliosis; (2) the possible role of adjuvant treatment with recombinant human erythropoietin (EPO) in facilitating PABD and reducing the exposure to ABT; and (3) to assess the evolution of PABD use in our area over the last ten years.

Patients and methods

Study design

We conducted a retrospective review of hospital charts and blood bank records from all consecutive patients who were referred to the blood banks before undergoing elective surgery for a variety of spine disorders, including channel stenosis, degenerative spondylolisthesis, idiopathic scoliosis and neuromuscular scoliosis.

Data were obtained from two A-category blood banks (more than 15,000 donations per year): Sant Pau i Creu Roja Hospital (HSP, Barcelona), which also serves another six institutions (El Pilar, FIATC, Asepeyo, Dexeus, Teknon and Hospital del Mar), and University Hospital Miguel Servet (HUMS, Zaragoza). We also included data from elective spine surgery at Hospital de la Esperanza (HESP, Barcelona), in which orthopaedic surgery represents 50% of the total surgical activity. Although we collected data from 1994, the analytic study period was from the last quarter of 1995 to December 2003.

Surgical procedures

All surgical procedures included instrumented vertebral fusion, and a spondylodesis with allogeneic or autologous bone from the iliac crest was added to the instrumentation. All anticoagulant and nonsteroidal antiinflammatory medications were discontinued at least 1 week before surgery. Normovolaemic haemodilution, perioperative blood salvage or antifibrinolytic drugs were not used in any patients.

Transfusion criteria were not predefined. 70.5% of the surgery was for fusions and 29.5% was for scoliosis. Some 68% of all the scoliosis surgery was performed at one centre (HUMS), although 29% of this surgery was for patients from another centre (HSP); at the third centre, this pathology only affected up to 1% of the PABD patients (p <0.001).

PABD schedule

All patients scheduled for surgery were asked to preoperatively donate at least two units of autologous blood. In accordance with Spanish and European regulations, requested PABD units were drawn once a week during 2–5 weeks prior to surgery, stored in citrate-phosphate-dextrose-adenine solution or in adenine-dextrose-saline-mannitol, and used within 5 or 7 weeks respectively.

Some patients were unable to donate blood for a variety of reasons, including geographic limitations, patient refusal, bad venous access for phlebotomy, insufficient time before surgery, low weight, and pre-existing medical limitations (e.g. viral hepatitis, coronary artery disease, cerebrovascular disease, uncontrolled hypertension, severe anaemia).

Patients with previous Hb≤130 g/l (who were asked to donate ≥3 autologous units) received EPO since 2000: 600 U/kg bw sc at the time of each donation and on the day of surgery (HUMS), or 600 U/kg bw sc twice a week (HSP, HESP), with a maximum of six doses.

Demographic and clinical data

General patient demographics, including age, weight, gender, number of PABD units requested, donated, transfused and wasted, and allogeneic units transfused were determined from blood bank records by the centres. Baseline haemoglobin was defined as the level obtained before PABD, whereas preoperative haemoglobin was defined as the level obtained after donation of the last autologous unit. PABD success was defined as the requested to donated unit ratio, PABD adjustment or yield was defined as the donated to transfused unit ratio, and PABD effectiveness was defined as the percentage of patients who avoided exposure to ABT [11].

Data analysis

Data from the small clinical centres were analysed together with those of their reference hospital (HSP) to avoid dispersion, so we analysed three groups of patients: HUMS (n =400), HESP (n =187) and HSP (n =132). We also analysed the evolution of PABD by years, and determined the statistical significance of variations in patients' characteristics and outcomes. Statistical univariant analysis included the Student's t -test for numeric variables and the Pearson's Chi square test for string variables. Differences were considered to be statistically significant at p <0.05.

Results

We reviewed the blood bank charts of 763 patients referred for PABD from nine different clinics and hospitals between 1994 and 2003. Fifty-four patients (7%) were not allowed to participate in the PABD programme. The causes of rejection were anaemia (14), lack of time (12),

Table 1 Some demographic and clinical characteristics of the patients who entered the PABD programme, and their distribution by centres (*HUMS* University Hospital Miguel Servet, Zaragoza, *HSP* Sant Pau i Creu Roja Hospital, Clinica El Pilar, Clínica FIATC, Clínica Asepeyo, Clínica Dexeus, Clínica Teknon, and Hospital del Mar, Barcelona, *HESP* Hospital de la Esperanza, Barcelona, *Hb previous* Hb at admission to the PABD programme, *+EPO* patients receiving EPO to facilitate PABD, *M* male, *F* female). Data are the incidence, the percentage, or the mean±standard deviation

Hospital	Number n (%)	Gender M/F	Age (years)	Weight (kg)	Hb previous (g/L)	Diagnostics		+EPO n (%)
						Fusions	Scoliosis	
HUMS	400 (55.6)	193/207	39±16	65±20	143±15	312 (78.0)	88 (22.0)	50 (12.9)
HESP	187 (26.0)	71/116	53±14	73±13	140±14	185 (98.9)	2 (1.1)	40 (23.1)
HSP + others	132 (18.4)	54/78	38±17	70±17	139±13	93 (70.5)	39 (29.5)	30 (22.7)
P (inter-centres)		<0.05	<0.05	<0.05	<0.05	<0.05	<0.001	<0.001

Table 2 Results of the PABD programme for the total series and according to the type of surgery. *PABD success*: ratio between requested to donated units, *PABD effectiveness*: percentage of patients who avoided exposure to ABT, *PABD adjustment*: ratio between donated and transfused units, *P*: level of statistical significance between types of surgery

	Patients n (%)	PABD success (%)	Transfused patients (%)	PABD effectiveness (%)	PABD adjustment (%)	Patients with EPO (%)
Total series	680 (100)	91.8	71.1	78.8	50.9	17.6
Vertebral fusions	556 (81.8)	91.7	65.9	85.7	46.5	13.6
Scoliosis	124 (18.2)	92.1	94.7	47.8	70.8	38.5
P	<0.0001	NS	<0.0001	<0.0001	<0.0001	<0.0001

positive serologies (8), cardiopathy (5), other comorbidities (8), bad venous access (5), and patient refusal (2). The surgical indications for the remaining 719 patients were grouped into 590 cases of spinal fusion (82%) and 129 cases of scoliosis (18%), with most of the scoliosis being treated at two centres (88 at HUMS and 26 at HSP). The male/female ratio was 0.79, with this rate varying among centres. EPO was administered to 120 patients (17.6%), but this varied from 11.9% to 23.1% among the centres (p <0.001) (Table 1).

Six hundred and eighty out of 719 PABD patients (556 fusions and 124 cases of scoliosis) had medical records available and were included in the analysis. As shown in Table 2, 91.7% of the patients completed the PABD programme, without any differences regarding the type of pathology or medical centre. More than 70% of the patients were transfused with at least their own blood. However, although the overall transfusion rate varied from 50% to 100% among the centres (p <0.001), the overall PABD effectiveness in avoiding exposure to ABT was 78.8%. This effectiveness varied from 47.8% for scoliosis to 85.7% for vertebral fusions (p <0.0001). However, PABD adjustment was achieved in only 51% of the patients who entered the programme. The PABD adjustment varied from 0% to 100% among the centres (p <0.001), and from 46.5% to 70.8% for vertebral fusions and scoliosis, respectively (p <0.0001). Overall, 1,632 PABD units were drawn and 1,032 units were transfused, with a wastage of 0.86 units per patient (95% CI 0.77–0.94; range 0–3 units).

As expected, detailed data analysis as a function of the type of surgery revealed significant differences (p <0.05) in both demographical and clinical parameters, with scoliosis patients (n =124) being younger, having lower weight and previous Hb, and needing more blood reposition than fusion patients (n =556) (Table 3). Patients who received EPO (introduced in 2000 as an adjuvant to facilitate PABD), were also younger, had lower weight and previous Hb (≤130 g/L), and were asked to donate more units than patients who did not receive EPO (p <0.05) (Table 4). However, there were no significant differences between groups in the number of donated units to the number of transfused autologous or allogeneic units, regardless of whether or not they received EPO during PABD (Table 4).

Finally, we analysed pooled data from the nine centres regarding the evolution of PABD use during the study pe-

Table 3 Some demographic and clinical data of the patients who entered the PABD programme, classified according to the type of surgery. All data are the mean±standard deviation (*Hb previous* haemoglobin before PABD, *U* blood units, *U/pt* units per patient, *auto* autologous blood, *allo* allogeneic blood)

	Fusion (n =556)	Scoliosis (n=120)	*P*
Age (years)	47±14	20±10	<0.05
Weight (kg)	72±17	56±12	<0.05
Hb previous (g/L)	143±14	135±12	<0.05
Requested units (U/pt)	2.54±0.60	2.95±0.68	<0.05
Donated units (U/pt)	2.33±0.76	2.72±0.91	<0.05
Transfusion auto (U/pt)	1.36±1.13	2.23±1.15	<0.05
Transfusion allo (U/pt)	0.34±1.67	1.38±1.67	<0.05
Total transfusion (U/pt)	1.69±1.69	3.61±2.11	<0.05

Table 4 Some demographic and clinical data of the patients who entered the PABD programme, classified according to whether adjuvant treatment with EPO was used or not. All data are the mean±standard deviation (*Hb previous* haemoglobin before PABD, *U* blood units, *U/pt* units per patient, *auto* autologous blood, *allo* allogeneic blood)

	EPO (124)	No EPO (556)	P
Age (years)	37±20	44±16	<0.05
Weight (kg)	62±15	71±17	<0.05
Hb previous (g/L)	128±11	145±13	<0.05
Requested units (U/pt)	2.77±0.64	2.61±0.58	<0.05
Donated units (U/pt)	2.49±0.97	2.38±0.76	NS
Transfusion auto (U/pt)	1.72±1.24	1.47±1.16	NS
Transfusion allo (U/pt)	0.66±1.38	0.50±1.20	NS
Total transfusion (U/pt)	2.38±2.13	1.96±1.85	NS

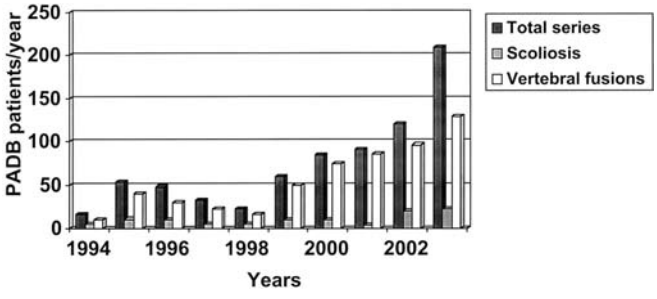

Fig. 1 Pooled data from the nine medical centres included in this study, regarding the evolution of the use of PABD by patients undergoing spine surgery over the last ten years (1994–2003)

riod. As depicted in Fig. 1, from 1994 to 1998, the use of PABD programmes was not a common practice in these centres (with a mean of 32 patients included per year). However, from 1999 to 2003, PABD use steadily increased from 60 patients in 1999 to 209 patients in 2003.

Discussion

Since the AIDS epidemic of the early 1980s, a paradigm of blood safety in established blood delivery systems has evolved which proposes the "safety tripod": appropriate donor selection, screening tests for pathogens and pathogen reduction [5]. With the increasing burden of "zero risk" in public and political perception, it is difficult to question the immutability of this paradigm, but in practice these measures have obviously increased the number of deferred donors and the number of discarded blood units. In addition, the progressively aging population is reducing the number of altruist donors, although there is an increasing demand for blood to meet transfusion requirements of surgical procedures (orthopaedic, cardiac, cancer) [15]. The low birth rate in most European countries will be a further problem in the near future. As a consequence, allogeneic blood has become so scarce that orthopaedic surgery delays have occurred in Spain as well as in Europe [19].

On the other hand, there are several other deleterious ABT side effects through storage-dependent mechanisms, errors in blood administration, and immunosupression

Table 5 Results obtained in several international studies regarding the use of PABD in spine surgery (*P* prospective, *R* retrospective, *IBS* intraoperative blood salvage, *FS* fibrin sealant, *EC* electrocauterious, *ABT* allogeneic blood tranfusion, *NA* not assessed)

Author (reference no.)	Study period	Type of study	Patients (total)	Additional methods	Diagnostics	Efficacy (%)	Wastage (%)	ABT (%)	Donated (U/pt)
Ridgeway et al. [18]	Jan 1998–Dec 2001	R	27 (45)	IBS	Scoliosis	92.6	5.2	7.4 (88.9)[a]	3.6
Lo et al. [11]	2002	R	77	No	Scoliosis	88	6.5	12	NA
Murray et al. [16]	1989–1994	R	164 (243)	No	Idiopathic scoliosis	91	NA	<10	NA
Moran et al. [13]	Jan1989–Jan 1993	P	116 (147)	FS, EC, adrenalin	Scoliosis, kyphosis	89	NA	11 (60)	3
Oga et al. [17]	1992	-	101	No	Scoliosis, others	90 96.2	NA	<10	NA
Johnson et al. [9]	1989	-	63	IBS	-	98.4	54	1. 6	NA
Cha et al. [4]	1996–1998	R	129 (191)	No	Laminectomy, fusions	82.2	77 28 16	0 (12) 16 (55)[a] 37 (78)[a]	2.2
Goodnough et al. [8]	July1985–June 1988	R	150 (595)	No	Elective spine	87	NA	13 (26)	2.4 3.0
Seltzer et al. [22]	3.5 years	R	174 (224)	IBS	Revision, fusion, fixation	99	4	7	96

[a] $P < 0.05$

which are not included in the "safety tripod". In fact, there is increasing evidence that TRIM effects of ABT may be responsible for at least a 10% higher rate of postoperative infection in transfused patients, with longer hospital stays [6, 25, 27, 28]. Several studies and clinical observations suggest that AUT might be clinically and immunologically less detrimental than ABT [26].

For all these reasons, the interest in alternatives to ABT has particularly grown for elective surgery. One alternative that currently accounts for over 5% of the blood donated in the United States and some countries in Europe is AUT, obtained primarily by PABD. However, Brecher and Goodnough recently wrote in Transfusion that the global interest in PABD is decreasing, but we feel that this statement should not be applied universally [2, 3]. Although PABD is underused in most European Union (EU) countries, there are several reasons to believe that the use of PABD and other blood saving strategies is rising in Europe and will rise further in the near future [15]. Our data showing a steady increase of PABD use over the last years (Fig. 1) seem to support this view.

With regard to spine surgery, PABD (which is considered as the "gold standard" in AUT) can not only be safely and effectively used in adults (e.g. vertebral fusions) but also in adolescents (e.g. scoliosis surgery) (Table 5) [4, 8, 9, 11, 13, 17, 18, 19, 22]. Data from our series showed that PABD avoided exposure to ABT in almost 80% of the patients, even though PABD was far more effective in fusions (85.7%) than in scoliosis (47.8%) (Table 2). However, the patients who underwent surgery for scoliosis had lower body weight and previous Hb levels together with higher perioperative blood loss, and consequently needed a higher volume of blood reposition [1, 7, 12, 30]. All this led these patients to have an increased ABT rate, despite the fact that more PABD units were available (Table 3) although the amount of AUT transfused correlated negatively with the amount of ABT [12]. Thus, these data clearly indicate the need to associate other blood saving methods (e.g. perioperative blood salvage, haemostatic drugs or EPO) with PABD in scoliosis [4, 7, 9, 11, 12, 13, 16, 17, 18, 21, 22, 29].

PABD wastage is a serious problem because up to half of the blood collected may be discarded, and this wastage leads to PABD costs that are higher than those for ABT [29]. Data from the OSTHEO study (a multinational survey conducted in Europe on lower limb arthroplasty) are promising in this regard since 87% of the autologous units collected were actually transfused [1, 9]. In our series, PABD adjustment varied among the centres (p <0.001) and from 46.5% to 70.8% for vertebral fusion and scoliosis, respectively (p <0.0001) (Table 2). According to data shown in Table 3, the overall blood discard rate was 37%, with rates ranging from 18% in scoliosis to 42% in vertebral fusions. However, we feel that wastage in the later surgery can be reduced by adjusting the number of units collected to each hospital's transfusion experience, or each surgical team's or patient's characteristics, and not to general surgical blood-ordering schedules [7]. This strategy, together with periodical audits of PABD use, should avoid over-collection, prevent excessively decreased postoperative haemoglobin levels, reduce administrative errors, and improve cost-effectiveness [15, 24].

In the clinical setting of spine surgery, adjuvant treatment with EPO might facilitate the collection of the requested PABD units and result in higher perioperative haemoglobin levels and a further reduction in the exposure to ABT. In our series, 120 patients (38.5% scoliosis) with previous Hb≤130 g/l received EPO (4.13 doses per patient). As shown in Table 4, despite their lower Hb levels (128±11 g/L) they were able to donate autologous blood and avoid ABT to the same extent as those patients who did not receive EPO (Hb=145±13 g/L) – whilst blood wastage was lower in the EPO group (30.9% vs. 38.2% for EPO and non EPO groups, respectively). Therefore, our results are partially in agreement with those of previous studies involving patients with similar surgical pathologies [10, 17, 23].

Conclusions

Autologous transfusion is one of several techniques used to reduce the need for allogeneic transfusion and is most widely used in elective surgery, obtained primarily by PABD. However, the implementation of PABD programmes requires careful organisation, a guarantee that the surgery will proceed at the right date, as the donated blood has a caducity of 5 or 7 weeks, and excellent communication between the surgeons, anaesthetists, haematologists and blood bank personnel.

We have shown that this multidisciplinary collaboration is possible in three different organization models. First, a blood bank inside a tertiary hospital; second, a blood bank with one special section exclusively dedicated to autotransfusion which obtains and supplies autologous blood to several hospitals and clinics; and third, a general hospital half dedicated to orthopaedic surgery with a dynamic and involved transfusion committee that controls all transfusions.

Overall, in our series PABD avoided exposure to ABT in almost 80% of the patients, although there were significant differences between those who underwent scoliosis surgery (47.8%) and those who underwent vertebral fusions (85.7%), with a blood wastage acceptable in the former (18%) and perhaps too high in the latter (41%). In addition, adjuvant treatment with EPO facilitated completion of PABD in moderately anaemic patients.

Despite the limitations of this retrospective study without comparisons to a control group, we feel that PABD is an excellent alternative to ABT in spine surgery. The effectiveness of spine surgery may be enhanced if an individualized approach is taken into account, considering

both the patient's likelihood of requiring ABT and the risks and benefits of PABD for that individual, and also associating ABT with other AUT modalities or other blood saving techniques, such as antifibrinolytic drugs, fibrin sealant, controlled hypotension, autologous platelets, etc.

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Preoperative erythropoietin in spine surgery

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Abstract Spine surgery may be associated with profuse intraoperative bleeding that often requires blood transfusions. In recent years several techniques have been developed to avoid allogenic transfusions and their potential complications to surgical patients. In this study we review and analyse the role of preoperative recombinant human erythropoietin (rHuEPO) administration in spine surgery as a blood conservation strategy. Between 1998 and 2002, a total of 250 patients scheduled for spine surgery were included in our blood-sparing program: 114 patients (group 1), operated on before rHuEPO approval (2000), underwent preoperative autologous blood donation (ABD) alone, and 136 patients operated on after rHuEPO approval (groups 2 and 3) received rHuEPO while undergoing ABD. Adding rHuEPO to ABD resulted in higher haemoglobin and haematocrit values the day of surgery, more ABD units retrieved per patient and, consequently, reduced allogenic transfusion requirements. The effectiveness of rHuEPO as the only preoperative blood conservation technique was evaluated in ten patients with a predicted blood loss of less than 30% of their total volume, scheduled for lumbar surgery. Data from these patients were matched with those from a similar group of patients who had undergone ABD. Patients receiving rHuEPO alone had higher haemoglobin levels the day of surgery than did patients in the ABD program. Neither group required allogenic transfusions. Conclusions: preoperative rHuEPO is useful for reducing allogenic blood requirements in elective spine surgery. In patients with an expected blood loss of around 50% of blood volume, rHuEPO improves ABD, minimising preoperative anaemia and increasing the number of ABD units collected. In patients with expected blood loss below 30% of total volume, rHuEPO administration may replace ABD.

Keywords Erythropoietin · Spine surgery · Autologous donation · Perioperative bleeding · Blood-sparing technique

Introduction

Surgery for spinal deformities or degenerative lumbar disease may be associated with blood loss ranging from 30% to 100% of the patient's total blood volume [18, 26, 68, 79, 85, 87]. This loss of blood is related to the complexity of the procedure, duration of surgery, number of fused levels, anaesthetic technique and the patient's comorbid conditions [18, 26, 68, 76, 79, 85, 87]. Extensive bleeding may lead to rapid fatal consequences and to risks associated with allogenic blood transfusion [4, 8, 36, 40, 81]. Measures should be taken to minimise these risks [18, 26, 50, 58, 64, 65, 66, 68, 79].

Over the last 30 years, considerable efforts have been made to develop new blood-conservation strategies that

will avoid allogenic transfusion. The most common include drug therapy (desmopressin [2, 58], aprotinin [25, 85], tranexamic acid [27, 65], hypotensive anaesthesia [59, 83], and autotransfusion techniques, such as normovolemic acute hemodilution [14, 19, 56, 67], perioperative salvage [3, 28, 56], postoperative salvage and autologous blood donation (ABD) [39, 49, 57, 64, 80, 88]. During the 1990s a new drug, recombinant human erythropoietin (rHuEPO), was added to the repertory of blood-conservation techniques [6, 9, 32, 33, 73]. This hormone plays a major role in patients undergoing elective surgery in which moderate or profuse blood loss is expected [22, 48, 74]. However, despite its approval for this purpose more than 3 years ago, very little information is available on its effectiveness in elective spine surgery [76, 77, 79, 86].

Erythropoietin

Erythropoietin (EPO) is a hormone that regulates erythropoiesis, acting on erythroid-colony-forming units by stimulating progenitor cell differentiation in the bone marrow. EPO accelerates maturation of proerythroblasts to reticulocytes, stimulates the synthesis of haemoglobin (Hb), and promotes the release of reticulocytes to the circulation and their differentiation into mature red blood cells [10, 20].

Erythropoietin is a 165-amino-acid glycoprotein with a molecular weight of 30,400 dalton. Approximately 90% is produced in the interstitial peritubular cells of the kidney. Normal plasma levels range 5–30 mU/ml and are regulated by tissue hypoxia and the various factors that influence oxygen availability in peripheral tissues [10, 20]. The human gene for erythropoietin is present as a single copy on chromosome 7 (q11–q22) and is comprised of 5 exons (582 base pairs) [10, 20, 48].

Recombinant human erythropoietin (rHuEPO) is a biosynthetic form of the natural hormone having the same biochemical structure and biological effect [12, 13, 20]. There are two types of rHuEPO: the alpha type and the beta type, presented in lyophilised form and reconstituted with saline solution [12, 13, 73].

Erythropoietin in surgery

Based on its success in the treatment of anaemia associated with chronic renal failure and chemotherapy [45, 52, 60], rHuEPO was contemplated for use in surgical patients to elevate preoperative haemoglobin values and facilitate the predeposit of autologous blood, thereby decreasing the need for allogenic blood transfusions. This hypothesis was confirmed in several studies involving orthopaedic surgery, [9, 16, 22, 23, 30, 53, 74], and this led to the registration of rHuEPO for clinical practice in Spain in October, 2000. It is now also used in cardiac, prostate and oncologic surgery for this purpose [52, 71, 73].

Dosing

Recombinant human erythropoietin can be administered intravenously or subcutaneously. It reaches peak plasma concentration faster by the intravenous route, although the half-life is shorter (5–10 h) [73]. Availability is lower with subcutaneous administration, but the half-life is longer (12–18 h) [73], and this route is usually recommended for the management of perioperative anaemia [12, 13, 48, 73].

Initially, the recommended dose was 300 IU/kg/day during 15 days [15]. However, Goldberg et al. [30] demonstrated that a weekly dose of 600 IU/kg starting 3 weeks before the procedure achieved a higher increase in haemoglobin (1.44g/dl vs 0.73 g/dl) with comparable safety and efficacy, and lower cost.

Current recommended dosage is 600 IU/kg of subcutaneous rHuEPO weekly, given over 3 weeks (days 21, 14, and 7 before the surgical procedure) and on the day of surgery. In practice, administration of a 40,000 IU vial weekly is recommended in adults with a mean weight of around 65 kg. The 40,000 IU dose is authorised exclusively for preoperative rHuEPO treatment. When haemoglobin levels reach 15 g/dl at any of the preoperative analyses, rHuEPO administration is interrupted indefinitely [6, 12, 13, 22, 23, 48, 82].

The dosing regimen for patients in the ABD program is somewhat different. Recommended dosage in these patients is 600 IU/kg (or a 40,000 IU vial), twice a week during the period that blood is being collected [5, 22, 23,24, 30, 41, 74, 82]. Again, when haemoglobin reaches levels above 15 g/dl, the dose is not administered.

Blood levels of ferritin, folic acid and vitamin B_{12} should be checked before initiating rHuEPO therapy. When concentrations of these blood components are low, additional treatment to recover adequate levels is essential before administration of rHuEPO. Oral administration of 200–300 mg/day of iron is necessary to compensate for the expenditure of ferritin reserves, due to the increasing erythrocyte mass in response to rHuEPO [6, 22, 51]. If possible, iron supplementation should be started at least 1 month before rHuEPO therapy to achieve adequate reserves and assure the efficacy of the hormone [29, 73].

Side effects

Recombinant human erythropoietin is considered to be a safe drug, although some side effects, such as headache, flu-like states and higher blood pressure levels in hypertensive patients have been observed [13, 21, 35].

Hemostasis studies in patients treated with rHuEPO have demonstrated a minimum effect on the coagulation cascade. No changes have been found in thrombin time, prothrombin time or activated partial thromboplastin time. A transient increase in platelet values, without exceeding normal limits, has been described [16, 31, 35].

With regard to increases in blood viscosity as the haematocrit rises, most authors agree that there is only a risk when the haematocrit exceeds 51% [13, 16, 31, 35, 51]. Analysis of the rHuEPO safety profile in 619 patients treated before orthopaedic surgery showed that the use of this hormone does not increase the risk of thromboembolic events [16, 31, 82].

Role of rHuEPO in preoperative autologous blood donation

Increasing awareness of the risks linked with transfusion of allogenic blood products has led to much more widespread use of preoperative autologous blood donation [72]. Nevertheless, ABD may involve certain problems inherent to the process, such as anaemia or adverse reactions on the part of the patient during donation, wastage of blood units due to delayed surgery, or clerical errors in blood labelling and storage [1, 4, 38, 74, 84]. Moreover, in certain circumstances it may be difficult to collect sufficient blood to cover the estimated loss during surgery [7, 17, 41, 43, 48, 70].

Even with the availability of anticoagulant preservation solutions, it is still necessary to perform blood withdrawal within a maximum of 42 days before the operation. For this reason, a considerable percentage of patients following an ABD program reach surgery with a lower haemoglobin value than when they entered the program [1, 37, 39, 42, 46, 61, 63], and when this value is significantly lower, their transfusion requirements increase [7, 11, 33, 43, 44, 48].

The interval between donations should not be less than 3 days, and the final collection should be performed at least 72 h before the operation [38, 72]. Patients with a moderate degree of anaemia (Hb 10–13 g/dl) and requiring a predeposit of more than 4 units will have serious difficulties providing sufficient autologous blood [17, 42, 46, 61, 62]. Erythropoiesis stimulation with rHuEPO can be very beneficial in these patients [17, 23, 41, 61, 71, 72, 84].

Since 1998, 250 patients have participated in the program of blood-sparing techniques in our spinal surgery unit. Candidates for this program include all patients undergoing spinal surgery whose expected blood loss is greater than or equal to 20% of their total blood volume and who have no contraindications for ABD. The exclusion criteria are urgent surgery, or predicted perioperative blood loss of less than 20% of the total volume. Approval of rHuEPO use in October 2000 resulted in changes in the treatment protocols for patients included in the program.

The 114 patients participating between 1998 and 2000 (group 1), 39 men and 75 women, were managed with ABD exclusively. The large majority had scoliosis or degenerative lumbar disease. Between 2001 and 2002, 136 patients were included in the program. These were divided into two groups according to their preoperative diagnosis and expected blood loss. Group 2 included 88 patients, 31 men and 57 women, with multilevel (two or more lumbar segments) degenerative lumbar disease and an expected perioperative blood loss of around 50% of the total volume. Group 3 comprised 48 patients, 10 men and 38 women, with idiopathic or degenerative adult scoliosis, or complex adult deformities and an expected blood loss of nearly 100% of the total volume. Demographic data from these groups are detailed in Table 1.

All patients followed a standard ABD program consisting of serial blood collection every 7 days (provided that haemoglobin levels remained above 10 g/dl) and 525 mg of ferric sulphate 3 times daily, starting approximately 2 months before surgery. Groups 2 and 3 additionally received subcutaneous rHuEPO at a dose of 40,000 IU, according to the above-described dosing regimen.

The baseline haemogram showed no major differences among the patient populations, although baseline haemoglobin levels were slightly higher in group 1 than in groups 2 and 3. A gradual decrease in haemoglobin was observed in group 1 as patients underwent serial blood collection (Table 2). In groups 2 and 3, haemoglobin levels remained constant at around 12.5 g/dl after the second collection and up to the day of surgery. The effect of rHuEPO on haemoglobin levels and the haematocrit in the three groups is shown in Figures 1a and 1b.

Table 3 summarises the proportion of patients meeting ABD previsions for each study group. The percentage of patients able to donate the anticipated required units was 83.9% in group 1, 100% in group 2 and 98% in group 3.

Table 1 Demographic data for the three study groups (*w* women; *m* men; *ASA* number of patients in each of the ASA classifications). Values for age, weight and height are expressed as mean and range

	Group 1	Group 2	Group 3
Number of patients	114	88	48
Sex	75 w/39 m	57 w/31 m	38 w/10 m
Age (years)	31.48 (21–72)	43.3 (19–73)	32.75 (18–64)
Weight (kg)	61.52 (40–89)	69.1 (47–103)	62.76 (45–94)
Height (cm)	157.3 (148–174)	163 (146–184)	163.1 (140–190)
ASA (I, II, III)	I, 68 / II, 46	I, 28 / II, 59 / III, 1	I, 18 / II, 30
Condition	Degenerative & deformity	Degenerative (≥2 levels)	Adult deformity

Table 2 Effect of erythropoietin on haemoglobin recovery during preoperative blood collection in ABD program

	Group 1 ABD alone	Group 2 ABD+ EPO	Group 3 ABD+EPO
*Hb before 1st ABD	14.05	13.9	13.6
*Hb before 2nd ABD	12.39	12.59	12.38
*Hb before 3rd ABD	11.54	12.51	12.21
*Hb before 4th ABD	10.83	12.52	12.58
*Hb before 5th ABD	10.20	12.26	12.55
*Hb day of surgery	11.07	12.42	12.01
**Hb day of surgery when ≤5 ABD	11.08	12.48	12.12

*Haemoglobin concentration (Hb, g/dl) was evaluated before starting ABD. **Haemoglobin was also analysed on the day of surgery for patients who had five or fewer collections (≤5)

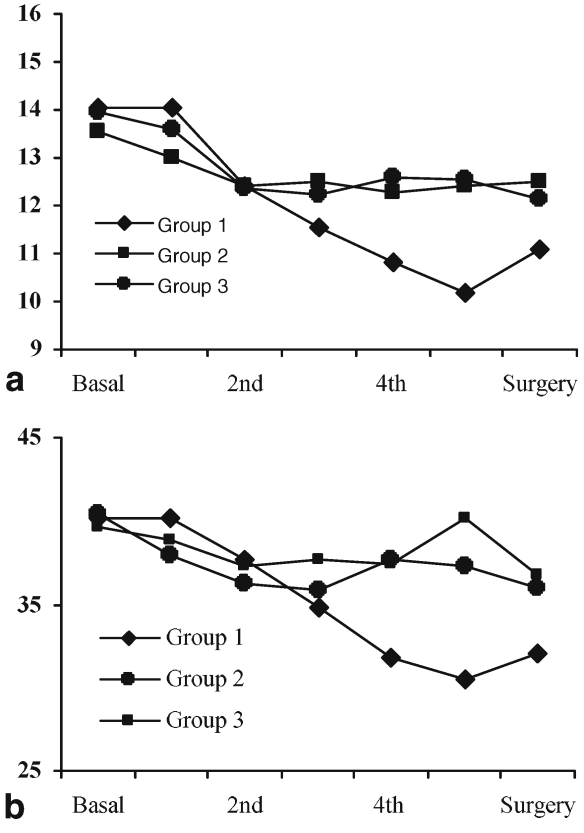

Fig. 1 Haemogram values during the study. Haemoglobin **a** and haematocrit **b** were determined at the beginning of the study (baseline), before each rHuEPO administration and/or ABD and on the day of surgery. Groups 2 (●) and 3 (■) underwent up to five ABD and five rHuEPO administrations; and group 1 (◆) underwent ABD only

Recombinant human erythropoietin administration resulted in a higher number of donated autologous blood units (Tables 4 and 6), with a mean of 1.57 units per patient in group 1, 2.96 units per patient in group 2 and 4.19 units per patient in group 3 (Table 6). In groups 2 and 3

Table 3 Predicted ABD requirements. Results are expressed as the percentage of patients in each group able or unable to complete ABD program

	Group 1	Group 2	Group 3
Unable to complete ABD program	6.3	0	2
Able to complete ABD program	83.9	100	98
Nº of patients	114	88	48

Table 4 ABD units in the study groups: the number and percentage of patients giving 0, 2, 3, 4 or 5 ABD units

			Groups	
			1	2–3
ABD unit *n*º	0.00	*N*	0	1
		%	0	1.0
	2.00	*N*	15	12
		%	13.4	12.2
	3.00	*N*	55	36
		%	49.1	36.7
	4.00	*N*	40	31
		%	35.7	31.6
	5.00	*N*	2	18
		%	1.8	18.4
Total		*N*	114	136
		%	100.0	100.0

Table 5 Operative bleeding. Results expressed in mean and range

	Group 1	Group 2	Group 3
Duration (min) of surgery	372 180–930	296 120–720	548 300–1,020
Perioperative bleeding (ml)	950 250–4,800	1,062 300–3,500	1,710 400–5,450
Postoperative bleeding (ml)	909 160–2,860	719 50–2,060	1,629 70–12,180
Total bleeding (ml)	1,862 500–7755	1,793 390–4,820	3,408 470–16,180

Table 6 Transfusion requirements

	Group 1	Group 2	Group 3
*No. donation units in ABD program	180 (1.57 u/p)	260 (2.93 u/p)	197 (4.19 u/p)
*No. allogenic units (effectiveness)	23 units (14 patients) 87.72%	5 units (2 patients) 97.73%	26 units (7 patients) 85.42
No. unused autologous units (waste)	35 units (19.44%) 80.56%	45 units (17.30%) 82.7%	16 units (8.2%) 91.8%
**Erythropoietin units administered	0	3.28	4.75

*Values for the number of donation units and the number of allogenic units are given as the sum of all units. The numbers in parentheses correspond to the patients receiving or donating these units
**Erythropoietin units expressed in means

(ABD plus EPO), 50% of patients gave more than 3 units, whereas only 37.5% of patients in group 1 (ABD alone) were able to donate more than 3 units (Table 4). In group 3, which included patients with complex spinal deformities, expected blood loss of nearly 100% of total volume, and actual average blood loss of 3,408 cc (Table 5), 5 units were obtained in 18.4% of patients. This meant that 24 patients (50%) arrived at surgery with the anticipated coverage. In contrast, only 1.8% of patients in group 1 were able to provide 5 units.

In terms of effectiveness and waste, rHuEPO provides evident advantages in blood-sparing programs. First, it increases the efficacy of ABD by reducing the number of allogenic blood units required. With a similar mean blood loss in groups 1 and 2 (Table 5), transfusion of allogenic blood was necessary in 14 patients in group 1 (12.28%) and only two patients in group 2 (2.27%) (Table 6). Only seven patients (14.58%) in group 3 required allogenic blood, even though two of these seven patients had withdrawn from rHuEPO treatment during the study. A third patient in this group suffered a major complication during surgery (massive bleeding from vascular injury and loss of 16 l of blood). Excluding these three exceptional cases, the efficacy of ABD plus rHuEPO in this complex group would be 91.7%.

Autologous blood-donation waste, reflected in the number of non-transfused autologous blood units, was 16 ABD units in group 3 (8.12%), 45 ABD units (17.30%) in group 2 and 35 units (19.44%) in group 1 (Table 6).

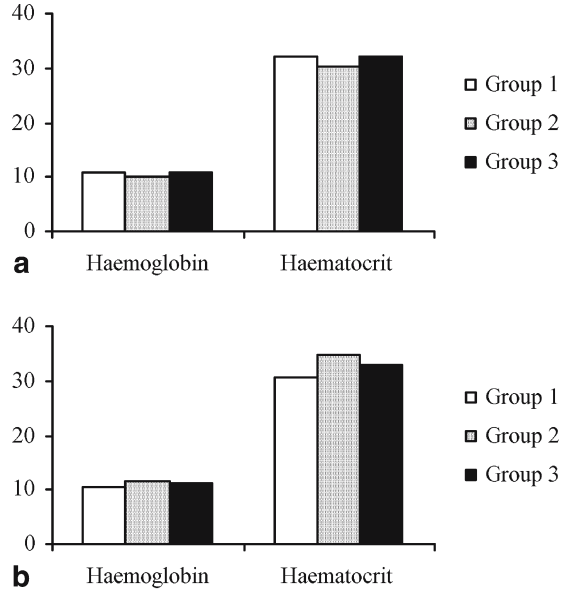

Fig. 2 Haemogram values after surgery. Follow-up of haemoglobin levels and haematocrit was done on **a** day 5 after surgery and **b** on the day of hospital discharge. *White bars* indicate group 1, *dotted bars* group 2 and *black bars* group 3. Haemoglobin values are given as g/dl and haematocrit as %

Some of the patients in the program did not receive all of the rHuEPO anticipated, since their haemoglobin values exceeded 15 g/dl. In addition, the mean rHuEPO doses administered in both the treated groups were lower than those recommended [31]. In group 2, with a mean of 2.96 ABD units per patient, mean rHuEPO received was 3.28 doses per patient. In group 3, with 4.19 ABD units per patient, the number of rHuEPO doses was 4.75.

No adverse events were recorded in any of the patients receiving rHuEPO. Two patients from group 3 decided to stop rHuEPO treatment after the second blood collection, one because she was not convinced of the efficacy of this measure and the other because of general fatigue.

On the fifth postoperative day and at hospital discharge, all the patients studied presented haemoglobin levels and haematocrit within the normal range (Figures 2a and 2b).

Role of preoperative rHuEPO in elective surgery as the only blood-sparing technique

Various clinical trials have assessed the usefulness of rHuEPO as the only blood-sparing technique used in elective orthopaedic surgery (other than spine surgery) [15, 23, 24, 30, 55, 74, 82]. In several randomised, placebo-controlled trials, preoperative rHuEPO administration significantly reduced transfusion requirements. Treated patients present higher haemoglobin levels than controls on the day of surgery. This effect is evident in procedures where blood loss is expected to be approximately 30% of the patient's total calculated volume [23, 53, 55, 74, 78]. Generally, this degree of blood loss is typical in primary, unilateral hip or knee arthroplasty.

A number of clinical trials [15, 22, 23, 24, 30, 31] have been conducted to determine the ideal preoperative dosing regimen for rHuEPO and the type of patient that can most benefit from this treatment. These studies included a total of 824 patients undergoing scheduled orthopaedic surgery, mainly arthroplasty of the hip, knee or shoulder, in which moderate blood loss (900–1800 ml or 25%–30% of total volume) was anticipated. Two different doses of rHuEPO (100 IU/kg or 300 IU/kg, subcutaneously) were used, beginning administration 10 days before surgery and ending 4 days after (15 doses) [15, 22, 23, 24, 30, 31].

The results of these studies suggest that a preoperative haemoglobin value greater than 13 g/dl is a good indicator that transfusion will not be needed [24]. Patients with haemoglobin levels of 10 to 13 g/dl at the beginning of treatment benefit the most from the effect of rHuEPO, with reductions in allogenic transfusions of 50% to 70% [15, 30, 31, 69]. In moderately anaemic patients approaching scheduled orthopaedic surgery, rHuEPO as a first-line treatment is well-tolerated and is associated with a shorter hospital stay [15]. As mentioned above, the recommended regimen nowadays is four doses of 600 IU/kg/week, beginning 3 weeks before surgery [31].

Using this dosing schedule, Stowell et al. [82] performed an open, randomised, multicenter study with parallel groups comparing the safety and efficacy of rHuEPO treatment (600 IU/kg on days –21, –14, –7 and 0) with that of standard ABD (2 predonated units). The study included 490 patients scheduled for total hip or knee arthroplasty, with baseline haemoglobin values of 10 to 13 g/dl. Haemoglobin levels over the entire preoperative period were higher in the rHuEPO group than in the ABD group. Mean haemoglobin values on the day of surgery were 13.8 g/dl in the patients receiving rHuEPO and 11.1 g/dl in the ABD patients. These differences resulted in a lower total transfusion rate (12.9% in rHuEPO vs 74.4% in ABD) and a lower rate of allogenic blood transfusion (12.9% in rHuEPO vs 19.2% in ABD). These data suggest that in patients with haemoglobin values greater than 13 g/dl, this type of surgery can be performed with lower transfusion requirements.

This technique has been applied in orthopaedic surgery in which the typical bleeding risk is around 30% of the total blood volume [24, 30, 33, 70, 82]. The characteristics of this type of surgery are similar to those of lumbosacral procedures.

Table 6 shows that there is a high percentage of wasted units of autologous blood in groups 1 and 2 of our series (19.4% and 17.3%, respectively). These two groups (particularly group 2) are comprised of patients who underwent lumbosacral surgery with blood losses (1,862 cc for group 1 and 1,793 cc for group 2) of around 30% of the total volume. We hypothesised that this type of patient could be managed without ABD, if haemoglobin values were above 13 g/dl at the day of surgery.

To investigate this idea we designed a case-control study comparing rHuEPO administration with ABD as single blood-sparing approaches in patients undergoing lumbosacral surgery, with expected blood losses of 30% of the total blood volume. The study included 20 patients scheduled for surgery to treat degenerative lumbar spine disease. Ten patients (EPO group) received treatment with 40,000 IU of rHuEPO in four separate doses given 21, 14 and 7 days before surgery and on the day of surgery. Data from these patients were cross-matched with data from patients managed with ABD alone (ABD Group). We identified 10 patients with diagnoses and surgical procedures similar to those of the EPO group, from whom an average of 2.8 units of autologous blood had been retrieved preoperatively.

As is shown in Table 7, the duration and type of surgery were similar in the two groups (p=0.1), although perioperative blood loss was significantly higher (p=0.03) in those who received rHuEPO. Baseline haemoglobin values were also comparable in the two groups (EPO group's 12.9 g/dl vs ABD group's 13.05 g/dl, p>0.1). Nevertheless, whereas in the EPO group haemoglobin had increased to 14.2 g/dl on the day of surgery, in the ABD patients haemoglobin had dropped to 10.7 g/dl (p=0.004).

Table 7 Demographic and operative parameters from the case-control study for EPO/ABD (*w* women; *m* men; *PSFI* posterior spinal fusion with instrumentation; *PLIF* posterolateral interbody fusion)

	EPO	ABD
Sex	8 w/2 m	7 w/3 m
*Age (years)	51.5 (39–66)	39.3 (26–51)
Type of surgery	PSFI 11 PLIF 8	PSFI 12 PLIF 8
Hb baseline (g/dl)	12.9	13.05
**EPO units administered	3.1 units/patient	0
**ABD units	0	2.8 units/patient
Hb day of surgery (g/dl)	14.2	10.7
**Surgery duration (min)	3 h 12 min	3 h 29 min
***Total bleeding (ml)	1,176±360.1	814.2±307.5
Allogenic transfusion	0	0
Hb at discharge (g/dl)	11.1	11.1
Days hospitalisation	9.2	9

*Age is expressed as mean and range
**Values for EPO administration, ABD units and surgery duration are expressed as means
***Data for total bleeding are expressed as the mean±standard error

Haemoglobin levels on the day after surgery were still higher in the EPO group (11.9 g/dl vs 8.8 g/dl, p=0.005), but similar values were recorded on discharge from the hospital (EPO group's 11.1 g/dl vs ABD group's 11.1 g/dl, p>0.1). None of the patients in either group required allogenic blood transfusion.

In summary, the group treated with rHuEPO presented higher preoperative haemoglobin levels than those of the ABD group. Despite significantly greater intraoperative bleeding, none of the rHuEPO patients required allogenic blood transfusions and, upon discharge, haemoglobin levels were similar to those of the ABD group. Our results suggest that lumbosacral surgery with estimated blood losses lower than 30% of total blood volume can be performed without the need for allogenic blood if preoperative haemoglobin concentrations are higher than 13 g/dl. Recombinant human erythropoietin therapy is a safe, effective method to reach these levels.

Discussion

Autologous blood donation has become the gold standard for blood conservation in elective spine surgery. Nevertheless, this technique has some limitations, one of the most important being the anaemia caused by repeated blood collection, which can limit the number of units recovered and, in some cases, lead to clearly insufficient haemoglobin levels at the time of surgery [38, 41, 43, 47, 48, 57, 64]. Addition of rHuEPO therapy to the predonation program allows patients to undergo surgery with haemoglo-

bin levels and haematocrit similar to those present before starting the program [74, 77, 79, 86]. Blood retrieval is not recommended in patients with haemoglobin levels lower than 11 g/dl. By maintaining adequate haemoglobin concentrations during repeated blood collection, it is possible to reduce the interval between donations and retrieve a larger number of autologous blood units, thereby covering the predicted requirements [17, 22, 23, 41, 50, 61]. The fact that patients approach surgery with high levels of haemoglobin despite autologous donation reduces transfusion requirements and confers important benefits with regard to postoperative recovery [23, 24, 69, 70, 71].

Blood management is most difficult in adult patients with complex deformities requiring very aggressive surgery with circumferential approaches and long spinal instrumentation. These patients, comprising group 3 of our series, can present blood losses equal to their total blood volume [79, 85]. Shapiro et al. [79] published a randomised controlled trial analysing the effect of rHuEPO treatment on patients in an ABD program. The patients had been scheduled for complex spinal reconstruction and were very similar to the patients in group 3 of our series in terms of type and duration of surgery, blood loss and number of days of hospitalisation. All those in the group treated with rHuEPO were able to comply with the foreseen perioperative autotransfusions, as compared to 78% of patients in the control group. Moreover, only 24% of patients receiving rHuEPO required allogenic transfusions, as compared to 83% in the control group. Our experience yielded findings similar to those reported in this study. In our complex patients, 98% complied with ABD estimations and only 14.6% required allogenic blood transfusion.

In patients with less aggressive surgery (group 2) and a predicted blood loss of around 50% of total volume, nearly 97% did not require allogenic transfusions when rHuEPO treatment was associated with the ABD program. However, a significant percentage of autologous donation units were not used (17.3%) in this group, whereas only 8.2% of donated units went wasted in the complex surgery group. Typically, 10% to 25% of autologous blood units are wasted in less aggressive surgery [32, 33, 34, 36, 47, 64, 81, 84].

The total recommended rHuEPO dose for ABD support is 3,600 IU/kg [31, 70, 82]. Our results show, however, that equally satisfactory results are obtained with lower doses: Group 2 received a total of around 1,900 IU/kg and group 3 received 2,800 IU/kg. Our data concur with those of Lee et al. [54], who reported improved performance in the ABD program (3 predeposit units) with administration of 1,200 to 1,500 IU/kg to patients scheduled for lumbosacral surgery. We believe it is advisable to adjust the total rHuEPO dose according to the haemogram. The total recommended dose can be decreased while maintaining the efficacy of the treatment. This will reduce the high cost of rHuEPO use, which is one of the disadvantages of this therapy.

In lumbar surgery with blood loss at around 30% of the total volume, the use of blood conservation strategies is questionable. Systematic application of ABD will lead to a high rate of wasted blood units, since it is difficult to estimate the autotransfusion requirements. Our results suggest that surgery in these patients can be carried out without recurring to transfusion, when the patient's haemoglobin levels on the day of surgery are greater than 13 g/dl. This type of surgery would be equivalent to other orthopaedic techniques [6, 22, 24, 30, 70]. With rHuEPO administration, the required haemoglobin levels can be attained quickly and safely.

There were no adverse incidents associated with rHuEPO administration in our series. The high level of satisfaction indicated by the patients during the entire process was remarkable and contrasted with the discomfort associated with repeated blood collection. However, it is important that rHuEPO administration be individualised. Periodic haemograms must be performed to monitor both the haemoglobin levels and the haematocrit. The earliest response showing the effectiveness of rHuEPO administration is an increase in the number of reticulocytes, occurring between day 3 and day 10. The treatment should be withdrawn if haemoglobin levels exceed 15 g/dl [22, 30, 48]. This was the case in three out of ten patients who received treatment with rHuEPO alone, without ABD.

We conclude that surgery involving blood losses under 30% of the patient's total volume can be accomplished without the need for allogenic transfusion, if the baseline haemoglobin level is greater than 13 g/dl. Recombinant human erythropoietin administration is very effective for attaining this level and can be used as the only blood-sparing technique in these patients.

When the expected blood loss is around 50% of the total volume, ABD is the standard technique applied. Addition of rHuEPO to ABD in these patients improves haemoglobin levels and facilitates retrieval of the autologous blood units required. This combination can avoid allogenic transfusion in 95% of the patients.

When surgery is associated with a predicted blood loss close to the patient's total blood volume, the combined blood-sparing technique should always be used. Despite the complexity and aggressiveness of the procedure, with the combination of ABD and rHuEPO, more than 80% of the patients operated will not require allogenic transfusions.

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Positioning on surgical table

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Abstract Positioning on the surgical table is one of the most important steps in any spinal surgical procedure. The "prone position" has traditionally been and remains the most common position used to access the dorsolumbar-sacral spine. Over the years, several authors have focused their attention on the anatomy and pathophysiology of both the vascular system and ventilation in order to reduce the amount of venous bleeding, as well as to prevent other complications and facilitate safe posterior approaches. The present paper reviews the pertinent literature with the aim of highlighting the advantages and disadvantages of various frames and positions currently used in posterior spinal surgery.

Keywords Spinal frame · Prone position · Batson plexus · Blood loss · Posterior spinal approach

Introduction

The ideal position for spinal surgery should facilitate exposure, minimize both bleeding and the likelihood of damage to vital structures, and allow proper ventilation of the anesthetized patient. Additionally, it is imperative to avoid any postoperative morbidity secondary to the position during surgery.

These goals are more important, or potentially more difficult to achieve, in spinal surgery because of the deep exposures, and occasionally related difficulties, the accuracy required to identify the correct level, and the inherent risks of the various positions [4].

Neither supine nor lateral positioning directly affects intraoperative bleeding, because neither alters the physiology of the cardio-pulmonary system. On the contrary, a common complication of the prone position is increased bleeding, mostly due to damage to engorged vertebral veins or to excessive stretching of muscles. This decubitus is frequently required for patients undergoing posterior spinal operations for lumbar disc herniation, fusion surgery, and surgical correction of scoliosis. The prone position is comfortable for surgeons, providing an adequate vision of both bone and neural structures. Surgical frames, kneeling attachments and special operating tables have been designed over the years to promote good prone positioning, lower intra-abdominal pressure, and reduce epidural bleeding.

Factors affecting blood loss

To avoid complications in spinal surgery it is necessary to consider the anatomy and physiology of vertebral veins and the effects of their engorgement or damage during spinal operations. As a matter of fact, there are several plexuses of thin-walled, valve-less veins in relationship to the vertebrae. They normally contain blood at low pressure, and the direction of flow is reversible. The vertebral veins are connected with those in the chest through the vertebral canal, and with the ones in the abdomen and pelvis through the intercostals, lumbar and other connecting veins.

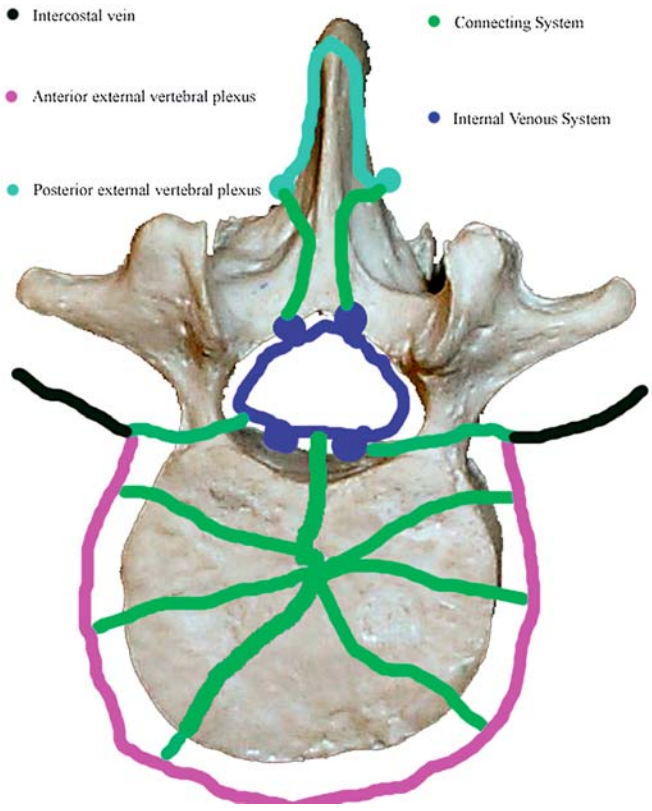

Fig. 1 Batson's plexus

Oscar Batson's pioneering experiments on monkeys, confirmed a few years later by Norgore, showed that, in cases of vena cava obstruction, the venous return from the lower parts of the body could be diverted into the vertebral venous system. This demonstrated definitively that this vertebral venous system acts as a supplementary channel of blood discharge [2, 22].

There are three components to Batson's plexus: the internal venous system, the external venous system and the rich net of connecting or anastomotic veins (Fig. 1).

The internal venous system

Within the spinal canal there can be found:

- The anterior internal veins (AIVV) on the posterior surface of the vertebral bodies (the basivertebral vein drains into this part of the system)
- The posterior internal vertebral veins (PIVV) on the anterior surface of the lamina (in the posterior part of the canal)
- The anastomotic veins connecting the two systems within the spinal canal

The internal venous system represents a continuous venous pathway from the sacrococcygeal region to the base of the skull [18].

The external venous system

Longitudinally traveling veins lie anterior to the vertebral bodies, on the outer aspect of the lamina (posterior external vertebral plexus) and on the outer aspect of the transverse process.

Connecting or anastomotic veins

There is a rich anastomotic system of veins connecting the internal to the external vertebral system and connecting both parts of the vertebral venous system to the systemic vena cava circulation. It consists of the following: a basivertebral branch that passes laterally and anteriorly to penetrate vertebral bodies, radicular branches to veins lying along the spinal roots (intervertebral veins), posterior anastomotic channels that penetrate the ligamentum flavum, and anastomotic links between the AIVV, between the PIVV, and the AIVV and the PIVV within the spinal canal [18].

Bearing in mind these anatomic considerations, many factors may be responsible for causing partial or complete obstruction of the inferior vena cava during operations, thus causing a significant rise in the caval pressure and diversion of blood into the vertebral veins. Pressure on the anterior abdominal wall is transmitted to the inferior vena cava and only moderate external pressure is needed to cause a big rise in caval pressure [25]. A rise of intra-abdominal pressure may be caused by extrinsic factors such as sandbags, bolsters or the mattress of the operating table or by excessive abdominal muscle tension.

Moreover, if abdominal compression occurs while the patient is in the prone position, particularly in obese patients, the respiratory dynamic can be altered because of a decreased respiratory compliance. In the setting of reduced compliance, very high airway pressures may be required to ensure an adequate ventilation for the patient. High airway pressures may, in turn, impair venous return to the heart, decrease cardiac output and increase systemic venous pressure [23].

In addition, high venous pressure may result in decreased spinal cord perfusion pressure (mean arterial pressure – spinal venous pressure), putting the patient at increased risk of neurological complications [23]. Thus, less bleeding may be expected if the patient is supported with the abdomen pendulous and free from external pressure.

Methods to reduce blood loss (positions without frames)

Spinal posterior surgery has essentially two requirements: an adequate position of the column and an unrestricted abdomen with reduction of bleeding due to engorged vertebral veins. Yet, the prone position in spinal surgery may be complicated by the need to use a C-arm.

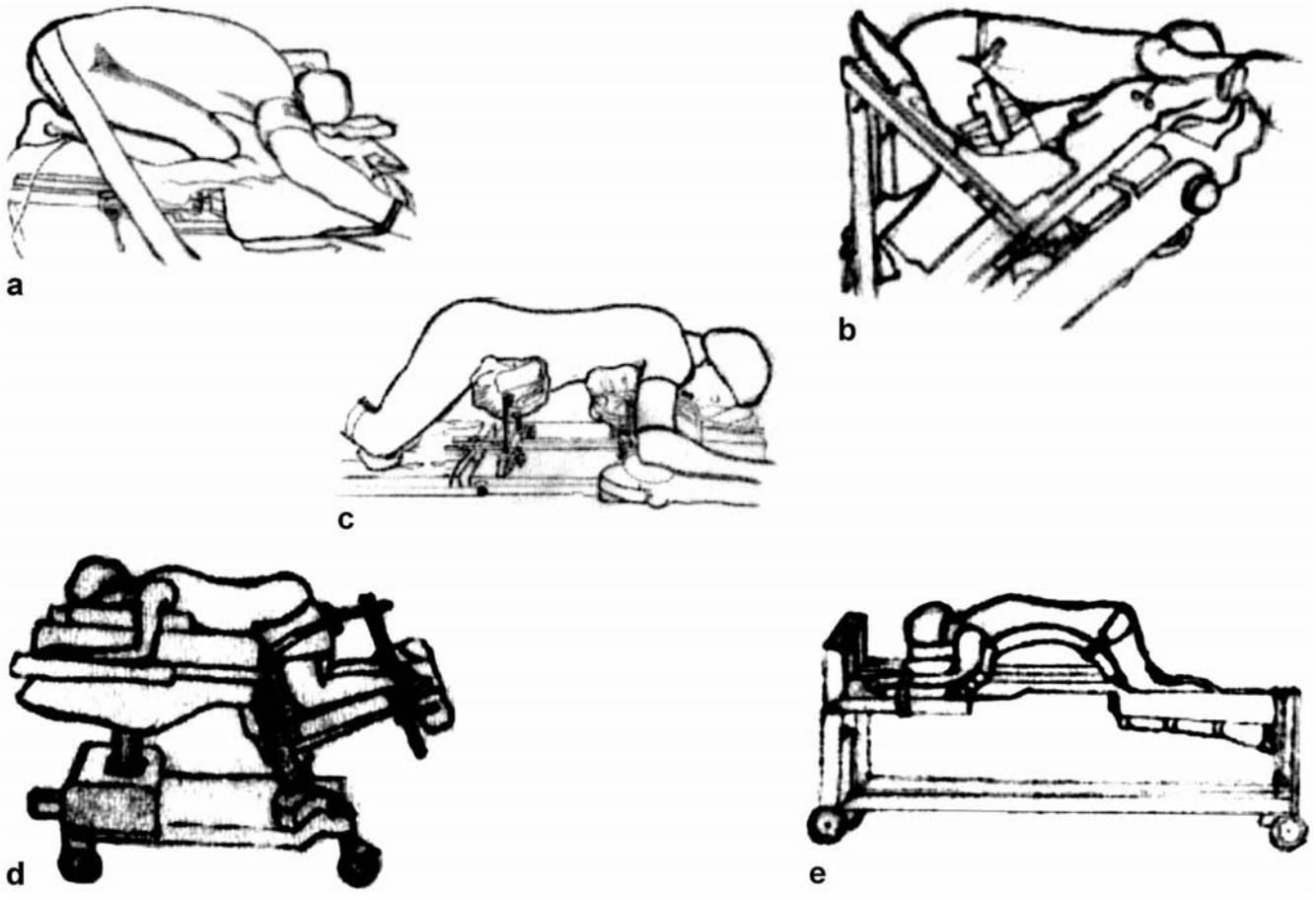

Fig. 2 Positioning for spinal surgery. **a** Tuck position; **b** Canadian frame; **c** Relton Hall type frame; **d** Andrews frame; **e** Wilson frame

Good exposure of the contents of the segmental spinal canal is a sine qua non condition in surgery for lumbar disc herniation. In these cases, a position that decreases the lordosis of the lumbar spine and opens the posterior intervertebral spaces, facilitates the access to the inner spinal canal.

Use of chest rolls remains an effective and inexpensive technique to obtain an unrestricted abdomen during prone spinal surgery. This can also be achieved by the kneeling position, first described by Ecker in 1949 [9]. Lipton in 1950 described a variant of the Ecker position, the so-called Mohammedan praying position [17]. The knee-chest position, another evolution of the first position reported, was than described by Tarlov in 1967 [31]. The tuck position, an extreme fixed position, was than described in the same year by Wayne [32] (Fig. 2a). However, considerable flexion of the spine, hips, and knees occurs in this extreme tucked position, and this may produce vascular and nerve compression in the popliteal compartment. Moreover, after prolonged spinal surgical procedures, massive release of myoglobin can cause acute renal failure [11, 16]. In addition, this extreme flexed position may tighten the posterior paraspinal muscles so that lateral retraction, particularly important in cases of lateral stenosis, may be quite difficult [11]. Finally, prolonged maximal joint flexion is potentially dangerous in patients with hip or knee disorders, joint degeneration, or implanted prostheses [26].

Methods to reduce blood loss (the jungle of frames)

Preservation of the normal sagittal spinal alignment is critical in spinal reconstructive surgery. In these cases, positioning devices have to balance the goals of both abdominal decompression and lordosis preservation [12, 28]. Relton and Hall in 1969 described a frame that may be still considered a standard for comparison (Imperial Surgical, Halpern Dorval, Quebec, Canada). Their device consists of four padded supports arranged in two V-shaped pairs. The rostral pair supports the lateral aspects of the upper thoracic cage – below the clavicles and as far down as the xiphisternum. The caudal pair supports the anterolateral aspects of the pelvic girdle between the iliac crests and the greater trochanters of the femora, so that they do not encroach on the lower parts of the anterior abdominal wall.

The supports are set at a 45° inward tilt and are individually adjustable for length and width. With suitable adjustment they give adequate support and prevent external pressures from being applied to the anterior abdominal wall during the procedure. The tendency towards hyperextension of the vertebral column is partially counteracted by lowering the legs [27], (Fig. 2c).

Furthermore, many devices were designed to obtain an abdomen free of restriction and to decrease lordosis during posterior spinal operation for lumbar disc herniation. Hastings described in 1969 the so-called Canadian frame (Fig. 2b) [13]. This complex device allowed the patient to be placed in a knee-chest position, without overstretching the joints. (The Cloward surgical saddle and Heffington frame were proposed by neurosurgeons with the same objective [29]).

However, two popular devices actually warrant a safe prone surgical position for lumbar disc herniation: the "Andrews" and "Wilson" frames. On the Andrews table, patients are positioned in a modified knee-chest position with a chest pad and an adjustable tibial support lowered to obtain 90° hip flexion. The tibial support may be adjusted to produce 60° hip flexion for spinal fusion operations. It allows C-Arm integration for both A/P and lateral intraoperative views (OSI, Union City, CA, USA) (Fig. 2d).

The Wilson supporting frame provides a convenient and stable method of maintaining patients in a flexed position for spinal surgery. It has two curved full-length pads, which provide continuous support for chest and pelvis and adjust laterally to improve ventilation and relieve pressure from the abdomen. A recent evolution of this frame (Wilson Plus) offers 360° of unobstructed radiolucency, for easily obtainable images by either C-arm or X-ray (OSI, Union City, CA, USA) (Fig. 2e).

The Jackson surgical table has a 360° axis rotational capability and thus facilitates safe and efficient rotation of particularly traumatized patients during combined approaches. It also offers 360° of unobstructed radiolucency for easily obtainable images with either C-arm or X-ray (OSI, Union City, CA, USA).

Human studies

In 1967 Wayne et al. first measured the pressure in the vena cava (intra-caval venous pressure ICVP) in six male patients, by introducing a long venous catheter through the femoral vein. Two patients representing each of the three body types (tall muscular, medium, and obese) were tested in each of the following positions: supine, prone, prone with rolls supporting the shoulders and iliac crests, prone on a foam rubber horseshoe pad, and in the tuck position. Only in the tuck position were consistently favorable readings obtained even in the obese subjects, whose abdominal contents produced a venous pressure of 220 mm of water in the supine position. In the tuck position it was possible to reduce pressure significantly, whereas, pressure increased markedly in the other prone positions [32].

In 1969 DiStefano et al. measured intraoperatively the ICVP in ten patients affected by spinal instability or disc herniation, using the same technique as Wayne. Venous pressure determinations were recorded in six positions: prone with bolsters; on a Wilson frame; kneeling; lateral decubitus; in the tuck position; and on a Canadian Frame. Hastings's Canadian frame was found to result in significantly lower ICVP, with negative pressure recordings in three occasions. However, the comparison of the effects of different support systems was not made in the same patient, and no obese subjects were included in the study [7].

In 1992, McNulty et al. measured IVCP in 18 patients undergoing elective lumbar laminectomy. Those patients were assigned randomly to one of the three prone support systems (Andrews frame, Cloward surgical saddle, and longitudinal bolsters). The IVCP in the group with their abdomens extremely pendulous (on an Andrews frame) was significantly lower than that in the other two groups. However, again in this series, the comparison of the effects of different support systems was not made in the same patient [19].

In 1990 Botsman et al. reported a retrospective analysis of 436 standard operations for herniated lumbar discs during a period of 8 years. The aim of this study was to evaluate the relation between blood loss and operating time with various positions. Prone position on bolsters was used in 216 cases and a frame-supported position (with a modified Hastings frame) was used in 192. The choice between these two positions was based solely on the personal preference of the operating surgeon. First and second operations, irrespective of the vertebral spaces explored were included, but cases requiring complete laminectomy were excluded, to obtain an homogeneous study group. The blood loss was assessed by weighting the gauze packs used and by measuring the amount drained by suction from the operating field. The mean calculated blood loss in prone position was 376 ml (interquartile range 150–450 ml) in the first operations and 504 ml (interquartile range 200–110 ml) in reoperations. In the kneeling, supported position the calculated mean blood loss was 150 ml (50–300 ml) and 218 ml (100–400 ml), respectively. The mean operating time with prone position was 74 min (standard deviation (SD) 32) in the first operations and 97 min (SD, 36) in reoperations. With kneeling position it was 52 minutes (SD, 23) and 82 min (SD, 29), respectively [3].

In 2000 Park et al. conducted a detailed studied of the effects of the width of Wilson-frame-pad supports for posterior lumbar spinal fusion operations. His study was a prospective analysis of 40 patients undergoing surgery. Patients were randomly assigned to group 1, narrow (36.6± 1.2 cm), or group 2, wide (43.8±1.2 cm) support. There were no significant differences between groups for sex, weight, height and preoperative MAP (mean arterial pres-

sure). IAP (intra abdominal pressure) by rectal balloon was measured as estimation of ICVP for the following positions: supine, prone on a gurney, prone on the Wilson frame before and after incision, and supine after tracheal extubation. Moreover, intraoperative blood loss was calculated by weighing blood-soaked gauzes as they were passed off the surgical field. Blood contents of the suction bottle were also measured, excluding the irrigation solution. IAP in the prone position on the gurney was not different from that in the supine position in each group. IAP in the prone position on the Wilson frame before incision (8.8 cmH_2O) was significantly more than that in the supine position after the induction (6.9 cmH_2O) in group 1 ($p<0.05$). However, in group 2, IAP in the prone position on the Wilson frame before incision (3.6 cmH2O) was significantly less than in the supine position after induction (7.0 cmH_2O) ($p<0.05$). IAP in the prone position on the Wilson frame after incision was 10.6 cmH_2O in group 1 and 4.7 cmH_2O in group 2 and was higher than that for pre-incision in each group ($p<0.05$). IAP in the supine position after tracheal extubation was the highest in each group. Comparing the different groups, IAPs in the prone position on the Wilson frame before and after incision in group 2 were significantly less than those in group 1 ($p<0.05$). Intraoperative blood loss in group 2 (436±159 ml) was significantly less than in group 1 (878±521 ml) ($p<0.05$). In conclusion, blood loss and IAP were less in the group positioned on a wider Wilson pad support. [24].

Tao-Chen Lee et al. in 1998 reported a prospective study including 20 patients undergoing lumbar spinal surgery in a prone position under controlled isoflurane-induced hypotension. For each patient, IVCP was measured: with the patient positioned supine, prone on a conventional pad, and, subsequently, prone on a Relton-Hall frame. The mean IVCP was 15.3 mmHg (range, 8.2–23.4 mmHg) when patients were positioned prone on a conventional pad, and this dropped to 8.2 mmHg (range, 4.6–13.6 mmHg) when they were subsequently positioned on a Relton-Hall frame. It is important to note that in every case, the measured IVCP in patients on a conventional pad was 1.5× higher (range, 1.5–2.4×; mean, 1.9×) than that measured in those on a Relton-Hall frame. They concluded that a device allowing the patient's abdominal viscera to hang freely in a prone position significantly reduces IVCP, and isoflurane-induced hypotension, with reduction of the patient's mean arterial pressure by 20 mmHg, does not influence IVCP [30].

Complications of positioning

Injury to the lateral femoral cutaneous nerve (LFCN) was found to be a common complication during spine surgery and occurs in 20% of the patients [20]. Neuropathy of this nerve is usually associated only with hypoesthesia, but in some patients it may cause pain and dysesthesia in the anterolateral aspect of the thigh [10]. As the LFCN is sensitive, the signs of injury may be missed, mainly in the first postoperative days when the patient has pain at the surgical site and is not completely alert under the influence of analgesics and narcotics.

Compression neurapraxia is most probably the cause of injury in patients undergoing operation on frames. In those positions, in fact, the posts supporting the pelvis can compress the nerve at the exit below the anterior superior iliac spine [20]. This complication, also known as meralgia paresthetica, usually has a benign course, and 89% of patients reported by Mirowski recovered completely 3 months after surgery [20]. Because of the relatively high probability of meralgia paresthetica after spine surgery, patients should be informed about the occurrence of this complication.

Direct pressure on the eye, especially as a result of a patient malposition, has been cited as a factor contributing to visual loss, often irreversible, in several published reports. The incidence of significant visual complications after spine surgery, according to a recent review, could be on the order of one case per 100 spine surgeons per year [21]. Long operative times, substantial intraoperative blood loss [14, 15] and intraoperative hypotension could be associated risk factors for this complication [6, 8]. Vigilance regarding eye protection during positioning by both the surgeon and the anesthesiologist is compulsory to avoid this dramatic event.

Shoulder dislocation [1], massive release of myoglobin with acute renal failure [11, 16] and ischemic medullary syndromes [5] are other sporadically reported complications.

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Aprotinin and major orthopedic surgery

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Abstract Aprotinin is a potent pharmacological agent that reduces bleeding and limits blood transfusion requirements in current surgical practice. Many studies have been conducted in orthopedic surgery. In several trials performed in total hip replacement (THR) and total knee replacement (TKN) patients, aprotinin only moderately decreased blood-loss-replacement requirements. Conversely, when aprotinin was used in patients at high risk for bleeding (cancer, sepsis, redone surgery), it developed a potent hemostatic activity and decreased blood transfusion significantly. No increase in deep vein thrombosis and pulmonary embolism was observed. The only major side effect could be the potential occurrence of an anaphylactoid reaction. Prophylactic administration of aprotinin should be considered in extensive spine surgery and in high-risk major orthopedic operations. The decision to use aprotinin should be guided by a risk/benefit analysis.

Keywords Aprotinin · Bleeding · Transfusion · Orthopaedic surgery · Thrombosis

Introduction

Aprotinin constitutes an interesting means to control or to reduce bleeding and to limit blood transfusion in current surgical practice. The interest in this antifibrinolytic drug dramatically increased when Royston et al. demonstrated, for the first time, the effect of high doses of aprotinin in reducing intraoperative blood loss and transfusions in cardiac surgery [26]. Since then, many studies have been performed in this type of setting. Aprotinin is widely used in cardiac surgery and trials have taken place in vascular [12] and liver transplant surgery [25], studying different dosages and modes of administration. Generally, aprotinin was able to decrease intraoperative and postoperative bleeding and blood transfusion. Many studies have also been conducted in orthopedic surgery [2, 3, 8, 13, 14, 15, 17, 19, 20, 22, 23, 28. 29, 30]. Some of the earliest trials were performed in total hip replacement (THR) and total knee replacement (TKN) patients. The general feeling was that aprotinin moderately decreased blood loss in these patients [8–14]. One or two packed red-cell units per patient could be saved when this drug was used. Therefore, it was doubtful that such a compound could be used systematically in such settings. In contrast, the use of aprotinin in a double-blinded study [3] in high-risk septic and cancer patients undergoing pelvic and hip surgery proved to be effective in significantly reducing the need for blood transfusion, as compared with a placebo group. Even with a small number of patients, Capdevila et al. isolated for the first time an orthopedic setting in which aprotinin was very effective [3]. Only major orthopedic surgery with major bleeding events and increased risk of transfusion benefited from aprotinin in this study. Starting from this observation, we will review aprotinin's mechanism of action and the different studies in which it has been used; and we will try to define precisely a frame for the use of this potent hemostatic agent.

How does aprotinin work?

Aprotinin is a naturally occurring single-chain 58 amino-acid polypeptide with a molecular weight of 6,512 dalton.

It develops a broad inhibitory specificity on serine protease, but its most important effect is to inhibit plasmin, trypsin and kallikreins of various origins [27]. It forms a stoichiometric complex and blocks the active site of the enzyme. It is a competitive inhibition. Nevertheless, the mechanism underlying the beneficial effects of aprotinin in orthopedic surgery have not yet been fully elucidated. Several hypotheses can be proposed. Aprotinin acts mainly as an antiplasmin agent. However, no systemic fibrinolysis has ever been reported in scheduled orthopedic surgery [3, 8, 14]. For instance, coagulation and fibrinolytic parameters (thrombin-antithrombin (TAT) and plasmin-antiplasmin (PAP) complex, alpha2-antiplasmin, tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI 1), D-dimers and factor XII were measured after a selective blood sampling in the femoral vein during total knee arthroplasty [8]. The only relevant result was an increase in the alpha2-antiplasmin level in the aprotinin group at 5 min and 240 min.

The occurrence of a local fibrinolysis has already been advocated, but never demonstrated. The anti-kallikrein activity of aprotinin interferes with the intrinsic coagulation pathway that is activated during severe sepsis. Therefore, aprotinin could prevent this activation, and, while decreasing thrombin generation, limit the extent of potential disseminated intravascular coagulation and platelet activation, both responsible for intraoperative bleeding.

Studies showing a lack of efficacy or a mild efficacy of aprotinin

Several trials first investigated the usefulness of aprotinin in hip or knee replacement patients [8, 14]. The results on blood loss and transfusion sparing were not so impressive and did not lead to any significant modification of the care of these patients. In 1994, Janssens was the first to compare, in a double-blinded fashion, giving either aprotinin as a bolus of 2 million kallikrein-inhibiting units (KIU) followed by an infusion of 0.5 million KIU/h until the end of surgery, or giving an equivalent volume of normal saline, in patients undergoing total hip replacement surgery [14]. Aprotinin reduced total blood loss from 1,943 ml to 1,446 ml. Total amounts of blood transfused were 3.4 units/patient in the control group and 1.8 units in the aprotinin group.

A study by Murkin was performed in patients undergoing revision or total hip arthroplasty [22]. The difference was statistically significant, but the amount of spared blood loss was not very large and the RBC transfusion decreased from 3 units in the control group to 2 units in the aprotinin group. Of note, the patients were also assessed for development of deep vein thrombosis (DVT) by lower-limb-compression ultrasound. None of the aprotinin patients and three placebo-treated patients demonstrated DVT.

In a second study from the same author, three aprotinin groups were compared with placebo in patients undergoing primary total hip replacement [23]. Aprotinin reduced total intraoperative blood loss and postoperative drainage volume, with a mean total of 1,408 ml for the placebo group compared with 1,079 ml in the "high-dose" group (i.e., 2 million KIU bolus + 0.5 million KIU/h), and a comparable moderate decrease was observed in the two other groups, with much smaller aprotinin doses. Furthermore, the percentage of patients who required any form of transfusion was small, 47% in the placebo group, leading to a reconsideration of the benefit of hemostatic drugs in such a setting.

A randomized, double-blinded controlled study by Langdown compared the effects of aprotinin (1.5 million KIU as a bolus, with no continuous infusion) with saline during primary total hip replacement in 60 patients [19]. No effect either on blood loss or transfusion was observed. Once again, as is often observed in negative studies, intraoperative and postoperative bleeding was small both in the placebo group (303 ml+525 ml) and in the aprotinin group (284 ml+550 ml).

Negative results were also found in 40 THR patients treated by aprotinin (2 million KIU) or placebo [13]. Total blood loss only reached 1,200 ml in both groups and transfusion requirements were unchanged.

Kasper reported negative results when comparing, retrospectively, two cohorts of patients (total n= 372) who had undergone unilateral primary hip arthroplasty [16]. No difference was observed between the patients treated and not treated by aprotinin (almost 1.5 million KIU as a bolus before surgery). As expected, the blood loss in the control group was small (810 ml).

In total knee replacement (TKN) patients, the median blood loss of aprotinin patients (total dose 2 million KIU) was decreased to 663 ml as compared with 960 ml in the control group, and the median number of RBC units transfused was 0 in the aprotinin group as compared with 2 in the control group [29]. One patient with peripheral vascular disease developed an ischemia and underwent an amputation. This adverse event led to the study's interruption.

A second study was conducted more recently in 36 TKN patients [8]. No difference was observed between the aprotinin group (1 million KIU bolus followed by an infusion of 0.5 million KIU), the tranexamic acid group and the placebo. The mean blood loss (810 ml (245 ml–1,370 ml) was comparable in the three groups.

A study by Khoshhal including 43 patients over the age of 12 years demonstrated a moderate benefit of aprotinin (dose equivalent to the 2 million KIU+0.5 million KIU dose) vs placebo in spinal fusion for idiopathic scoliosis (10 levels of fusion in each group) [17]. The aprotinin group had less blood loss (831 ml vs 1,403 ml) and the transfusion requirement was less in the aprotinin group than the placebo group (–46%). However, the difference was

not significant statistically. It should be emphasized that the lack of efficacy could be related to the small amount of bleeding.

Finally, a randomized, double-blinded, placebo-controlled trial by Amar et al. included 69 adults with malignancy, scheduled for either pelvic, extremity or spine surgery during general anesthesia. It compared aprotinin (n=23, bolus of 2 million KIU, followed by an infusion 0.5 million KIU/h) with epsilon-amino caproic acid (EACA) (n=22, bolus of 150 mg/kg, followed by a 15 mg/kg/h infusion) and saline placebo (n=24) [2]. The study was negative; the groups did not differ in age, duration of surgery, perioperative blood loss or number of packed erythrocyte units transfused. However, this well-designed study could be criticized for several things: first, it was unfortunately underpowered, because it was terminated before full accrual of the projected sample size, based on the results of an early interim analysis; second, the population was very heterogeneous; and the third, and probably major, concern was that the amounts of blood loss and transfusion were very small in the control group – respectively 1.3 l (0.6–1.9 l) and 1 packed red-cell unit (0–2 units) 48 h after surgery. This very small amount of bleeding could be related to active warming and/or controlled hypotension, or to very meticulous care of intraoperative hemostasis.

To summarize, major bias can be evidenced from all these studies. Obviously, hip or knee surgeries do not seem to be the most appropriate settings to use aprotinin. Bleeding is limited, and the usual perioperative amount of transfused RBC units generally does not exceed 3 units, which can be provided by a scheduled predonation. Surprisingly, these disappointing results can also be observed in spine and/or major orthopedic surgery, provided that the amount of perioperative bleeding is not large.

Prophylactic administration of aprotinin should be considered in extensive spine surgery and in high-risk major orthopedic operations

Several studies have investigated the benefit of aprotinin in spine surgery. A large prospective study by Lentschener in posterior lumbar spine fusion has shown interesting results in regard to the design of the surgical setting [20]. Seventy-two patients were randomized into two groups: the aprotinin group received the usual 2 million KIU dose as a bolus followed by a continuous infusion (0.5 million KIU/h). An additional bolus of 0.5 million KIU of aprotinin was infused every three RBC units. Each patient in the control group received equivalent volumes of saline solution. One to three spine levels were fused. The total blood loss was significant in the placebo group (2,760 ml (1,160 ml–5,000 ml) and reduced to 1,935 ml (600 ml–4,280 ml) by aprotinin. The total number of RBC units (either autologous or homologous) was not as high in the control group (2.5 units (0–6 units), but it was decreased by aprotinin (0 units (0–5 units)). However, in this study, despite (or because of?) strong transfusion triggers, aprotinin therapy significantly decreased autologous, but not homologous, transfusion requirements in posterior lumbar spine fusion.

Sixty patients scheduled for elective, sequential anteroposterior thoracolumbosacral fusion were randomly assigned into three groups: control, epsilon aminocaproic acid (Amicar) and aprotinin (1 million KIU bolus + 0.25 million KIU/h infusion) [15]. The total amount of intraoperative estimated blood loss (EBL) was greater than 5 l (5,181 ml) in the placebo group, and only aprotinin was able to decrease EBL significantly (3,628 ml). The mean number of transfused pints was decreased with aprotinin (fresh-frozen plasma, from 9 to 0; platelets, from 3 to 0; RBC units, from 6 to 4). Once again, the efficacy of aprotinin was demonstrated in patients with major bleeding and large amounts of transfusion. Aprotinin also preserved the thromboelastogram mean clot-formation time, clot strength, and clotting index as compared with EACA or control.

A very small double-blinded study by Jeserschek included 18 patients scheduled for major orthopedic surgery (revision arthroplasty of the hip or knee (n=16), or for resection of a soft-tissue sarcoma (n=2)) [15]. Mean intraoperative blood loss was reduced from 1,957 ml in the control group to 736 ml in the aprotinin group (1 million KIU + 0.5 million KIU/h), and the mean requirement for intraoperative homologous blood transfusion in the aprotinin group was reduced to 1.4 units (95% confidence interval, 0;2–2.7) as compared with 3.1 units (1.7–4.6) in the control group. A non-significant decrease in the length of hospital stay was also observed.

Capdevila et al. demonstrated that aprotinin was able to dramatically reduce blood loss (1,783 ml vs 5,305 ml in the placebo group) and the number of packed RBC units (3 vs 7) used in patients undergoing major orthopedic surgery of the hip or pelvis for sepsis or malignant tumors [3]. Of note, preoperative donation and/or intraoperative cell-saving procedures are generally not performed in these cancer and/or septic patients, although massive intraoperative bleeding frequently occurs. These conditions and the severity of the patient's clinical condition, i.e., severe sepsis or cancer, provide a good rationale for the use of this type of hemostatic agent. The greater the bleeding the more beneficial the effects of aprotinin appears to be.

However, when the Capdevila study was published, the optimal aprotinin dose was still debated, and objective assessment of deep vein thrombosis was not systematically performed in these high-risk patients. Therefore, we decided to conduct a prospective, multicenter double-blinded dose-ranging study to compare the risk/benefit ratio of high- and low-dose aprotinin with placebo after major orthopedic surgery [28]. After IRB approval and informed consent, 58 patients were randomized into three groups:

– High-dose aprotinin, 4 million KIU bolus before surgery, followed by a continuous infusion of 1 million KIU/h until the end of surgery
– Low dose aprotinin, 2 million KIU bolus + 0.5 million KIU/h
– Placebo

Bleeding was measured and calculated. A bilateral ascending venography was systematically performed on the third postoperative day. Measured and calculated bleeding decreased in the high-dose-aprotinin group. (Calculated bleeding, whole blood, hematocrit (HT) 30%: 2,023 ml, range 633–4,113 ml; as compared with placebo, 3,577 ml, range 1,670–21,758 ml). The total number of homologous and autologous units also decreased significantly in the high-dose aprotinin group (2 units, range 0–5) as compared with placebo (4 units, range 0–42). No increases in clinical or venographic deep vein thrombosis or in pulmonary embolism were observed in the aprotinin-treated groups as compared with placebo. High-dose aprotinin was safe and effective in dramatically reducing the measured and calculated bleeding, and the amount of transfused RBC units. (Tables 1 and 2) One non-fatal allergic reaction was observed in one aprotinin-treated patient.

The results of the HACOL study show that, in patients undergoing major orthopedic surgery, high-dose aprotinin significantly reduced intraoperative and postoperative blood loss and packed RBC requirements. The observed difference between calculated bleeding and measured bleeding provides additional data suggesting that occult postoperative bleeding (mainly hematomas) was also decreased by aprotinin.

Table 1 Bleeding in the HACOL study (*HT* hematocrit). Results are expressed as median and range

	Placebo (n=18)	Medium-dose aprotinin (n=22)	High-dose aprotinin (n=18)
Aspiration ± cell-saver (ml)			
Median	1,265	838	600
Range	(250–6,000)	(200–16,000)	(200–2,200)
Swabs (ml)			
Median	700	310	275
Range	(100–3,960)	(100–3,000)	(0–1,800)
Postoperative drainages (ml)			
Median	1,190	590*	625*
Range	(0–3,060)	(130–3,080)	(42–2,470)
Total measured bleeding (ml of whole blood)			
Median	2,795	1,943	1,715*
Range	(950–12,760)	(780–19,000)	(472–3,490)
Total calculated bleeding (ml of RBC units, HT 100%)			
Median	1,073	711	607*
Range	(501–6,528)	(315–3,900)	(190–1,234)
Total calculated bleeding (ml of whole blood, HT 30%)			
Median	3,577	2,370	2,023*
Range	(1670–21,758)	(1050–12,999)	(633–4,113)

*p<0.05 vs placebo

Table 2 Transfusion in the HACOL study (*RBC U* red blood cell units; *FFP* fresh-frozen plasma units). Results are expressed as median, range and total amount of units per treatment group

	Placebo (n=18)	Medium-dose aprotinin (n=22)	High-dose aprotinin (n=18)
Homologous RBC U			
Median	2	0	0*
Range	(0–42)	(0–26)	(0–2)
Total	101	53	7
Number of exposed patients	11	8	4*
Homologous + autologous RBC U			
Median	4	3	2*
Range	(0–42)	(0–26)	(0–5)
Total	123	83	42*
Number of exposed patients	17	19	14
Cell-saver units			
Median	1	2	1
Range	(1–3)	(1–4)	(0–2)
Total	9	15	10
Homologous FFP units			
Median	0	0	0
Range	(0–13)	(0–12)	(0–2)
Total	13	12	2

*p<0.05 vs placebo

Most of our patients fulfilled the inclusion criteria regarding perioperative bleeding, with median measured bleeding of 2,795 ml (900–12,760 ml), suggesting that, in patients scheduled for major orthopedic surgery, bleeding and transfusion are frequent and that blood-sparing protocols should systematically be part of the perioperative care of the patient. All our patients underwent spine, pelvic or hip surgery. Most of these procedures belong to one of the four supposed high-risk categories with regard to bleeding: revision, trauma, cancer and sepsis. The remaining patients were only operated on for the spine or pelvis. We initially thought that their theoretical bleeding risk would decrease slightly, as compared with the four other groups. Among all the patients of the study who bled more than 1,000 ml (calculated bleeding, HT 100%, n=17/57), 7/18 patients belonged in the "other-types-of-surgery" group (NS). Obviously, these procedures posed the same bleeding risk.

As a potent hemostatic agent and an in vitro inhibitor of activated protein C [9], aprotinin has been accused of inducing a hypercoagulable state and promoting graft occlusion after coronary artery bypass [1, 4] or liver transplantation [10]. It could theoretically increase the venous thromboembolic risk in patients undergoing major orthopedic procedures, despite the use of a daily low-molecu-

lar-weight prophylaxis. In studies of low-molecular-weight heparins (LMWH) in patients undergoing THR, the global venographic DVT rate on day 10 generally reached 15–25% in patients treated with LMWH [11]. The theoretical venographic DVT rate in our patients was supposed to be as high. Ours was the first double-blinded aprotinin study to assess, systematically, venous thromboembolism with a venography performed at day 3. The number of thromboembolic events was very low and not significantly different from one group to another. This is consistent with previous reports. However, in this regard, the sample of 58 patients is far too small to draw any definite conclusion or to rule out any prothrombotic effect of aprotinin. One can only notice that no thrombotic event was detected in the high-dose group and that, in our study, the increase in the aprotinin dose did not increase the thrombotic risk.

One non-fatal allergic reaction was recorded, leading to discontinuation of the treatment in a young patient. Since aprotinin is a polypeptide derived from bovine lungs, it possesses antigenic properties. Therefore, the possibility of an adverse reaction to this agent exists, especially in patients re-exposed to this drug. Allergic reactions after re-exposure have been described [5, 6]. The incidence of hypersensitivity reactions in one study was 2.8% in 248 patients re-exposed to aprotinin [7]. A time dependency for the risk of adverse reactions exists: the shorter the time interval between the two exposures, the higher the risk of a reaction. Therefore, the drug should not be given within 6 months after the last exposure. In addition, exposure of patients with moderate expected bleeding (i.e., patients scheduled for total hip replacement) to this significant allergic risk does not seem to be justified, considering the potential severity of aprotinin-induced anaphylactic shock.

Two doses of aprotinin were compared with placebo in the HACOL study: the low dose, as already described in several papers, and a higher dose. Our original hypothesis was based on an equal efficacy of the two doses. However, the final results showed a clear benefit for the high dose over the placebo. The results in the low-dose group did not reach statistical significance, despite a real efficacy. In the high-dose group, however, bleeding and the total amount of blood transfusion decreased dramatically. It could be assumed that intraoperative bleeding is responsible for a partial washout of the product. Low doses could be beneficial in cardiac surgery when shed blood is immediately reinfused in the bypass, but appear ineffective when a consistent blood volume is discarded. A high plasma concentration has to be reached [21], and a continuous infusion of a high dose seems to be mandatory to maintain such a level. Furthermore, higher doses may be responsible for a larger decrease in thrombin generation than common doses. An indirect anticoagulant effect of high-dose aprotinin could be reported, in conflict with the supposed prothrombotic effect of high doses.

Our results clearly demonstrate that prophylactic high-dose aprotinin was able to dramatically decrease perioperative blood loss, RBC transfusion and the number of patients exposed to transfusion in major orthopedic surgery, without any significant side-effects. In high-risk orthopedic patients who haven't already been exposed to the product, aprotinin use should be considered.

Conclusion

It is now well-recognized that major orthopedic surgery is associated with an increased risk for perioperative bleeding and subsequent need for blood transfusion [18, 24]. Therefore, aprotinin should be dedicated to this type of procedure. Mainly extensive spine surgery, cancer or sepsis surgery are concerned. However, as already observed, aprotinin has sometimes been effective in revision hip studies, since the total amount of bleeding was high. In addition, although data are scarce, aprotinin does not seem to increase the risk of deep vein thrombosis. The only major side-effect could be the potential occurrence of an anaphylactoid reaction. Finally, the decision should be guided by a risk/benefit analysis.

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Tranexamic acid for major spinal surgery

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Abstract Patients who undergo major spinal surgery often require multiple blood transfusions. The antifibrinolytics are medications that can reduce blood-transfusion requirements in cardiac surgery and total knee arthroplasty. The present role of synthetic antifibrinolytics, especially tranexamic acid, in reducing perioperative blood-transfusion requirements in spine surgery is still unclear. The majority of studies exploring the role of these drugs in spine surgery have limited patient enrolment and report mixed results. The goal of the present review is to discuss the pharmacology of tranexamic acid briefly. A brief synopsis of the studies using the synthetic antifibrinolytics for spine surgery is presented. Finally, the potential risks and the benefits of antifibrinolytics are discussed.

Keywords Blood transfusion · Coagulation · Tranexamic acid · Antifbrinolytics · Spine surgery · Scoliosis

Introduction

Major spinal surgery has the potential for massive blood loss [20]. Concerns surrounding the accompanying blood transfusions have spawned considerable interest in reducing peri-operative blood loss. Improved surgical techniques and peri-operative management may reduce blood requirements, but the majority of patients are still subjected to blood transfusions [26]. The prophylactic administration of synthetic antifibrinolytics, including tranexamic acid, has therefore been investigated for improving haemostasis for orthopaedic surgery. The goal of this review is to discuss synthetic antifibrinolytics briefly and explore their role in major spinal surgery.

Review of haemostasis

A discussion of antifibrinolytics requires a brief synopsis of the normal haemostatic process. Injury to blood vessels initiates the four components of haemostasis. First, the blood vessel attempts to vasoconstrict to reduce blood loss. Subsequent to this, exposure of the injured endothelium initiates platelet adhesion. The glycoprotein-Ia platelet receptors adhere to the damaged vessel wall with von Willebrand factor serving as a bridge. Platelet degranulation, which follows adhesion, liberates substances which in turn further augment platelet aggregation and vessel vasoconstriction. The third phase of haemostasis is the contact phase of coagulation, which includes the intrinsic and extrinsic coagulation cascades. The consequence of the third phase is fibrin clot formation and activation of the fibrinolytic system. Fibrinolysis, the fourth stage of haemostasis, results in dissolution of fibrin clots mediated by plasmin. Evidence suggests that plasmin also inhibits haemostasis at other levels, including inhibition of platelet aggregation through cleavage of the glycoprotein-Ia receptors on platelets and inactivation of fibrinogen [7]. Thus, a patient who develops a relative excess of fibrinolysis will be more likely to experience considerable blood loss during surgery.

A relative increase in fibrinolysis occurs in cardiac surgery primarily owing to the use of the cardiopulmonary

bypass machine. The use of a tourniquet in total knee arthroplasty has been implicated as the cause of increased fibrinolysis [13, 19]. Enhanced fibrinolysis has also been suggested to be a contributing factor to blood loss during spinal surgery [15, 16]. Drugs that counter fibrinolysis, including tranexamic acid, would therefore have a potential beneficial role in these procedures.

Antifibrinolytics

Tranexamic acid (TXA) is a synthetic antifibrinolytic drug released in the 1970s. Although it is similar to the prototypical synthetic antifibrinolytic drug, Σ-amino-caproic acid (EACA), TXA is considered to have ten times the potency of EACA [7]. The mechanism of action for synthetic antifibrinolytics is competitive blockade of the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator [7]. The reversible blockade impedes fibrinolysis and blood-clot degradation [7]. Plasmin inhibition by TXA may also help prevent platelet degradation. Relative to EACA, TXA has higher and more sustained antifibrinolytic activity in tissues, but both have a similar toxicity profile [7]. Although TXA would appear to be the synthetic antifibrinolytic drug of choice, both drugs may be beneficial in states where there is an excess of fibrinolysis relative to the coagulation cascade.

The half life of TXA is approximately 80 min, provided there is normal renal function. A wide range of TXA dosing has been advocated, depending on the indication. Oral and topical applications of TXA have been used peri-operatively, but the majority of studies use intravenous TXA. Bolus and infusion dosing again vary, but pharmacokinetic evidence would suggest the use of 10–15 mg/kg loading dose, followed by an infusion dose of 1 mg/kg per h or repeated bolus dosing [10]. Dosage adjustments are recommended in patients with renal insufficiency.

TXA has been safely used in many different situations where it has beneficial effects. Nonsurgical uses of TXA include the management of bleeding associated with leukaemia, ocular bleeding, recurrent haemoptysis, menorrhagia, hereditary angioneurotic angio-oedema and numerous other medical problems. The prophylactic administration of TXA reduces both blood-transfusion requirements and the financial cost of cardiac surgery [6, 14]. Interest in TXA for orthopaedic surgery was rekindled in part by the work of Hiippala et al. who explored the use of the drug for total knee arthroplasty [8]. In this prospective double-blind study, 75 patients scheduled for 77 total knee arthroplasty were randomized to receive either TXA or saline. A TXA bolus dose of 15 mg/kg was given intravenously before deflation of the tourniquet, followed by two 10 mg/kg additional doses given postoperatively. Blood transfusions were used to keep haemoglobin levels above 10 g/dl. The results from Hiipala et al. demonstrate a significant reduction in estimated total blood loss (689±289 ml versus 1509±643 ml). The use of TXA reduced the mean number of transfused red cell units in the TXA group (1.0±1.2) compared to the placebo group (3.1±1.6), which was significantly different ($P<0.0001$). Subsequent to this study, numerous other studies support the premise that TXA reduces blood loss and, more importantly, significantly reduces transfusion rates [2, 11, 25]. A meta-analysis of studies using TXA for total knee arthroplasty supports the premise that it reduces total blood loss and reduces both the proportion of patients requiring allogeneic blood transfusion and the total number of units of allogeneic blood transfused [9]. The use of TXA does not increase the risk of thromboembolic complications such as deep-vein thrombosis, pulmonary embolism, thrombotic cerebral vascular accident, or myocardial infarction [9, 11, 25]. Intravenous TXA thus appears to be both safe and effective in reducing allogeneic blood transfusion and blood loss in total knee arthroplasty. In contrast to the substantial evidence supporting the use of TXA for total knee arthroplasty, there have been a limited number of studies that have investigated the role of TXA and the other antifibrinolytics for major spinal surgery.

Urban et al. assessed the efficacy of two different antifibrinolytics to reduce peri-operative blood loss for adult patients undergoing complex spine reconstructive surgery [24]. Sixty patients undergoing anteroposterior spinal fusion were randomly assigned to EACA, aprotinin, the natural antifibrinolytic, or placebo. A 5-g load of EACA was administered, followed by an infusion of 15 mg/kg per h. Patients received scavenged blood once they were processed. Stored blood products, both autologous and allogeneic blood units, were transfused to maintain haemoglobin above 8 g/dl. Although both drugs reduced total blood loss and transfusion requirements, only aprotinin reached significance levels. There was no increase in thrombotic complications in either of the treatment groups.

Florentino-Pineda et al. evaluated the use of EACA for paediatric patients undergoing posterior spinal fusion surgery for idiopathic scoliosis [5]. Twenty-nine patients were consecutively assigned to EACA at a dose of 100 mg/kg (up to 5 g) intravenous load, followed by 10 mg/kg per h for the duration of surgery. Thirty-one consecutive patients formed the control group. Transfusions were performed to maintain a haemoglobin above 7 g/dl or in response to several predefined clinical criteria. The EACA patients had significantly lower intra-operative and postoperative blood loss than the control group. The total number of units of blood transfused was also significantly lower in the EACA group. There were no complications associated with the use of EACA. Unfortunately, the results of the study are limited by the use of a historical control.

Adult patients with malignancies undergoing surgery for pelvic, extremity, or spine surgery were randomly assigned to aprotinin, EACA, or placebo [1]. The patients assigned to EACA received an intravenous loading dose of 150 mg/kg, followed by 15 mg/kg per h for the duration of surgery. Transfusions were administered to keep the haemoglobin above 8 g/dl. The study by Amar et al. found

Table 1 Demographics values. Values are expressed as mean ±SD unless stated otherwise (*TXA* tranexamic acid)

Characteristics	Control (n=18)	TXA (n=22)	P value
Weight (kg)	50.6±20.2	41.8±16.7	0.15
Cobb angle (degrees)	59±16.6	68±21.6	0.15
Scoliosis form (1:2)	8:10	7:15	0.62
Median levels fused (range)	15 (7–18)	14 (8–17)	0.96
Intra-operative blood loss (ml)	2703±1292	2453±1526	0.58
Total blood transfused (ml)	1784±733	1253±884	0.045
Transfused packed cells[a] (ml)	1254±542	874±790	0.08

[a]Transfused packed cells include predonated autologous units, directed donation units, and allogeneic units

no benefit from the use of either drug in regard to blood loss or transfusion requirements [1]. The overall incidence of deep venous thrombosis and pulmonary embolism was not different among the groups. Unfortunately, only 17 of the total number of patients in this study underwent spinal surgery, with 7 receiving EACA, 3 placebo, and 7 receiving aprotinin.

Two studies have investigated the use of TXA for paediatric patients undergoing spinal surgery for scoliosis. An abstract from Dell et al. reported on the use of TXA for idiopathic scoliosis surgery [3]. The preliminary results of 20 patients did not report any differences in intra-operative blood loss or intra-operative transfusion [3]. The second study, conducted by our group, investigated the role of TXA in 40 paediatric patients undergoing posterior spinal fusion for primary and secondary scoliosis [17]. Management was standardized, including the anaesthetic approach, fluid guidelines, and patient positioning. Since the primary outcome was blood transfusion, the most critical component of the study was a uniform transfusion policy for the intra-operative period and the first 24 h after surgery. Transfusions of stored blood, autologous or allogeneic, were given to keep haemoglobin levels above 7 g/dl. The treatment group received a 10 mg/kg intravenous loading dose of TXA, followed by an infusion of 1 mg/kg per h for the duration of the operative period. The control group received a saline placebo.

The TXA group had significantly lower blood transfusion requirements in the peri-operative period (Table 1). The intra-operative blood loss in the TXA group (2453± 1526 ml) was however not significantly different (P=0.58) than the control group (2703±1292 ml). Since the haemoglobin levels measured at the end of surgery and on the first postoperative day were similar, transfusion practice was similar in both groups. Transfusion violations were the same in both groups. TXA was well tolerated with no cases of haemodynamic instability, clinically overt thrombotic complications, or other adverse effects associated with its use.

Although the demographic data of the two groups was not significantly different, the groups were not identical. Generally, the differences put the TXA group at increased risk for peri-operative blood transfusions. Most notably, the greater proportion of patients with secondary scoliosis and lower weight in the TXA group would predispose this group to more peri-operative blood transfusions [1, 13, 26]. Despite these discrepancies, the TXA group still had less blood transfused. Further tests to assess the impact of these potential confounders were conducted with a multivariate analysis. Weight was not significant (P=0.11), but treatment group (P=0.028) and scoliosis form (P=0.001) were significant predictors for total blood transfused.

The lack of difference in operative blood loss should not lessen the significance of the study. Blood loss is often used as a surrogate outcome for transfusion requirements, but the use of surrogate endpoints is not recommended [4, 21]. Also, despite considerable effort, estimating blood loss has been demonstrated to be highly imprecise [18]. The described study was however primarily designed to determine the effect of TXA on the requirement for blood transfusion. Indeed, while studies that use blood loss as the primary outcome are helpful, they may not answer the more clinically important question regarding effects on blood transfusion. The design of future studies should therefore focus upon the effects of antifibrinolytics on blood transfusion rather than blood loss.

The major concern surrounding the use of TXA and other antifibrinolytics is the potential for an increase risk of thrombotic events. No patient in our study experienced a complication from the use of TXA, although no investigations beyond a physical examination and history taking were indicated [17]. No increased thrombo-embolic events occurred in the other spinal fusion studies [1, 5, 24]. The studies examining the use of TXA in patients undergoing total knee arthroplasty also did not experience an increased incidence of deep venous thrombosis [2, 8, 9]. Reports of thrombo-embolic events attributed to TXA are uncommon, occur in the non-operative setting, and are primarily anecdotal in nature. A common misconception is that these drugs are procoagulants and that they will increase blood clotting. The drugs do not alter blood clotting, but instead slow dissolution of blood clots. Sites where clots have formed will therefore remain or enlarge, but spontaneous formulation of clots should not occur. Benoni et al. suggested that TXA was not associated with thrombo-embolic events because the effects of TXA are more pronounced in operative wounds than in the peripheral venous blood [2]. The beneficial effects are believed to probably be due to inhibition of local fibrinolytic activity in the surgical field. TXA has no significant effects on peripheral fibrinolysis or other coagulation variables [2]. Although topical application of TXA theoretically could reduce widespread thrombotic complications, its efficacy and safety for this application are unknown. Although the majority of evidence suggests that TXA can be safely used

in patients undergoing posterior spinal fusion, constant vigilance for deep venous thrombosis is recommended.

Although the prevention of complete exposure to allogeneic blood products was not the primary outcome of the aforementioned studies, a beneficial reduction in blood transfusion would suggest that patients would be exposed to less allogeneic blood. Although the infectious and immune-suppressing risks of blood transfusions have been reduced in recent years, risks still remain [12]. Reduced allo-immunization to foreign antigens is important in paediatric patients and especially so in female patients [22]. These risks, along with recurrent shortages of allogeneic blood products, warrant the consideration of using of TXA for major spinal surgery. The cost of TXA ($CAN 29) is considerably less than the cost of one allogeneic unit ($CAN 210) or an autologous unit ($CAN 338) [23]. The potential advantages of TXA for posterior spinal fusion are considerable even if complete prevention of allogeneic exposure does not occur.

In conclusion, emerging evidence supports the safe use of tranexamic acid and other antifibrinolytics for the prevention of blood transfusion for major orthopaedic procedures. Although the benefit and safety of tranexamic acid in patients undergoing major spinal fusion have yet to be thoroughly established, tranexamic acid appears to have a potential beneficial role in the management of such procedures. Hopefully, future studies will clarify the exact role tranexamic acid has in spine surgery.

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Controlled hypotension for spinal surgery

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Abstract Controlled, deliberate hypotension during anesthesia for major spinal surgery reduces intraoperative blood loss and transfusion requirement. Hypotension may be achieved with increased doses of volatile anesthetic agents or by continuous infusion of vasodilating drugs. Safe application of this technique requires knowledge of the physiology of hemorrhagic shock and close intraoperative monitoring to avoid vasoconstriction and end-organ ischemia.

Keywords Spinal surgery · Deliberate hypotension · Posterior ischemic optic neuropathy · Review

Introduction

Controlled, or deliberate, hypotension has been used for many years as a means of reducing intraoperative blood loss and facilitating surgical exposure. Reduced intraoperative blood pressure leads to a direct reduction in bleeding from surgically injured arteries and arterioles. Venous dilation, in turn, decreases venous bleeding, especially from cancellous bony sinuses that do not collapse when transected. Decreased bleeding improves surgical visualization of the wound, resulting in faster surgeries (in some series) and, thus, further reducing transfusion dependence. Anecdotal reports describing this technique have been published since the 1970s [14, 18], and there have been a number of prospective trials demonstrating the efficacy of deliberate hypotension, alone or in combination with other techniques, at reducing the blood loss and transfusion requirement of major spinal surgery [12, 13, 14, 15, 16, 17, 18, 19, 20].

Because of its simplicity, deliberate hypotension is a widely used technique. The physiology of hemorrhage is complex, however, and the potential consequences of this approach are not always readily apparent. The ischemic threshold for individual patients (and individual organ systems) cannot be defined prospectively and is not indicated by any existing operating room (OR) monitor. Further, differences in tissue perfusion that are related to different methods of achieving hypotension (anesthetic agents vs pure vasodilators, for example) are not fully understood. Recently published cases describing the occurrence of blindness after spinal surgery have highlighted the potential risks of deliberate hypotension. These have led to renewed interest in determining how broadly this approach can be applied, and what levels of hypotension over what periods of time will be safe for the majority of patients.

Physiology of hemorrhage

Loss of circulating blood volume produces a cascade of physiologic effects intended to preserve perfusion of the heart and brain at the expense of more peripheral organs. Shock is the clinical term for the physiologic disease of hypoperfusion. It is a common finding in patients with on-

going hemorrhage. In the un-anesthetized individual, hemorrhage leads directly to vasoconstriction, with blood pressure falling little until the limits of compensation are exceeded (usually at a total blood loss of 30–40%) [7]. Cardiac output is maintained initially by increased heart rate and contractility, but this may fall substantially before a change in blood pressure occurs. While severe hemorrhage is fatal through the obvious mechanism of decreased cerebral perfusion, lesser degrees of blood loss may still cause death through the accumulated effects of end-organ hypoperfusion, manifesting as the syndrome of multiple-organ-system failure. The "dose" of sub-acute shock is defined by the degree of organ-system hypoperfusion and the length of time it is sustained. Fatal subacute shock occurs as the result of too great a failure of peripheral oxygen delivery. Because blood pressure may be sustained by vasoconstriction, even in the face of severe fluid volume loss, this marker in isolation is not a good indicator of the presence or absence of shock and the potential for ischemic injury [5].

Anesthetic agents, particularly induction drugs and volatile gases, interfere with the normal response to hemorrhage. As direct vasodilators, they prevent or reverse compensatory vasoconstriction. Anesthetic agents also inhibit sympathetically mediated increases in heart rate and contractility. This effect makes accurate assessment of the patient's fluid-volume status both easier and harder. On the one hand, anesthetic inhibition of vasoconstriction will create a more direct link between central filling pressures and blood pressure, meaning that blood loss will more rapidly produce hypotension than in the awake patient with active compensatory mechanisms. On the other hand, decreases in blood pressure that result from decreased intravascular volume may be erroneously attributed to the effects of anesthetic agents, delaying the recognition and treatment of hypovolemia. Hypotension in the operating room must therefore be assessed in terms of both fluid-volume status and anesthetic depth. The patient who is hypotensive primarily from blood loss is very different physiologically from one who is hypotensive due to anesthetic overdose [9]. The former patient is vasoconstricted, with low cardiac output and low blood flow. This patient is at much greater risk for ischemic complications than the patient who is hypotensive due to vasodilatation, who is in a high-flow state with preservation of peripheral oxygen delivery. Blood loss may also be affected by vasomotor tone, independent of blood pressure. Techniques that produce vasodilatation, such as epidural anesthesia, have been reported to reduce blood loss during orthopedic operations, even when normotension is maintained [21]. The goal of minimizing surgical hemorrhage by keeping the blood pressure low is, therefore, best achieved by the use of agents that produce hypotension through vasodilatation in the presence of adequate intravascular volume, rather than through vasoconstriction due to under-replacement of fluid-volume losses.

Monitoring

The anesthesiologist intending to induce and maintain deliberate hypotension during major spinal surgery must obviously observe the blood pressure closely. An arterial catheter and continuous pressure-monitoring system is strongly recommended; this will also allow for frequent blood sampling for laboratory study. The radial artery is the most common site for arterial line placement, because it is technically easy to access, away from the site of surgery and not the sole blood vessel supplying the hand. Femoral artery cannulation is also possible, but the anesthesiologist must take great care that the line remains patent and functional during prone positioning of the patient for surgery. This is also a concern with radial lines if the arms are to be tucked alongside the patient, as for cervical or high-thoracic procedures. Arterial line placement can occur preoperatively or following induction of anesthesia, depending on the need for close pressure monitoring prior to surgery.

As important to deliberate hypotension as close observation of the blood pressure is an accurate understanding of the patient's fluid-volume status and degree of vasoconstriction. While no single monitor can indicate this with complete reliability, the experienced anesthesiologist will make this assessment based on the integration of several different pieces of data. First is the arithmetic calculation of "ins and outs," the kind and amount of fluid administered and the estimated fluid lost or consumed, including hemorrhage volume, metabolic maintenance, and insensible losses to interstitial edema and atmospheric evaporation. This is an important exercise to perform, particularly for long cases, but is dependent on both visual estimates (blood loss) and crude approximations (interstitial losses). Even when meticulously calculated, paper estimates of fluid requirements often woefully underestimate actual need.

The second critical piece of data is the patient's anesthetic requirement: the total dose of narcotic, volatile, and sedative medication maintaining the anesthetized state. It is seductively easy for the inexperienced practitioner to incrementally reduce the anesthetic dose in response to decreases in blood pressure caused by hypovolemia, particularly in the presence of muscle relaxants that prevent patient movement. This runs the obvious risk of allowing intraoperative patient awareness. Even more insidious, however, this may move the patient to a physiologic state of occult shock, in which severe hypovolemia is being compensated for by catecholamine production and peripheral vasoconstriction. As was indicated above, deliberate hypotension achieved by volume contraction and vasoconstriction puts the patient at higher risk for ischemic complications. The patient's requirement for anesthesia can be established during the early stages of the procedure, prior to significant fluid volume shifts, providing a benchmark for future reference. It is unlikely in any pa-

tient that the appropriate dose of anesthetic agents to balance a given surgical stimulus will be different at the end of the case than it was at the beginning.

A third measure of intravascular volume is the response to fluid administration indicated by direct monitors of central pressure. Central venous pressure (CVP) and pulmonary-artery pressure values in isolation may be difficult to interpret, due to the effects of positive pressure ventilation, prone positioning and anesthetic technique, but serial values over time may be of value. This is particularly true when pressure changes are interpreted following maneuvers likely to change filling volume (increases or decreases in anesthetic depth, fluid administration, bleeding, use of vasoactive agents). If CVP falls during the case, compared to a baseline value established following induction and positioning but prior to hemorrhage, then the patient is most likely hypovolemic. If a fluid bolus increases central pressures but not cardiac output, then the patient is adequately volume replaced. Most commonly, however, fluid administration will increase cardiac output without a significant increase in pressures. This patient has "recruitable perfusion" and – all things being equal – should receive more fluid. In patients with limited cardiac function, an additional variable is added to the equation, and the risk of lowering perfusion through fluid overload and cardiac dysfunction is introduced. Frequent measurement of cardiac output is necessary to guide fluid therapy in these patients, or continuous direct observation of cardiac filling and contractility via trans-esophageal echocardiography.

A fourth way to examine fluid volume is through laboratory assessment of blood chemistry, which should be performed as often as necessary to confirm the adequacy of perfusion. Inappropriately high hematocrit or serum osmolarity indicate hypovolemia, while low hematocrit or elevated coagulation times indicate the need for specific blood products. Acute hypoperfusion will be indicated by development of metabolic acidosis, reflected in the pH and base deficit of the arterial blood gas. Hypoperfusion occurring over a period of time will cause a rise in serum lactate, which correlates well with morbidity and mortality due to hemorrhagic shock [1]. Any evidence of systemic acidosis indicates the need for fluid volume administration to improve tissue perfusion, regardless of whether the blood pressure is low or normal. Elevated lactate, indicating an ongoing "oxygen debt," should be regarded as an extremely serious sign in any elective surgical case, and it should mandate immediate correction of the underlying cause and resuscitation of the patient.

Finally, the anesthesiologist must be attentive to monitors of individual organ-system perfusion. Cardiac dysrhythmias and ST-segment changes have been reported as indicators of ischemia during deliberate hypotensive anesthesia in an animal model [11]. Changes in nerve conduction amplitude and latency are monitored during spinal surgery as indicators of procedure-specific over-distraction of the spinal cord, but global changes may be a warning sign of systemic hypoperfusion. Decreases in urine output indicate decreased renal perfusion, while failure of the pulse oximeter may indicate progressive systemic vasoconstriction. Mixed venous oxygen saturation is a very sensitive marker for the adequacy of perfusion, but is seldom available in the operating room. A fall in end-tidal carbon dioxide concentration is a late indicator of severe hypoperfusion, most likely to occur just moments before complete cardiovascular failure.

Pharmacology

Understanding the physiology of hemorrhage and the necessary monitoring to induce and maintain hypotension safely will allow the experienced provider to apply this technique to most spinal surgery patients. The specific agents used to induce hypotension are almost a secondary consideration, but there have been numerous publications examining the options and attempting to define a difference between the choices. The first level of discrimination is between, on the one hand, those agents that are primarily anesthetics but are capable of producing hypotension, and, on the other hand, those agents that are purely vasoactive.

Anesthetic agents used to induce deliberate hypotension in current practice include the volatile gases (isoflurane, desflurane and sevoflurane) and intravenous sedative medications (thiopental and propofol). For pelvic and lower extremity orthopedic surgery, epidural administration of local anesthetics is a common choice. While adjuvant epidural anesthesia has been used in the past for major spinal surgery, this technique is uncommon today, both because of the technical challenges involved and because of its interference with neuromonitoring and postoperative neurologic assessment. Interference with the ability to measure and compare somatosensory or motor evoked potentials is the principal limitation to using any anesthetic agents to produce hypotension. Pentothol, in fact, is commonly used in patients undergoing complete circulatory arrest or with severe traumatic brain injury as a means of reducing neurologic activity to the lowest possible level [23]. Further, both pentothol and propofol reduce blood pressure in large part through a direct, negative inotropic effect on the heart, which may be less desirable physiologically. The volatile gases produce hypotension mostly through vasodilatation [16], and thus may be more effective at reducing intraoperative blood loss [26]. There is little to discriminate among the different volatile agents in terms of efficacy, although desflurane and sevoflurane may be easier to titrate, due to their faster onset and elimination [2]. Isoflurane begins to depress evoked potentials at a concentration of about 1% (1 MAC) in most patients, but there is substantial variability in this value [25]. Use of volatile gases to produce deliberate hypotension can be

facilitated by the administration of intravenous narcotics to blunt the patient's sympathetic response. Although narcotics have no direct cardiovascular effect and will not produce hypotension as the sole agent in a euvolemic patient, they will potentiate the effects of other anesthetics, allowing a lower blood pressure to be achieved for a given concentration. Deliberate hypotension for spinal surgery is, thus, most commonly achieved by the use of increased concentrations of a volatile agent (typically isoflurane) on top of a balanced general anesthetic.

When higher concentrations of volatile agent are contraindicated, either due to interference with neuromonitoring or to some other patient characteristic, there are a number of other agents that can be used to induce and maintain hypotension. Examples include sodium nitroprusside (SNP), nitroglycerin, trimetaphan, esmolol, nicardipine, and fenoldopam. In the presence of an adequate general anesthetic, any of these agents offers the ability to titrate the patient's blood pressure to any desired level of hypotension, maintain it that way throughout the surgery, and allow it to rapidly return to normal at the end of hemorrhage. Historically, SNP has been the model for direct vasodilatation, but concerns over cyanide toxicity resulting from long periods of administration led first to its combination with the ganglionic-blocking agent trimetaphan [19], and more recently to its abandonment in favor of newer agents. Esmolol (a rapid-acting, beta-blocking agent) and nicardipine (a rapid-acting, calcium channel-blocking agent) have both been used by continuous infusion to maintain hypotension [3]. Each acts through a combination of vasodilatation and negative inotropy. Recent literature examining regional blood flow has suggested that the physiology of hypotension induced by nicardipine may be different than that produced by volatile anesthetics. This implies a variable response on the microcirculatory level [17]. Fenoldopam is a dopaminergic agonist that could in theory preserve splanchnic and renal blood flow during deliberate hypotension, but experience with this agent is still limited [15, 27].

Risks

While deliberate hypotensive anesthesia has a long record of safety, there are a few potential risks that the anesthesiologist must be aware of. Hypotension makes the patient more susceptible to cardiac arrest if a sudden surgical catastrophe, such as massive hemorrhage or tension pneumothorax, occurs. More worrisome for the anesthesiologist is the risk of an ischemic complication that occurs despite the successful application of the planned technique. Because the ischemic threshold of individual organs is impossible to estimate, and because monitoring of perfusion is indirect at best, there have been occasional case reports of complications noted following uneventful anesthetics [22].

New onset or worsening of neurologic deficit below the level of surgery may result from direct injury or overdistraction of the spinal cord, hypoperfusion, or a combination of the two. Continuous electrophysiologic monitoring of either the anterior spinal cord (motor evoked potentials) or posterior cord (somatosensory evoked potentials) is the standard of care for most complex spinal surgeries, and is a sensitive monitor of physiology. Baseline values are obtained prior to anesthetic induction and following surgical positioning. Increase in latency or amplitude of electrical response from baseline should be promptly investigated, and the cause corrected if possible. Electrical evidence of decreased spinal cord function should lead the provider to abandon the hypotensive technique, accepting the potential for increased hemorrhage in exchange for maximizing perfusion.

Myocardial ischemia or infarct is rare following hypotensive anesthesia, and is usually the result of unrecognized hypovolemia and vasoconstriction, anemia, occult coronary disease, or a combination. Sudden desaturation has been described during deliberate hypotension [4], which may put vulnerable patients at risk. Risk factors for decreased myocardial reserve, such as advanced age, diabetes, atherosclerosis, or resting hypertension, are all relative contraindications to deliberate hypotension. These patients may already have flow-limited myocardial perfusion, as well as altered autoregulatory thresholds in other organ systems.

There have been a number of reports describing the development of unilateral or complete visual loss following spinal surgery in the prone position, including a recent presentation by the Anesthesia Closed Claims Project of the American society of Anesthesiologists [8, 13, 22, 28]. Originally thought to be due to pressure on the eye due to careless prone positioning (anterior ischemic optic neuropathy, AION) [25], most cases of blindness are now recognized as the result of posterior ischemia (PION), due to hypoperfusion of the optic nerve [8, 13, 22]. Analysis of published case reports and closed claims suggests that risk factors for this disastrous complication include prolonged surgery, hypotension, and anemia, often in combination. The development of a vasoconstricted – shock – state due to unrecognized hypovolemia is an important risk factor, emphasizing the importance of monitoring tissue perfusion and not just blood pressure when employing a deliberate hypotensive technique.

Summary

The author's recommendations for the conduct of deliberate hypotensive anesthesia are shown in Table 1. While deliberate hypotension has been repeatedly shown to reduce transfusion requirement during major spinal surgery, alone or in combination with hemodilution, cell salvage, erythropoietin administration and other techniques, the risks

Table 1 Recommendations for deliberate hypotensive anesthesia (*CVP* central venous pressure, *SSEP* somatosensory evoked potentials, *PA* pulmonary artery)

Patient selection	Patients scheduled for multilevel or complex spinal surgery with an anticipated risk of homologous blood transfusion
Contraindications	Patients with altered baseline autoregulatory mechanisms (hypertension) or those likely to be vulnerable to ischemic complications (diabetes, coronary artery disease, stroke, chronic renal failure, etc.)
Monitoring	Standard monitors, plus continuous arterial pressure catheter, neurophysiologic monitor (SSEP or motor evoked potential), and monitor of intravascular volume (CVP or PA catheter). Frequent laboratory assay is indicated to monitor hematocrit, coagulation factors, and markers of tissue hypoperfusion (base deficit and lactate)
Positioning	Careful attention to all pressure points, with special attention to the face and eyes. If the arms are to be tucked out of sight, access lines and monitors must be carefully secured
Anesthesia	Balanced general anesthesia using narcotics and inhaled volatile agents. The patient's anesthetic requirement should be established prior to the induction of deliberate hypotension, and used as a baseline for subsequent judgment of volume status
Technique	During surgical dissection and implantation of hardware, maintain systolic blood pressure 20–30% below baseline (80–90 mmHg in normal patients) using (1) an increased concentration of volatile gas or (2) continuous infusion of a rapid-acting vasodilator
Cautions	Deliberate hypotension should be abandoned in the presence of changes in nerve conduction signals, decreased urine output, EKG changes, anemia (HCT <20%) or tissue acidosis

are still difficult to quantify. There are some patient groups, such as Jehovah's Witnesses, in which it may be life-saving [6]. Direct assessment of microvascular perfusion in individual organ systems is not possible, making any decision to deliberately induce hypotension a judgment between the small but serious risks of ischemic complications such as PION or MI and the larger but less severe risks of transfusion. Based on current literature and clinical practice, moderate degrees of hypotension (80–90 mmHg systolic) are efficacious at reducing blood loss, and safe in any patient without specific risk factors. When employing a deliberate hypotensive technique, the anesthesiologist must be mindful of the physiology of hemorrhage and shock, attentive to direct and indirect markers for hypoperfusion, and responsive to ischemic risk factors such as prolongation of surgery, sudden blood loss, and anemia.

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Acute normovolemic hemodilution

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Abstract Patients and physicians continue to be motivated to find methods to reduce the use of allogeneic blood. Even though donor screening has increased the safety of donated blood products, autologous blood is the most desirable source of red cells during the perioperative period. The methods commonly used to obtain autologous blood during the perioperative period can be initiated prior to the operative procedure (autologous preoperative donation, acute normovolemic hemodilution) or during surgery (cell scavenging). Acute normovolemic hemodilution (ANH) involves a controlled removal of whole blood immediately prior to the operation. The patient's intravascular volume is maintained with solutions that contain non-red cells. The operative procedure is conducted with a normal blood volume, but with a reduced red cell mass. At the conclusion of the operation, the stored autologous blood is restored to the patient. If operative blood loss is not excessive, the replacement of autologous blood may provide an acceptable red cell mass. In addition to surgical blood loss, some of the key factors in determining how effective acute normovolemic hemodilution will be in limiting allogeneic transfusion are: the patient's initial hematocrit and blood volume; the volume of autologous blood removed prior to the operation; the effectiveness of the hemodilution; and the timing of autologous blood replacement. In contrast to autologous pre-donation, autologous blood removed during acute normovolemic hemodilution is usually stored and re-infused in the operating room.

Keywords Acute normovolemic hemodilution · Surgery · Blood loss

Introduction

Strategies to reduce requirements for transfusion during surgery continue to be a high priority in clinical care. The long-term sequelae of blood transfusion such as latent viral or transfusion-transmitted infectious disease continue to be a source of concern to patients and physicians. Acute normovolemic hemodilution is one of the strategies used to reduce the need for blood transfusion.

The current approach to reducing blood transfusion during major surgery can be broadly divided into methods that decrease operative blood loss and methods that provide autologous red cells. The methods that reduce blood loss include: deliberate hypotension; the injection of local vasoconstrictive agents at the operative site; and systemic pharmacologic agents for reducing blood loss, such as aprotinin, aminocaproic acid, tranexamic acid and desmopressin. Autologous red cells can be obtained either prior to the operation or during the operation. Autologous preoperative donation via a blood bank or acute normovolemic hemodilution are two techniques that are used prior to the operation to obtain autologous blood. Cell scavenging provides autologous red cells by scavenging blood from the operative field. These strategies may be used in combination during the operation to reduce or eliminate the need for allogeneic transfusion.

Acute normovolemic hemodilution (ANH) reduces red cells lost during the operation by decreasing the patient's red cell mass immediately prior to operation [6, 9, 11, 13]. The first step in ANH is the acute, controlled removal of whole blood. The patient's intravascular volume is maintained with non-red-cell-containing solutions during the phlebotomy. The operative procedure is conducted in a hemodiluted patient. During the operation, fewer red cells (as well as formed elements) are lost because the patient's hematocrit is lower throughout the procedure. The autologous blood is reinfused at the conclusion of the operation. If the volume of red cells stored prior to operation is adequate and the operative blood loss does not result in profound red cell losses, then an acceptable hematocrit may be achieved without the use of allogeneic transfusion. While the amount of surgical blood loss is not appreciably changed by the use of hemodilution, fewer red cells will be lost due to the patient's acute anemia.

Critical red cell mass

One of the key concepts in applying hemodilution is to define a patient's "safe" lower limit for hematocrit [3, 10]. Healthy patients have a considerable usual reserve of red cells. This reserve is the principle reason that the acute removal of blood in the preoperative period is a viable therapeutic option. In ANH, patients experience two sources of red cell loss, the blood loss associated with hemodilution and operative blood loss. For this reason, a relatively profound anemia is expected during the operative procedure. Although the acute anemia associated with hemodilution is considerably different from anemia observed in clinical practice, the lowest safe red cell mass defined for anemic patients can be applied to guide acute normovolemic hemodilution. An abundance of case reports indicate patients can survive with extremely low hematocrits, but these anecdotal case reports are unlikely to provide a consistent "safe" lower limit of hematocrit [15].

The safe lower limit of hematocrit continues to be debated, yet an appreciation of the factors that define the lower limit of safety for red cell mass is an important consideration in implementing a hemodilution program. Critical red cell mass is the lower limit of hemoglobin associated with effective oxygen delivery. When cardiorespiratory compensatory mechanisms can no longer maintain effective oxygen delivery, a critical red cell mass exists. Anaerobic metabolism and/or tissue ischemia will occur when the red cell mass remains below this critical level. The critical red cell mass is reached first in tissue groups such as the myocardium and central nervous system, because a greater proportion of oxygen extraction occurs in the coronary or cerebral circulation under normal circumstances. The myocardium is particularly sensitive to decreased oxygen availability, because systemic compensatory responses to reduced red cell mass increase cardiac output. This higher cardiac output leads to increased myocardial work and heightened myocardial oxygen requirements. The increased cardiac energy expenditure puts additional demands on myocardial oxygen reserve at a time when oxygen supply is limited due to anemia. At hematocrits less than 20%, myocardial metabolism may be compromised by the decreased supply and heightened oxygen demand. Subendocardial ischemia and myocardial infarction can occur in healthy patients with normal coronary arteries when hematocrits are less than 15%. These changes are often manifested by EKG changes with ST segment elevation. In the liver and kidneys, centrilobular hepatic necrosis and acute renal failure may occur when hematocrits are sustained at hematocrit levels less than 15%.

Hemodilution to relatively low hematocrits may be better tolerated, because the period of anemia is brief and oxygen requirements are reduced by anesthesia. For this reason, hematocrit values of less than 20% are often recorded in a hemodiluted patient during the intraoperative period. If blood loss is replaced with crystalloid and replacement is withheld until a hematocrit of 20% is observed, then more than one-half of a patient's blood volume could be removed by a combination of hemodilution and operative blood loss prior to replacing red cells.

Factors determining efficacy of hemodilution:

1. Red cell mass. Patients with greater red cell masses can donate more blood. Red cell mass is based on hematocrit and blood volume
   a) Initial hematocrit: Patient's with higher hematocrits are able to provide more red cells for storage prior to the operation. The patient's beginning hematocrit and blood volume are key factors in estimating the amount of blood that should be removed prior to surgery
   b) Blood volume. Blood volume increases with weight. The "ideal" 70-kg male has approximately a 5-l blood volume. Females have a slightly lower blood volume on a weight basis. For example, a 55-kg, adolescent female's blood volume would be approximately 3,500 ml (55 kg × 60–65 ml/kg)
2. Magnitude of hemodilution. When lower hematocrits are achieved following hemodilution, less red cell loss will occur as a result of surgical blood loss. For this reason, the more blood removed prior to the operation the greater potential efficacy in reducing red cell losses. However, at the same time, this hemodilution leads to more profound hemodynamic consequences. If more blood is removed, the operative hematocrit will be lower, and, consequently, fewer red cells will be lost during surgical dissection. For example, a profound hemodilution (four units of whole blood in a 70-kg healthy patient) requires the administration of large volumes of non-red-cell-containing solutions to main-

Table 1 Theoretical hematocrit changes expected prior to, during and following operation in three groups of patients. The patients are assumed to be 70 kg with a starting hematocrit of 40%. Patients' experience 1,500 ml of blood loss during the operation and another 500 ml of blood loss in the post-operative period

Treament groups	Pre- Op	Hemodilution (withdrawal)	Postoperative (1,500 ml blood loss)	Hemodilution (replace)	500 ml postoperative blood loss
No treatment	40%	–	30%		26%
Hemodiluted (2 units)	40%	32%	24%	32%	30%
Autologous (2 units)	36%*	–	26%		32%*

*Autologous donors have lower hematocrit prior to surgery. Timing of blood replacement for autologous donors is in the period following operation (after intraoperative and postoperative blood loss)

tain normovolemia. A more moderate degree of hemodilution (two units) may be more safely used, but may not be as effective in reducing red cell losses. This balance between the magnitude of hemodilution employed and theoretic red cell losses can be calculated by predicting changes in red cell mass with different levels of hemodilution (Table 1) [4, 8]

If a 70-kg patient with a hematocrit of 40% has four units of blood removed prior to operation, the operation begins after normovolemia is reestablished in a patient who has a hematocrit approximately 25%. If the operative blood loss is 1,500 ml, then intraoperative hematocrit reaches a nadir of less than 20%. Following replacement of the four units of stored blood, hematocrit is restored to a hematocrit of 34%. If the same patient had only two units stored, then hematocrit following operative blood loss of 1,500 milliliters would reach a lower limit of approximately 24%. Following replacement of the two units, then hematocrit would be restored to 31%. In contrast, if no hemodilution were used during the procedure, then the hematocrit following operative blood loss would be approximately 28%

3. Intraoperative blood loss. The most obvious main determinant of red cell loss is blood loss during the operation
4. Intraoperative management. If normovolemia is not effectively reestablished and maintained following removal of the autologous blood, then the procedure offers no benefit in terms of reducing red cell losses. In the absence of hemodilution, operative blood loss would occur at the higher preoperative hematocrit level. The timing of red cell replacement is another factor that influences the effectiveness of ANH. When the stored blood is replaced after the operative blood loss, then the patient will experience the least red cell losses. From a safety perspective, occasionally, blood removed prior to operation may need to be transfused to treat severe anemia during the operation

Special considerations for hemodilution

From a clinical management perspective, patients experience two sources of blood loss, the blood loss associated with hemodilution and operative blood loss. For this reason, larger volumes of crystalloid or colloid solutions will be required during the intraoperative period [6, 11, 13]. These changes in intravascular volume may need to be more closely monitored during the procedure to assure intravascular volume is maintained throughout the operation. If the patient is hypovolemic (i.e., hemoconcentrated), more red cells will be lost and hemodilution will be less effective in achieving a higher postoperative hematocrit. Postoperative edema is a frequent consequence of the need to maintain normovolemia with crystalloid and colloid solutions.

Intraoperative hematocrits of less than 20% are often encountered during hemodilution (Table 1). The lower hematocrits observed during the operation may demand additional cardiovascular monitoring. This monitoring provides a means to assess the impact of the lower hematocrit on systemic function. Invasive hemodynamic monitoring also establishes vascular access to frequently measure blood chemistry and pH. Serial hematocrits and arterial blood gases help confirm blood loss estimates, evaluate fluid replacement and provide information about adequacy of oxygen delivery. Persistent tachycardia and electrocardiogram changes suggestive of myocardial ischemia are often the first signs of inadequate oxygen delivery as a result of anemia. The decreased blood viscosity associated with hemodilution often decreases blood pressure. Consequently, profound hemodilution probably should not be combined with other techniques such as deliberate hypotension that also decrease tissue oxygen delivery.

Comparison of hemodilution, autologous donation and red cell scavenging

Autologous pre-donation of blood and intraoperative red cell scavenging are two techniques frequently compared to acute normovolemic hemodilution. These techniques share a common strategy of providing autologous blood source during the perioperative period. A theoretical comparison of autologous donation, ANH and no replacement is provided in Table 1.

Autologous donation was enthusiastically endorsed 20 years ago, but the decreasing risk of allogeneic blood

has led to a reevaluation of this approach to reducing allogeneic blood transfusion. A variety of studies have concluded autologous donation may not be a cost-effective strategy, primarily because of the reduced infectious risk of the current volunteer donor blood pool. The main limitations of autologous donation relate to efficacy, cost-efficacy and patient preference. In surgical patients, the factors that influence the efficacy of autologous donation include: the frequency of patient participation, whether autologous donors avoid allogeneic blood use, and the proportion of autologous blood that is reinfused used during the perioperative period [1, 2, 7, 13].

Autologous donation does offer some advantages to ANH, because the blood donation occurs in the weeks prior to operation. Unlike ANH, autologous donors will not require the larger volumes of crystalloid or colloid intravascular volume replacement to reestablish normovolemia. The delay between collections of autologous blood may effectively replace some of the autologous red cells removed preoperatively, but most autologous donors are unable to effectively restore a pre-donation hematocrit [5, 12]. An additional advantage of pre-deposit autologous blood is that the units can be reinfused at any time during the perioperative period (Table 1). The primary reason that blood replacement is necessary is the postoperative loss of red cells into drains or the surgical wound. Unlike ANH or cell scavenging techniques that are primarily an intraoperative method to return autologous blood, pre-donated autologous blood can usually be stored until later in the postoperative period. On the other hand, the use of a blood bank exposes autologous donors to the numerous sources of iatrogenic errors that are associated with collecting, labeling, storing and checking a patient's autologous blood. These clerical errors are the most common serious complications associated with the use of a blood bank.

Red cell scavenging from the operative site is also an effective method to preserve red cells [14]. The yield of red cells from blood lost during an operation is dependant on factors such as the amount of damage that occurs during the process of scavenging. In orthopedic procedures, a considerable proportion of red cells may be damaged during the collection and washing of the red cells.

In summary, acute normovolemic hemodilution allows patients to tolerate moderate degrees of blood loss without the requirement for allogeneic blood. The technique is an effective method to store autologous red cells prior to the operation and return the blood at a time when surgical blood loss has abated. The main advantage of ANH is that the technique can be used intraoperatively, without the need for long-term blood storage and testing. In order for hemodilution to reduce red cell losses, normovolemia must be maintained throughout the intraoperative period.

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Hemoglobin substitutes

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Abstract Orthopaedic patients frequently require blood transfusions to treat peri-operative anemia. Research in the area of hemoglobin substitutes has been of great interest since it holds the promise of reducing the reliance on allogeneic blood transfusions. The three categories of hemoglobin substitutes are (1) cell-free, extracellular hemoglobin preparations made from human or bovine hemoglobin (hemoglobin-based oxygen carriers or HBOCs); (2) fluorine-substituted linear or cyclic carbon chains with a high oxygen-carrying capacity (perfluorocarbons); and (3) liposome-encapsulated hemoglobin. Of the three, HBOCs have been the most extensively studied and tested in preclinical and clinical trials that have shown success in diminishing the number of blood transfusions as well as an overall favorable side-effect profile. This has been demonstrated in vascular, cardiothoracic, and orthopaedic patients. HBOC-201, which is a preparation of cell-free bovine hemoglobin, has been approved for clinical use in South Africa. These products may well become an important tool for physicians treating peri-operative anemia in orthopaedic patients.

Keywords Hemoglobin substitute · HBOC · HBOC-201 · Perfluorocarbons

Introduction

Considerable progress has been made in recent years in understanding the biochemical properties and clinical efficacy of hemoglobin substitutes. Cell-free bovine hemoglobin was approved for clinical use in South Africa in 2001, and active clinical trials using the same product are well underway internationally, including in the United States. This technology will likely prove to be a useful adjunct in treating anemia following major orthopaedic surgery.

Blood requirements in orthopaedic surgery

The impetus to develop hemoglobin substitutes stems from the fact that allogeneic blood transfusions are frequently required for surgical patients. Approximately two-thirds of all transfusions in the United States are related to surgical procedures [12]. The average hemoglobin drop is 3.85±1.4 g/dl for single total knee replacement, 4.07±1.74 g/dl for total hip replacement, and 5.42±1.8 g/dl for bilateral knee replacement [13]. Bierbaum et al. prospectively evaluated 9,482 patients undergoing hip or knee arthroplasty and found that 30% received autologous blood and 16% received allogeneic blood during the post-operative period [3]. The risk factors associated with the need for allogeneic transfusion were a lack of autologous blood and a pre-operative hemoglobin below 13 g/dl. Of 8,561 patients whose pre-operative hemoglobin was known, 3,020 (35%) had a level of 13 g/dl or below. Of these 3,020 patients, 29% required allogeneic blood transfusion. It bears mention that the incidence of anemia is correlated with increasing age [2], so that older patients undergoing orthopaedic procedures are more likely to need allogeneic transfusions.

Complications of allogeneic and autologous blood transfusion

Both allogeneic and autologous blood transfusion have inherent complications that make it desirable to avoid them if possible. While allogeneic blood is safer than it has ever been, the risk of acquiring an infectious agent from a transfusion is still a concern for patients and their physicians. All donated blood undergoes testing for ABO group, Rh type, antibody screen, hepatitis B surface and core antigens, hepatitis C, HIV-1 and HIV-2, human T-cell lymphotropic virus (HTLV) -1 and HTLV-2, and syphilis [7]. Despite this testing, there is a small incidence of viral transmission with an allogeneic blood transfusion [18]. This is estimated at 1:180,000 for Hepatitis B, 1:1.6 million for Hepatitis C, and 1:1.9 million for HIV. In addition to viral transmission, bacterial contamination of blood products is possible. It is estimated that septic complications caused 16% of the 182 transfusion-associated fatalities reported to the US Federal Drug Administration (FDA) between 1986 and 1991 [18]. Only 28% of these fatalities followed red blood cell (RBC) transfusions; the rest occurred after platelet transfusion. With regard to prion-mediated diseases such as Creutzfeldt-Jakob disease, no documented case of transfusion-related prion infection has ever been reported in animals or humans. However, there recently was a case of variant Creutzfeldt-Jakob disease (vCJD) that had a strong possibility of being the result of a blood transfusion, based on probability analysis [1, 17]. There are non-infectious risks of allogeneic transfusion as well [11]. These include transfusion-related, acute lung injury, graft-versus-host disease, anaphylaxis, hemolysis, and post-transfusion purpura. Transfusion-related acute lung injury is a syndrome of dyspnea, hypotension, and pulmonary edema that develops between the beginning of transfusion and up to 4 h afterwards [14]. It appears to be associated with the presence of human leukocyte antigens (HLA) class I and II antibodies, and is fatal in 5–10% of cases. Therefore, allogeneic blood transfusion is associated with several important risks and it remains true that minimizing allogeneic transfusions would be a worthwhile advantage of a hemoglobin substitute.

Although many adverse events are eliminated with preoperative autologous donation (PAD), autologous transfusion still has associated risks. First, there is the potential for patients to develop anemia as a result of repeated phlebotomy, particularly if the last unit of donated blood is given within 15 days of the anticipated surgery [7]. Furthermore, since the patients donating blood are frequently elderly or have medical comorbidities, there is a reported 12-fold increase in the number of post-donation adverse reactions, including hospitalizations, compared to allogeneic blood donors. This risk is higher in the elderly [7]. The complications related to fluid overload and bacterial contamination are still present with autologous blood. Finally, there is the cost and logistic effort involved in collecting the blood as well as the frequent wasting of unneeded units.

The rationale for hemoglobin substitutes

With almost half of all patients undergoing hip or knee arthroplasty requiring a blood transfusion, a reliable safe hemoglobin substitute would give the operative team a viable option in avoiding a transfusion. In addition, hemoglobin substitutes are useful in other patients who suffer from acute anemia, including victims of trauma and patients undergoing vascular or cardiothoracic procedures. A hemoglobin substitute that is stable at room temperature and does not require cross-matching may also be a life-saving measure in ambulances and at the scenes of mass casualties. Finally, a hemoglobin substitute can function as a "bridge," facilitating oxygen transport during the acute phase of blood loss, which allows the hematopoietic system an opportunity to stimulate its production of reticulocytes.

Research in the field of hemoglobin substitutes has led to the development of several substances that seek to reproduce the function of RBCs. Such a product must satisfy several criteria to be useful. First, it must mimic the oxygen-carrying capacity of hemoglobin; as explained below, no product in clinical trials has the exact affinity for oxygen at different oxygen concentrations as does erythrocyte-encased human hemoglobin. Second, it must be safe with a low side-effect profile compared to allogeneic blood transfusion. Third, it must be retained in plasma for a clinically relevant period of time. Finally, it must be cost-effective and convenient in order to achieve widespread use [24].

The physiology of hemoglobin and red blood cells

Familiarity with the structure and physiology of hemoglobin is critical to understanding the potential advantages and drawbacks of hemoglobin substitutes. Synthesis of hemoglobin occurs in the proerythrocyte in the bone marrow and continues in the early stage of the reticulocyte as it is released into the bloodstream [8]. First, the heme molecule is synthesized as the combination of protoporphyrin IX and iron (Fe^{++}). Each heme molecule then combines with a long polypeptide chain called a globin, producing a hemoglobin chain. Four hemoglobin chains bind loosely together to form the whole hemoglobin molecule (Fig. 1). There are slight differences between different globin chains (such as alpha, beta, gamma) based on amino acid sequence. The most common form of adult human hemoglobin is hemoglobin A, which is composed of two α and two β polypeptide chains. Therefore, each hemoglobin molecule has four heme groups that are capable of carrying one molecule of O_2 each. The molecular weight of the hemoglobin tetramer is 64,458. Hemoglobin is able to combine loosely and reversibly with oxygen. The globin subunits in a hemoglobin molecule that is free of oxygen (deoxyhemoglobin) are held together in a configuration that has a relatively low affinity for oxygen [19].

Fig. 1 The hemoglobin tetramer is composed of four globin molecules that form a complex three-dimensional structure

Once an oxygen molecule binds to a heme group, the electrostatic forces between the individual chains relax, leading to exposure of the other oxygen-binding sites and an increased affinity for oxygen. This explains the sigmoid shape of the hemoglobin oxygen-saturation curve. This relationship allows hemoglobin to serve its function of binding oxygen in a high-O_2 pressure environment (the lungs) and releasing it in the low-O_2 pressure peripheral tissues. The affinity of hemoglobin to oxygen is affected by several factors. Hydrogen and carbon dioxide decrease hemoglobin's affinity to oxygen, allowing more oxygen to be released to the end organs. 2,3-diphosphoglycerate (2,3-DPG) in the red blood cell stabilizes the deoxyhemoglobin configuration and reduces the affinity of hemoglobin to oxygen.

Hemoglobin is carried in high concentrations by RBCs, which have a lipid bilayer membrane. This membrane protects the hemoglobin tetramers; without it, the tetramers would quickly dissociate into dimers and monomers, which subsequently get cleared by the kidney [24]. The average RBC carries its hemoglobin for an average of 120 days before being destroyed [8]. This points to a major challenge with extracellular hemoglobin substitutes, namely, the relatively short half-life of the compound compared to allogeneic RBCs. The RBC also prevents the release of heme from hemoglobin, which would be damaging to peripheral tissues. Moreover, hemoglobin contained in the RBC does not get oxidized to methemoglobin, a molecule that is not capable of transporting oxygen and that can cause oxidative damage to surrounding tissues [24].

Development of hemoglobin substitutes

With this in mind, it is possible to understand the various materials that have been developed to reproduce the function of RBC. Three types of products are under development as hemoglobin substitutes. The first and most vigorously studied is hemoglobin-based oxygen carriers (HBOC), which are cell-free hemoglobin preparations using hemoglobin from animals or humans. The second approach is the use of perfluorocarbons, which are cyclic or linear carbon molecules substituted with fluorine. Lastly, liposome-encapsulated hemoglobin has been researched as a way to avoid the shorter half-life of extracellular hemoglobin; this approach is still in the preclinical development stage.

Hemoglobin-based oxygen carriers (HBOC)

Sources and sterilization

HBOCs are produced by lysing human or bovine RBCs, subjecting them to a rigorous sterilization process, and then treating them chemically (e.g., forming polymers) to allow them to be more stable after transfusion. The three potential sources for hemoglobin for hemoglobin substitutes are outdated human RBCs, bovine RBCs and recombinant human Hb. Only 5–10% of donated allogeneic blood becomes outdated and, therefore, the quantity of hemoglobin available from this source may not be sufficient for mass production of hemoglobin substitute [6]. The use of a transgenic pig to produce recombinant human hemoglobin has been reported [25], but this product has not been utilized in clinical trials [24]. Bovine hemoglobin, on the other hand, has no quantity constraints. It is the ingredient in the hemoglobin substitute actively studied in several clinical trials, including one involving orthopaedic surgery patients (Hemopure, Biopure Corporation, Cambridge, MA, USA). Bovine hemoglobin is obtained by lysing bovine RBCs and purifying the hemoglobin. Then, it is subjected to thorough sterilization and viral-inactivation methods that are not possible with whole blood [24].

Modification of hemoglobin structure

The purified hemoglobin is then modified chemically to prolong its durability in the bloodstream. Various manufacturers have accomplished this in several ways depending on different formulations. As described above, hemoglobin tetramer, if infused into the bloodstream, would rapidly dissociate into dimers and monomers, get filtered by the kidney and potentially damage renal tubular cells.

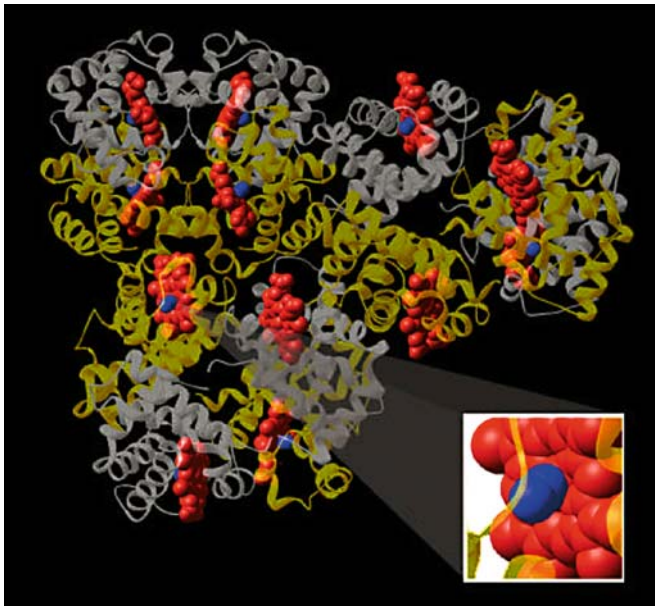

Fig. 2 Schematic representation of HBOC-201. Three bovine hemoglobin molecules are cross-linked to produce the hemoglobin-based oxygen carrier. Each globin subunit carries a blue heme molecule. In turn, each heme molecule is shown as carrying an oxygen molecule (Courtesy of Biopure)

Modification of the chemical structure of the purified hemoglobin prolongs the half-life to 18–58 h [24]. Some formulations stabilize hemoglobin by attaching small molecules such as polyethylene glycol or polyoxyethylene to the lysine residues on the surface of the hemoglobin molecule [5]. This increases the viscosity of the solution and prolongs its half-life. The hemoglobin tetramers can also be induced to form a large polymer of tetramers by reacting with glutaraldehyde [9]. Glutaraldehyde has a free aldehyde group on both ends, allowing it to bond two hemoglobin tetramers and producing a chain of tetramers (Fig. 2). It also forms intramolecular cross-links within each tetramer. Two products, Hemopure (Biopure) and Polyheme (Northfield, Evanston, NJ, USA) are made by polymerizing bovine and human hemoglobin, respectively, using glutaraldehyde. Finally, the α globin units within the hemoglobin tetramer can be cross-linked to each other by molecules such as bis-(3,4-dibromosalicyl) fumarate, producing a tetramer that is more stable in plasma than untreated hemoglobin [4].

Properties of HBOC-201

We would like to describe in more detail the properties of HBOC-201, since it is the only preparation that is approved for use in humans in South Africa, and since it has been tested in international clinical trials with orthopaedic patients. HBOC-201 is a sterile, ultra-purified, glutaraldehyde polymerized bovine hemoglobin in a balanced saline solution. Only cattle from the United States that are 30 months of age or less and that have been certified as disease-free are used as donors. The hemoglobin is sterilized extensively to eliminate RBC stromata, bacterial endotoxins, viruses, and the prions responsible for vCJD and bovine spongiform encephalopathy. The product has an average molecular weight of 250 kD [9]. Its shelf life is at least 2 years when stored at a temperature of 2–30°C. It does not need cross-matching or typing and can be infused directly without reconstitution. Transfusing such a product gives the post-operative anemic patient a large infusion of iron (which is naturally bound to heme), which would help offset the iron lost from surgical bleeding. HBOC-201's oxygen-dissociation curve is right-shifted, with a P_{50} (O_2 pressure at which 50% of oxygen-binding sites are saturated with oxygen) of 43 mm Hg, compared with 27 mm Hg for human hemoglobin. This lower affinity for oxygen allows HBOC-201 to release more oxygen in the peripheral tissues. Moreover, unlike human hemoglobin, whose affinity for oxygen is 2,3-DPG-dependent, bovine hemoglobin's oxygen affinity is chloride-dependent. Since HBOC-201 is an extracellular form of bovine hemoglobin, its affinity for oxygen is in the physiological range because of chloride ions in plasma. Extracellular human hemoglobin, on the other hand, must be modified by pyridoxylation to compensate for the lack of 2,3-DPG in plasma.

Animal and preclinical trials using HBOC

Several investigators have studied HBOCs extensively over the last few years and have shed light on their potential benefits. Hughes et al. [9] drew 15% of the blood volume of 18 healthy volunteers and 23 controls and subsequently transfused different doses of HBOC-201 (test group) or lactated Ringer's solution (control group). They found that, in the test group, there were dose-dependent increases in oxygen-diffusion capacity calculated from pulmonary function tests. The volunteers receiving the highest doses of HBOC-201 had higher diffusion capacity than they did at baseline. The product had a half-life of about 20 h, and it was not eliminated renally. The authors believed that this increased ability to transport oxygen was secondary to enhanced oxygen diffusion from the extracellular hemoglobin, compared with lipid bilayer-encapsulated hemoglobin. Moreover, the oxygen-dissociation curve for HBOC-201 was shifted to the right relative to human hemoglobin, meaning that HBOC-201 was more able to unbind oxygen in the periphery and release it to the target organs. Standl et al. [22, 23] compared HBOC with autologous blood as resuscitation for dogs after massive blood loss. They found that the increase in skeletal muscle tissue oxygen tension per gram of transfused hemoglobin was higher after HBOC transfusion than after autologous RBC transfusion. They attributed this to better

extraction of oxygen in the peripheral tissues because of HBOC's lower affinity for oxygen. Sampson et al. designed a similar study using a swine model for hemorrhagic shock [20]; they compared HBOC-201 with other low-volume resuscitation fluids, such as hypertonic saline, dextran, and pentastarch. They found that HBOC-201 was able to restore mean arterial pressure from 30 mm to 60 mm with a much smaller volume of infusion than the comparison fluids. They concluded that HBOC-201 could be an effective low-volume resuscitation fluid in the battlefield, rural areas, or other scenarios where efficient transport of fluid products was of prime importance. The same group of investigators evaluated pigs that had received HBOC transfusion, for evidence of end-organ damage [28]. The parameters used were lab values such as blood-gas analyses, urine output, and jejunal oximetry as well as analyses of different tissues at necropsy performed on post-injury day 3. The tissues analyzed were from the stomach, duodenum, ileum, lung, liver, and kidney. There was mild-to-moderate hepatocellular damage in four of six pigs infused with HBOC, accompanied by increases in serum aspartate aminotransferase. These changes were deemed transient, since levels of aspartate aminotransferase (AST) were returning to normal by post-injury day 3. The other tissues showed no histologic abnormalities.

Human trials using HBOC

A number of publications describe HBOC trials in different patient populations and several more studies are in the manuscript-preparation stage. LaMuraglia et al. reported on a single-blind multicenter study of 72 patients undergoing elective, infrarenal aortic operations [15]. Patients were assigned to the HBOC-201 group or the allogeneic group at random, when the decision to transfuse was made. Thirty-five of 48 patients in the HBOC-201 group and 24 of 24 patients in the allogeneic blood group required allogeneic blood transfusions. Therefore, the use of HBOC-201 spared 27% of patients (95% confidence interval (CI): 15–42%) from requiring allogeneic blood transfusions. The average number of RBC units needed in the HBOC group, albeit smaller (2.0 vs 2.5) than that of the allogeneic group, did not show a statistically significant difference. The authors explained that, while the use of HBOC did not reduce the overall demand on allogeneic blood, it did allow 27% of patients to avoid the risks of allogeneic blood. There was a 15% increase in mean arterial pressure and a transient increase in blood urea nitrogen (BUN) in the HBOC group. However, the overall complication and mortality rates between the two groups were statistically similar.

Levy et al. [16] performed a double-blinded trial of HBOC-201 in 98 patients undergoing cardiac surgery and in need of a transfusion. HBOC eliminated the need for allogeneic transfusions in 34% (95% CI: 21–49%) of 50 patients in the HBOC group. The number of transfused RBC units was 0.47 units less in the HBOC group (p=0.05). The short half-life of HBOC required the use of as much as 120 g of HBOC hemoglobin (equivalent of 2 units) to spare about one-half unit of allogeneic blood. Furthermore, by post-operative-day 2, about 40% of circulating hemoglobin was in the oxidized methemoglobin form. Similar to the aortic study, there was a slight increase in mean arterial pressure with HBOC infusion. This is hypothesized to be secondary to nitric oxide binding by HBOC or to stimulation of the production of endothelin-1, an endogenous vasoconstrictor. Of 50 patients in the HBOC group, 14 experienced jaundice, but all cases resolved by the time of hospital discharge.

HBOC in orthopaedic patients

The safety and efficacy of HBOC-201 was evaluated in patients undergoing orthopaedic surgery in a Phase III study [10]. In this single-blind, multicenter randomized study of 688 patients who underwent orthopaedic procedures and subsequently needed a blood transfusion, 350 patients received HBOC-201 and 338 received allogeneic blood transfusion. The use of HBOC-201 spared 59.4% of patients in the HBOC group the need for allogeneic transfusion. This was valid at 6 weeks post-operatively. Similar to the studies above, transient increases in blood pressure were observed in the HBOC group, but they were not associated with any clinical sequelae. Adverse events occurring more frequently in the HBOC group also included gastrointestinal and cutaneous events, but these events were mild and self-limited [10]. The two groups had comparable mortality and serious-adverse-event rates. This illustrates that in three different surgical fields, the use of HBOC spared a significant proportion of patients from receiving allogeneic blood. While there were consistently observed associated effects of HBOC transfusion, such as blood pressure elevation, jaundice, and changes in AST and alanine aminotransferase (ALT) levels, there were no increases in renal insufficiency, liver failure, or rates of morbidity and mortality in the HBOC group.

Other technologies: perfluorocarbons and liposome-encapsulated hemoglobin

Perfluorocarbons (PFCs) are molecules with linear or cyclic carbon backbones that are highly substituted with fluorine and occasionally other halogens [19]. They are immiscible with blood, so they must be prepared as emulsions using a phospholipid as a surfactant [7]. Instead of binding oxygen chemically as hemoglobin does, PFCs simply dissolve oxygen. PFCs have solubility for oxygen that is 20× greater than that of water [26]. Their oxygen-dissociation curve is linear, meaning that the patient needs to be ex-

posed to high fractional inspired oxygen (FiO_2) for the PFC to carry meaningful amounts of oxygen. The advantages of PFCs arise from their completely synthetic nature; therefore, they should have no infectious risk. They can be produced on a large scale and with relatively low cost. PFCs, however, have been observed to activate, complement and stimulate the reticuloendothelial system (RES), leading to bronchospasm and thrombocytopenia. Furthermore, they are cleared by the RES relatively quickly, with an intravascular half-life of 12–18 h [26].

Clinical trials have been performed over the last several years using different PFCs. Recently, perflubron (Oxygent; Alliance Pharmaceutical, San Diego, CA, USA) was investigated in a prospective multicenter, single-blind, randomized controlled study on 492 patients undergoing noncardiac general surgery [21]. The patients in the PFC group underwent acute normovolemic hemodilution (ANH) to a hemoglobin of 8.0 g/dl before incision. Intra-operatively, these patients were transfused with PFC. The autologous blood collected before surgery was transfused to the patients post-operatively. The purpose of this study was to evaluate if ANH/PFC would reduce the need for allogeneic transfusion since the autologous blood collected pre-operatively was returned to the patient after the surgical bleeding had been controlled. There was a statistically significant reduction in the number of allogeneic units transfused in PFC patients who lost >20 ml blood/kg. The overall incidence of adverse events was similar in the two groups. The mortality rate in the PFC group was 4% compared with 2% in the control group, but this was not statistically significant, and the deaths were thought to be related to underlying diseases such as malignancy. The authors concluded that the use of PFC may represent a new alternative for avoiding or minimizing the risks of allogeneic transfusions.

The concept of liposome-encapsulated hemoglobin has been intriguing, since placing the hemoglobin inside a lipid membrane obviates the need to chemically modify it and prolongs its intravascular half-life [24]. It is possible that 2,3-DPG and methemoglobin reductase could be encapsulated with the hemoglobin in the liposome to perform the other important functions of the RBC. However, this is still a concept in development. There will likely be difficulties in preparing liposomes that are uniform in size. There may also be unforeseen effects from the clearance of large amounts of this product by the reticuloendothelial system. This is a novel approach that merits more investigation.

Summary

The past several years have produced a large body of research into red blood cell substitutes. Hemoglobin-based oxygen carriers in particular are currently in use in South Africa and are actively being studied internationally, including in orthopaedic patients. The ability to address intra-operative and post-operative blood loss with a hemoglobin product that is sterile, non-allogeneic and universally accepted would have a significant impact on patient care and orthopaedic surgery. This is particularly important with regard to potential anticipated blood shortages, the reluctance of patients, families, and physicians to accept the risk of allogeneic blood, and the life-saving potential of such a product in the battlefield and other trauma settings.

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Richard B. Weiskopf

The use of recombinant activated coagulation factor VII for spine surgery

Abstract This article focuses on our current understanding of the role of activated coagulation factor VII (FVIIa) in coagulation, the current evidence regarding the efficacy and safety of recombinant FVIIa (rFVIIa), and thoughts regarding the use of rFVIIa in spine surgery. rFVIIa is approved in many countries (including the European Union and the USA) for patients with hemophilia and inhibitors (antibodies) to coagulation factors VIII or IX. High circulating concentrations of FVIIa, achieved by exogenous administration, initiate hemostasis by combining with tissue factor at the site of injury, producing thrombin, activating platelets and coagulation factors II, IX and X, thus providing for the full thrombin burst that is essential for hemostasis. This "bypass" therapy has led some clinicians to use rFVIIa "off-label" for disorders of hemostasis other than hemophilia. Based on clinical experience, case reports and limited information from clinical trials, rFVIIa may be efficacious in states of decreased concentration of coagulation factors, thrombocytopenia, and at least some states of altered platelet function. The former two can occur intra-operatively during spinal surgery as a consequence of substantial blood loss and normal consumption. Preliminary reports have indicated that rFVIIa does not increase the perioperative incidence of thromboembolic events. However, full reports from large clinical trials regarding the efficacy and safety of rFVIIa in settings other than hemophilia have yet to appear in peer-reviewed publications. Until adequate data demonstrating safety and efficacy are fully reported, it would seem appropriate to reserve the use of rFVIIa in spinal surgery to those instances where conventional therapy cannot provide adequate hemostasis, and "rescue" therapy is required.

Keywords Blood loss · Coagulation · Coagulopathy · Hemostasis · Recombinant coagulation factor VIIa

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Surgery of the spine encompasses a very broad range of procedures. The extent and blood loss encountered during these procedures varies enormously (Fig. 1). A simple laminectomy or discectomy does not create much blood loss. Surgery for spinal deformity can entail blood loss of several liters. Even within this latter sub-set, the variability is great. Correction of scoliosis in an otherwise normal teenager can be associated with small-to-moderate blood loss, but is not usually associated with extensive blood loss, while correction in a child with a neuromuscular disorder, or an elderly adult frequently involves substantial blood loss. In a recent 3-year period at the University of California, San Francisco, among those patients for whom intra-operative cell salvage was used (that is, patients in whom substantial blood loss was anticipated), the range of estimated blood loss for patients undergoing spinal surgery was nil to more than 10 l (Fig. 1).

When blood loss approaches or exceeds one blood volume, and replacement does not include coagulation factors, sufficient dilution of circulating coagulation factors

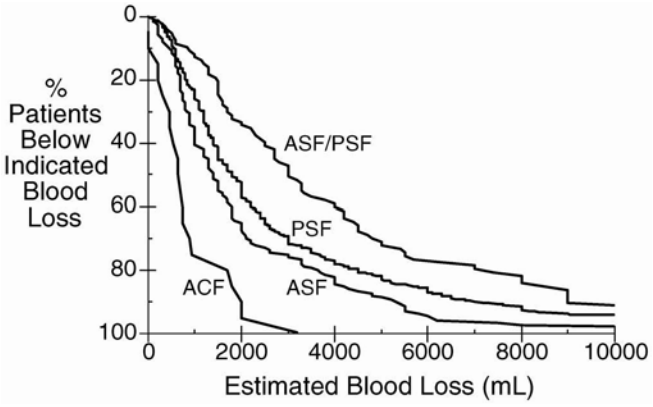

Fig. 1 Estimated blood loss in spinal surgery of 1,003 patients (March 2000–May 2003) for whom intra-operative cell salvage was used. Data for each procedure (*ACF* anterior cervical fusion; *ASF* anterior spinal (thoracic and/or lumbar) fusion; *PSF* posterior spinal (thoracic and/or lumbar) fusion; *ASF*/*PSF* anterior/posterior spinal fusion) show the cumulative number of patients who had that amount or less of blood loss. Data collected and analyzed with institutional review board approval (Committee on Human Research, University of California, San Francisco, CA, USA)

can produce a "dilutional" coagulopathy, adding to the potential for blood loss. Simultaneously, appropriate consumption of coagulation factors and platelets at the surgical site providing hemostasis can add some degree of a "consumptive" coagulopathy, further contributing to the potential for blood loss.

The usual appropriate treatment of dilution of coagulation factors or platelets, and their normal consumption during surgery, is to administer their replacement as needed: the former either as contained in whole blood or in fresh-frozen plasma, and the latter as either single-donor or pooled platelet concentrates. Some authors have concluded that excessive bleeding during spinal surgery can result from hyperfibrinolysis, that is, an abnormally activated fibrinolytic system with excessive fibrinolysis, and thus, they advocate the use of anti-fibrinolytic therapy during spinal surgery. It is my view that "hyperfibrinolysis" tends to be over-diagnosed and that in otherwise normal patients undergoing spinal surgery, observed "abnormal" fibrinolysis most likely is the result of a normal fibrinolytic system responding to an activated coagulation system. This, however, produces more than a normal degree of fibrinolysis, owing to a poorly formed clot and inadequate activation of coagulation factor XIII and thrombin activatable fibrinolytic inhibitor (TAFI), because of low concentrations of coagulation factors and platelets. Low concentrations of thrombin result in a poorly formed, less dense fibrin clot that is subject to rapid fibrinolysis. A denser fibrin clot formed with normal amounts of thrombin, is not vulnerable to this condition [8], which is produced by the dilution of coagulation factors that occurs with blood loss and asanguinous replacement.

This brief article focuses on our current understanding of the role of activated coagulation factor VII (FVIIa) in coagulation, the current evidence regarding the efficacy and safety of recombinant FVIIa (rFVIIa), and thoughts regarding the use of rFVIIa in spine surgery.

The vision of the process of coagulation, developed in the 1960s as a coagulation cascade, has a number of deficits, including the lack of involvement of cellular elements (for example, platelets and tissue factor bearing cells) and the inability to explain satisfactorily some clinical observations. More recent work has provided a better understanding of the events contributing to in vivo hemostasis. The initiating event is the formation of a complex of FVIIa and the tissue factor that is exposed on a tissue-factor-bearing cell (Fig. 2). The integrated concept of hemostasis has been recently reviewed by Roberts et al [34].

The development of an improved understanding of hemostasis has proceeded with, and been aided by, the development and understanding of the mechanism of action of activated coagulation factor VII. Circulating FVIIa accounts for approximately 1% of circulating coagulation factor VII (FVII) [41], and is enzymatically inactive until forming a complex with tissue factor (TF). When rFVIIa is administered exogenously, circulating concentrations of FVIIa greatly exceed the usual physiological concentrations. Activated coagulation factor VII initiates hemostasis by combining with tissue factor (a membrane-bound glycoprotein expressed by subendothelial cells) at the site of injury, forming a TF–FVIIa complex at the local site. The complex activates other factors, eventually producing limited thrombin generation and activated platelets (Fig. 2). Activated platelets and coagulation factors II, IX and X are critical for the development of a full thrombin burst. This thrombin burst is required to produce a stable, solid fibrin plug that is resistant to fibrinolysis [5, 8, 9, 40], and for the full activation of TAFI and of coagulation factor XIII, both of which are important for the stabilization of the fibrin plug and its resistance to fibrinolysis [27, 30]. Therapy with doses of rFVIIa that achieve supraphysiological concentrations saturate TF binding sites, activate platelets and produce clinically significant thrombin production, despite an absence of coagulation factors VIII or IX, or in the presence of antibodies to these factors (Fig. 3) [28]. Thrombin formation is impaired in thrombocytopenia and some types of platelet dysfunction [1]. rFVIIa increases thrombin generation in thrombocytopenia [23].

Hedner was the first to realize that FVIIa could be used as a "bypass" therapy for the treatment of patients with hemophilia and inhibitors (antibodies) to coagulation factors VIII or IX, which have developed either as a result of treatment of inherited hemophilia with these factors, or in patients with previously normal coagulation (acquired hemophilia), thus bypassing the need for these clotting factors [15, 16, 17, 18]. In an in vitro system, addition of rFVIIa to FVIII-deficient plasma, to achieve a concentration similar to that after administration of an in vivo dose

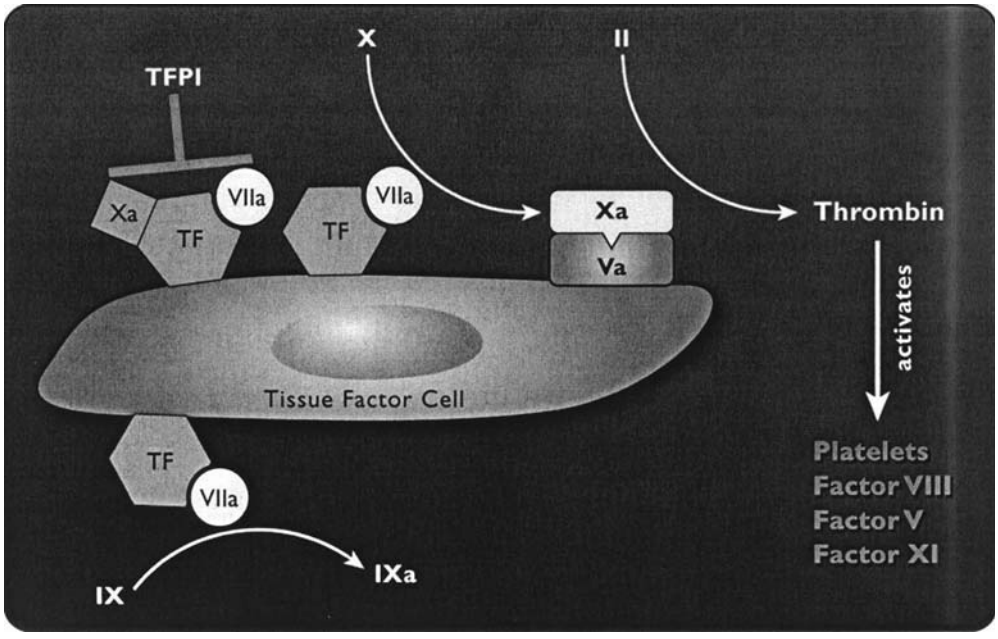

Fig. 2 The two main functions of tissue factor (TF) are shown: to activate factor X and to activate factor IX. Factor Xa remains in the vicinity of the TF cell and activates factor V. The complex of factors Xa/Va can convert a small amount of prothrombin (factor II) to thrombin, with the results shown. Tissue-factor pathway inhibitor (TFPI) then inhibits the complex of TF/VIIa/Xa as a control mechanism. Reproduced with permission from Bernstein, Jeffers, Erhardtsen et al. [2]

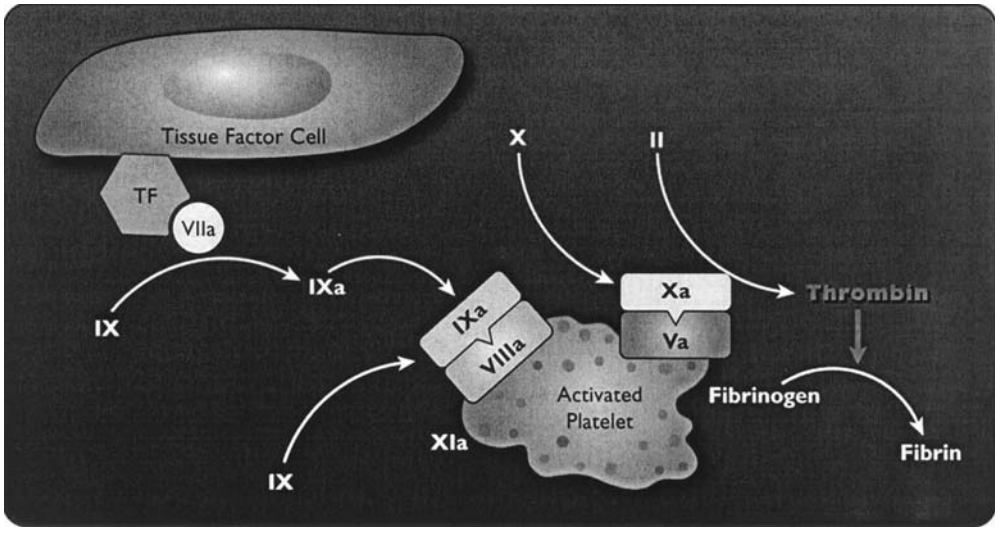

Fig. 3 The activated platelet derived from un-activated, circulating platelets resulting from the thrombin generation on the TF cell. Activated co-factors Va and VIIIa occupy sites on the activated platelet before binding of the respective enzymes, factors IXa and Xa. Factor Xa on the activated platelets is recruited from circulating factor X and is different from the factor X on the TF cell. The burst of thrombin generation takes place on the platelet surface. Thrombin generation can be boosted by further activation of factor IX by factor XIa. The burst of thrombin is sufficient to convert fibrinogen to fibrin. Reproduced with permission from Bernstein, Jeffers, Erhardtsen et al. [2]

of 90–100 μg/kg, restores to normal the abnormal clot permeability and the fibrin network (Fig. 4) [14]. rFVIIa has been demonstrated to be efficacious and safe for these indications, and until February 2004, use in patients with inhibitors to coagulation factors VIII or IX was the only use for which rFVIIa had regulatory approval. Hedner also suggested that rFVIIa might be efficacious for other disorders of hemostasis. Her suggestion resulted in an initial dramatic off-label use of rFVIIa, wherein rFVIIa provided hemostasis after clinicians had ceased all other therapies, including surgery, for a victim of major trauma with uncontrollable hemorrhage [22]. Following this apparent success, a great number of case reports have appeared, purporting to indicate that rFVIIa is efficacious for a broad group of disorders of hemostasis, including:

- Thrombocytopenia [24]
- Thrombocytopenia refractory to platelet transfusion owing to antibodies to platelet antigens [39]
- Some states of platelet dysfunction [33, 37]
- Von Willebrand's disease [7]
- Deficiency of other coagulation factors [4, 31]
- Cerebral injury-induced coagulopathy [29]
- Hepatic dysfunction (with normalization of prothrombin time) [2]
- Trauma [26]
- Reversal of warfarin therapy [3, 10]
- Necrotizing pancreatitis [36]
- Pulmonary hemorrhage following stem-cell transplantation [32] or cardiac surgery [25]
- Other bleeding following cardiopulmonary bypass [35]

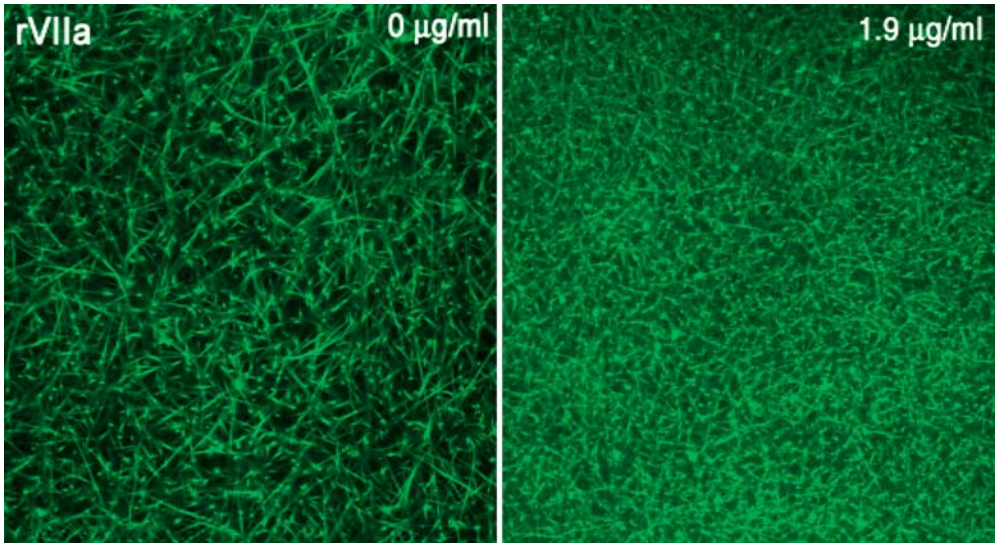

Fig. 4 **a** Plasma deficient in coagulation factor VIII produces a loose, porous clot that is readily subject to fibrinolysis; **b** addition of rFVIIa, 1.9 µg/ml, a concentration equivalent to that achieved with exogenous administration of approximately 90–100 µg/kg rFVIIa, to plasma deficient in coagulation factor VIII restores the fibrin clot to a tight, normal architecture, resistant to fibrinolysis. Reproduced with permission from Hedner and Kisiel [16]

– Gastrointestinal bleeding [20]
– Postpartum hemorrhage [6]
– Traumatic brain injury [42]
– Dilutional coagulopathy during spinal surgery [38]

These reports, and the substantial off-label use of rFVIIa has led to the unproven proposition that rFVIIa may be efficacious for providing hemostasis in abnormal states other than hemophilia. This has resulted in a substantial program to develop use of rFVIIa in non-hemophiliac populations, and the US National Institutes of Health has called for applications for research grants in this field. Recently, rFVIIa has been approved in the European Union (but not in the USA) for FVII-replacement therapy and for Glanzmann's thrombasthenia.

There have been a limited number of clinical trials, reported in the peer-reviewed literature, of use of rFVIIa for conditions other than hemophilia. rFVIIa normalizes the international normalized register (INR) of volunteers given acenocoumarol to produce an INR greater than 2.0 [12]; it corrects the prothrombin time in patients with cirrhosis [2, 21], and it provided for hemostasis in within 10 min for 74% of 66 patients with Childs-Turcotte B or C hepatic cirrhosis undergoing laparoscopic liver biopsy [21]. In an open-label, pilot study of six patients undergoing hepatic transplantation, patients given rFVIIa had less blood loss and required less transfused fresh-frozen plasma (FFP) and red cells than did matched controls [19]. In a double-blind, randomized, dose-escalation study of 36 patients undergoing prostatectomy, rFVIIa decreased blood loss and red cell transfusion compared to placebo-treated patients[13]. Recently (December 2003), Novo Nordisk announced the results of a phase II double-blinded, placebo-controlled, multi-center trial of 280 patients with severe trauma. Patients treated with rFVIIa reportedly needed fewer transfusions, had fewer complications, and spent less time in intensive care units than did the patients given placebo. In February 2004 Novo Nordisk announced the preliminary results of their phase II, randomized double-blind trial of rFVIIa for hepatic transplantation. They stated that those patients treated with rFVIIa had a significantly lesser incidence of requiring red cell transfusion than did those not treated with rFVIIa, and that there was a similar incidence of thromboembolic events in those treated or not treated with rFVIIa. The data from these two studies had not appeared in the peer-reviewed literature at the time of the writing of this article (February-March 2004).

Taken together, these case reports, and the limited data from clinical trials appear to indicate promising hemostatic applications for rFVIIa in non-hemophilia-related states of altered hemostasis: thrombocytopenia, decreased coagulation-factor concentrations causing elevated prothrombin time and partial thromboplastin time, and altered platelet function. The former two are of direct relevance to spinal surgery, in which extensive blood loss can produce these altered states by both dilution and, to a lesser extent, normal consumption. That is not to say that administration of rFVIIa should, at this time, replace the standard therapies of administration of coagulation factors (via whole blood or FFP) and platelets. There are insufficient data to confirm that rFVIIa is superior to, or even as good as, these conventional therapies during spinal surgery. However, there are times when it is difficult to correct the deficiency of decreased coagulation factors by conventional therapy, especially during ongoing, massive blood loss. When conventional therapy does not, or cannot, succeed, it is reasonable to administer rFVIIa as an attempted rescue therapy.

The appropriate dose under these circumstances is not clear. The studies and case reports cited above report the use of a wide range of doses: from 10 µg/kg to 100 µg/kg or more. Doses at the low end of this range are not likely to be efficacious. Most clinicians using rFVIIa as a rescue

drug for hemorrhage during surgery administer doses of approximately 90–100 μg/kg. However, it should be noted that the trauma trial discussed above used an initial dose of 200 μg/kg, followed by two additional doses of 100 μg/kg each, 2 h and 4 h after the initial dose. The hepatic-transplantation trial used a dose of 60 μg/kg or 120 μg/kg repeated every 2 h, while the prostatectomy study used doses of 20 μg/kg and 40 g/kg.

In addition to the uncertainty regarding the appropriate dose, the duration of action, and thus timing, of repetitive doses is not fully elucidated. The clearance of rFVIIa is approximately 30–35 ml/kg/hr in adults and greater in children [11]. This suggests that administration of rFVIIa should be repeated relatively frequently, if inadequate hemostasis persists; perhaps at 2 h intervals. However, it is not clear that the most important aspect of the mechanism of action relates to the plasma concentration of rFVIIa at any given time, rather than the peak concentration achieved shortly after administration. The latter may have greater importance for rFVIIa than for many drugs because of the need to produce the thrombin burst, which is essential to the mechanism of action of rFVIIa and hemostasis.

The issue of safety is also of importance in consideration of the use of rFVIIa. The safety profile of this biologic, following its approval in 1996 in the European Union and 1999 in the USA, has been excellent for the many doses and patients to which it has been given for treatment of hemophilia. Some of the reports cited above have described rare complications. However, in the absence of published full reports of large, randomized clinical trials, it is unknown if these complications are associated with rFVIIa administration more than they occur in patients not so treated, or in similar patients in whom altered hemostasis has been corrected by other means, or in patients with unaltered coagulation. The most important complications of theoretical concern are thromboembolic events. One of the six patients who underwent hepatic transplantation in the series reported by Hendriks et al. developed a hepatic artery thrombosis [19]. None of the 24 patients treated with rFVIIa in the double-blinded randomized trial of prostatectomy developed any adverse events during the study period, although one treated patient had a myocardial infarction on post-operative day 14, after the end of the 10-day study period [13]. Two clinical trials of substantial size have been completed: the trauma trial and the hepatic transplant trial discussed above. As these trials have been completed only recently, the results have yet to appear in the peer-reviewed literature. The sponsor, Novo Nordisk, reported that there were no differences in incidences of serious adverse events, including thromboembolic events, between rFVIIa and placebo-treated patients in both the trauma trial and the hepatic transplant trial.

In summary, rFVIIa appears likely to be efficacious in states of decreased concentration of coagulation factors, thrombocytopenia, and in at least some states of altered platelet function. While efficacy has been found in one small study, it has not been demonstrated in large, randomized, double-blinded, placebo-controlled trials published in the peer-reviewed literature. Many clinicians now use rFVIIa to treat intra-operative hemorrhages not easily controlled by conventional therapy. A trial of substantial size in spinal surgery may be undertaken in the near future. Until adequate data demonstrating safety and efficacy are fully reported, it would seem appropriate to reserve the use of rFVIIa in spinal surgery to those cases where conventional therapy cannot provide adequate hemostasis.

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The use of local agents: bone wax, gelatin, collagen, oxidized cellulose

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Abstract The use of local agents to achieve hemostasis is an old and complex subject in surgery. Their use is almost mandatory in spinal surgery. The development of new materials in chemical hemostasis is a continuous process that may potentially lead the surgeon to confusion. Moreover, the more commonly used materials have not changed in about 50 years. Using chemical agents to tamponade a hemorrhage is not free of risks. Complications are around the corner and can be due either to mechanical compression or to phlogistic effects secondary to the material used. This paper reviews about 20 animal and clinical published studies with regard to the chemical properties, mechanisms of action, use and complications of local agents.

Keywords Oxidized regenerated cellulose · Bone wax · Gelatin foam · Collagen fleece · Local hemostasis

Introduction

Hemostasis in spinal surgery requires different tools for each step. Bipolar electric coagulation allows controlling subcutaneous bleeding. Muscular dissection is often performed by monopolar electric coagulation. Hemostasis of the muscular layers is performed by bipolar coagulator and maintained by mechanical compression of spreaders. Each procedure on the bone (laminectomy, screw placement, etc.) carries the risk of conspicuous bleeding, mostly from cancellous bone. Its control is achieved by means of bone wax. The epidural phase of spinal procedures probably carries the longest and highest risk of bleeding. The explanation is that the surgical field is deeply seated, and the bleeders are usually difficult to find. Iatrogenic damage of the epidural venous plexus increases the risk of fighting against low pressure. However, continuous venous bleeding is difficult to control and time consuming. During this step, oxidized, regenerated cellulose and fibrillar collagen are very useful. The aim of this article is to review the most common topical hemostatics used in spinal surgery.

Historical background

In the event of hemorrhage, hemostasis is naturally carried out by vasal contraction, platelets, coagulation factors and blood flow. Sometimes during an operation, it is not possible to wait for the natural hemostatic process to occur, and, therefore, additive methods to obtain a stable coagulum have to be used [11, 23, 49].

In general, these methods fall into one of the three basic categories: thermal, mechanical, or chemical means [6, 49]. The use of thermal energy to obtain hemostasis dates to ancient Egypt, and the importance of electric coagulation in neurosurgery was stated in 1920 by Cushing and Bovie [11]. Mechanical hemostasis is principally ligature, but it has been said that the feature that most distinguishes spinal microsurgery as a specialty is control of hemorrhage without ligature.

Table 1 Topical hemostatic agents

	Bone wax	Gelatin	Microfibrillar collagen	Oxidized cellulose/ regenerated
Year of introduction	1886	1945	1970	1942/1946
Ingredients	Beeswax, Vaseline	Purified animal gelatin	Purified bovine corium collagen	Wood pulp (oxidized regenerated cellulose)
Action	Mechanical on trabecular vascularization of bone	Provides physical matrix, swells	Direct platelet release stimulation, provides a surface, does not swell	Mechanical action, swells, gel formation, interaction with proteins and platelets, low pH denatures globulin and albumin
Absorption	None	4–6 weeks in soft tissues	Less than 84 days in animal studies	Depends on the amount used, degree of saturation with blood and tissue bed
Complications	Allergic, granuloma, cord compression, infection, interferes with bone healing	Cord compression, interferes with bone healing	Interferes with bone healing, allergic reactions, infection	Cord compression, interferes with bone healing, encapsulation of fluid, foreign body reactions

Chemical hemostasis also has a very old origin. Hippocrates used caustics to achieve hemostasis, but the history of modern chemical hemostatics began at the end of the eighteenth century, when Carnot introduced gelatin. A few years later, Horsley, an innovative surgeon, observed in canine skullsthat modeling wax was efficacious in stopping bleeding. In 1886 he developed a mixture of beeswax, salicylic acid, and almond oil, thus leaving hislegacy of "antisepticwax." He advocated the application of muscle stamps anddeep anesthesia to control hemostasis during cranial and spinal surgery [46].

Research into the mechanism of blood coagulation led to the development of oxidized cellulose in 1942 [13] and gelatin foam in 1945 [27]. Until now the hemostatics most used in neurosurgery have been oxidized, regenerated cellulose (Surgicel), gel sponges (Gelfoam, Spongostan) and collagen fleece (Avitene). Local hemostatics should be removed at the end of the operation, but these materials are absorbable and so they are often left in place to avoid postoperative hematomas. Bone wax is a mixture of beeswax (70%) and Vaseline (30%). It is a non-absorbable material, becoming soft and malleable in the hand when warmed.

Gelatin foam (GF) was introduced as a hemostatic agent in 1945 and has been marketed by the present seller since 1952 [27]. Microfibrillar collagen (MFC) was developed in 1970 by Hait [17]. It is derived from purified bovine corium. The classical form (flour form) is a water-insoluble, partially acid salt of collagen, processed into microcrystals. It is dry, fluffy, white, and self-adherent. The sheet form is a non-woven web derived from compression of the flour form.

Oxidized cellulose (OC) was introduced in 1942, whereas oxidized regenerated cellulose (ORC) was developed in 1960 and is manufactured from wood pulp, which contains about 50% cellulose by mass. In order to arrive at a purified cellulose, it has to be decomposed and then recomposed into regenerated cellulose.

Chemical properties

Bone wax is a well-known topical hemostatic agent composed of beeswax and Vaseline. Its hemostatic effect is based on physical rather than biochemical properties: it allows clot formation by stopping the blood flow from damaged vessels into the bone (Table 1).

Gelatin foam (absorbable gelatin sponge) is made from animal-skin gelatin whipped and baked into its sponge form. Although it is derived from animals it is largely considered non-antigenic. At the end of the coagulation cascade, plasma still leaks through it. Its bond to surfaces is strong. Gelatin foam paste is derived from the parent gelatin foam. If soaked in thrombin, it directly acts on the coagulation cascade. Its effect is probably mostly mechanical on low-pressure bleeders [29].

MFC adheres tightly to bloody surfaces, with an immediate and complete hemostasis. Blood rarely leaks through it. The surfaces remain white and dry. It doesn't swell, as Gelfoam does. The hemostatic properties of MFC rely on the promotion of platelet aggregation. In vitro studies have shown that platelets adhere to MFC while undergoing normal morphological changes during the release reaction [54]. Similarly, in vivo studies have shown tight adhesion of MFC to the injured surface, with platelets tightly entrapped in the MFC. Furthermore, MFC has been shown to be effective in case of heparinization, but less effective in thrombocytopenia [1]. MFC hemostatic properties are also improved by its strong adhesion to injured surfaces: it physically blocks injured vessels. It remains tightly bound to the wound, even after hemorrhage has stopped. MFC is supposed to promote hemostasis by providing a surface to which platelets can adhere and undergo their release reaction and by accelerating clotting via direct action on platelets [2, 14, 30, 32]. Advantages of collagen fleece are fast induction of hemostasis, low

tissue reaction, and fast resorption [4] .Another significant advantage is that excess collagen can be carefully teased away from around the hemorrhage site without re-initiating bleeding. A major disadvantage of using the collagen fleece is difficulty in manipulating the agent during attempts to place it in the area of bleeding [34].

ORC is a chemically altered form of cellulose [26, 33, 48, 49]. In this form, the cellulose is first dissolved and then made into a continuous fiber. The greatest use of this material has been for the control of oozing from broad surfaces, but it can be also pressed under osteoplastic flaps to supplement bone waxing or used to stop oozing from dural surfaces. It can also be applied directly on brain surfaces, to control bleeding from small vessels [48].

Oxidized regenerated cellulose in the fibrillar form (ORMC) is not markedly different from the other Surgicel cellulose-based products currently available [26]. However, it seems to be more advantageous than the standard forms in dealing with venous bleeding and oozing from cortical surfaces after tumor resection. Additional advantages are related to the physical properties of the loosely knit, regenerated cellulose. This allows placement in certain areas where the product will rapidly conform to the recipient surface, giving a favorable three-dimensional structure for the clot organization. Oxidized regenerated cellulose also seems to confer hemostasis by decreasing the pH and acting as a caustic, thus generating an artificial clot. The clot is brownish because of the production of acid hematin [2, 26, 28]. ORC presents multiple mechanisms of action, including physical and mechanical actions in tamponade, food absorption, swelling and gel formation, and then surface interactions with proteins, platelets, intrinsic and extrinsic pathway activation.

One major advantage of oxidized cellulose is its definite and potent action against a wide variety of pathogenic organisms, both in vivo and in vitro. This beneficial effect is immediate and is exerted by a low pH effect. The current theory is that this chemical hemostatic reduces the effective initial inoculum with an acid hostile ambient, allowing the host's natural defenses to overcome the organism[49]. This has been confirmed by Spangler et al., who examined the antimicrobial effect of ORC against antibiotic-resistant organisms. ORC products were challenged with ATCC reference strains and clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococcus* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and non-resistant ATCC strains of *S. aureus* and *Pseudomonas aeruginosa*. Antimicrobial activity was seen with all three ORC products against the challenging organisms. Data indicate that antibiotic-resistant microorganisms remain susceptible to the antimicrobial activity of ORC. Since low pH affects a relatively broad spectrum of bacteria and does not act in a mechanism-specific manner, as do antibiotics, antibiotic-resistant strains of bacteria are unlikely to resist the ORC pH effect. Results of this in vitro assessment support the hypothesis that the antimicrobial activity of ORC is effective against antibiotic-resistant microorganisms. Moreover, an advantage of oxidized cellulose as compared to microfibrillar collagen, from the standpoint of infection, has been suggested [43]. Oxidized cellulose has previously been shown to be superior to gelatin sponge with respect to infection [38].

Platelet activation and aggregation play an important role in hemostasis. Topical hemostatics may interfere with platelet function. Five topical hemostatics (collagen fleece, bone wax, bioerodible polyorthoester, oxidized cellulose and gelatin sponge) have been investigated concerning their effect on platelet cascade. Fibrillar collagen fleece induced aggregation in the presence of a small amount of ADP and adrenaline. Bone wax needed a larger concentration of agonists to achieve the same result. In fact, GF, OC and polyorthoester did not promote platelet aggregation [41].

Masova et al. studied the effect of OC on platelet activation. As a marker of platelet activation they used serotonin release reaction. Serotonin release in platelet-rich plasma incubated with various concentrations of oxidized cellulose (0.5–2.0%) started in about 20 min. Washed platelets were not directly activated by oxidized cellulose within 1 h. Washed platelets reconstituted in plasma obtained from two patients with deficiency in coagulation factor XII were activated by oxidized cellulose with a prolonged lag phase. Their results demonstrate the significant influence of factor XII on blood-platelet activation by oxidized cellulose [28].

Use suggestions

Bone wax

Use it only if necessary and just for the time needed to achieve hemostasis. After hand manipulation, a bath in iodine is recommended. If the wax is left in place, we strongly recommend meticulously removing the excess. It should never be left in place in fusion sites and within the spinal canal. It must never be used in contaminated fields.

GF

Gelfoam sponge is widely used to fill the cavity of a laminectomy in a bloody field. Attention should be paid to removing the excess, and the surgeon should be aware that GF could interfere with bone healing. In infected spaces it is contraindicated, because it may enhance the infectious process. We suggest placing it dry with moderate pressure on the bleeding site. This agent can double in volume by swelling and can also cause compressive complications. If soaked in thrombin, GF has an increased hemostatic action.

Table 2 Clinical studies (*GF* gelatin foam, *MFC* microfibrillar collagen, *CF* collagen fleece)

Author	Year	Clinical material	Hemostatics	Conclusion
Taheri	1971	Anterior cervical procedures	GF paste	No differences concerning bone healing compared with the patients previously treated without GF paste
Harris	1978	Total hip replacement	GF paste, GF sponge + bovine thrombin, MFC	No difference was found in terms of bone healing in the three groups of patients
Weiss	1980	Anterior cervical procedure	GF paste	See Taheri
Rengachary and Manguoglu	1980	Cloward procedures	GF paste + bovine thrombin	Good results without any allergic reaction
Silverstein	1981	Liver lacerations and retroperitoneal bleeding	Loose vs compressed CF	Partially compressed CF is an effective topical hemostatic when compressed against the bleeding site and when folded and sutured against it
Zirna	1987	Foot surgery	Bone wax, GF paste	Reduction of postoperative edema and pain

ORC

Never use this soaked in thrombin. The latter, in fact, interferes with its natural action. Its power is maximal if applied dry; the fibrillar form when placed in small layers is almost transparent, so that bipolar coagulation trough it will still be possible. Bacteriostatic properties of this product should be preferred in particularly contaminated fields. Obviously, should this event occur, the use of no agent at all is always better. Wadding or packing in rigid cavities (neural foramina) should be avoided, due to risks related to swelling phenomena.

MFC

This should be applied dry with clean and dry instruments, and pressure with gloved fingers should never be placed, as the MFC would adhere to the glove more than on the hemorrhage site.

Postoperative adhesion of the hemostatic agent to neural structures is possible. Therefore, it is recommended to tease away the excess of product after 5–10 minutes. Swelling occurs, although less so than with other products, and surgeons should be aware of this when MFC is left in place in rigid compartments.

Clinical studies

Because GF is resorbable in the human body, the paste form represents an alternative to bone wax to avoid osteogenic inhibition. Taheri and colleagues used powdered gelatin foam in over 300 anterior cervical procedures, applying it on the interbody drill hole during drilling. Follow-up X-ray films showed no differences concerning bone healing with the patients previously treated without Gelfoam paste [44]. Weiss also used the same agent in anterior cervical fusions, achieving excellent results [50]. Rengachary and Manguoglu added bovine thrombin to the Gelfoam paste during Cloward procedures, without any allergic reactions to the thrombin [35]. Harris and colleagues presented a series of 45 patients operated on for total hip replacement. They applied Gelfoam paste, Gelfoam sponge plus bovine thrombin, or microfibrillar cellulose on bleeding cancellous bone surfaces of femoral osteotomies. They found bleeding reduced by, respectively, 85%, 75% and 47%, over a 3-min. interval. No difference was found in terms of bone healing in the three groups of patients [18] (Table 2).

Zirna at al. compared GF paste and bone wax for their effects on the occurrence of postoperative edema and pain in foot surgery. They found that 80% of patients treated with bone wax and 91% of patients receiving GF paste presented decreased amount of postoperative edema. Furthermore, postoperative pain was reduced in 90% of the patients treated with bone wax, and in 75% of patients treated with GF paste [53].

Silverstein et al. used GF in 21 patients with liver lacerations and retroperitoneal bleeding. They tested two forms: loose and compressed fleece. Partially compressed GF showed significantly higher hemostatic efficacy than the loose form. Their clinical experience was also confirmed by gravimetric determinations of blood loss in dogs. They concluded that partially compressed GF was an effective topical hemostatic when compressed against the bleeding site and when folded and sutured against it [40].

Animal studies

Bone wax is known to inhibit bone healing and osteogenesis. Howard and Kelley evaluated the effect of bone wax on bone healing in Albino rats. They made bony lesions in animal tibia. In the first group, the holes were filled with bone wax and then irrigated with saline solution. In the second group, the holes were simply irrigated with saline solution. After the animals were killed, the investigators

Table 3 Animal studies (*MFC* microfibrillar collagen, *GF* gelatin foam, *ORC* oxidized regenerated cellulose, *OC* oxidized cellulose)

Author	Year	Model	Hemostatic	Conclusion
Geary and Frantz	1950	Rib fractures in dogs	Bone wax	Fracture union was prevented by interposition of wax particles
Howard and Kelley	1969	Tibial lesions in albino rats	Bone wax	The use of bone wax should be contraindicated in surgical procedures requiring bone fusion
Brightmore	1975	Sternotomized goats	Bone wax	Bone wax causes absorption of cancellous bone and inhibits osteogenesis
Rybock	1977	Suction-evacuation lesions of canine cortex	MFC, GF	MFC appears to be as good or better than GF
Johnson and Fromm	1981	Iliac crest cancellous bone of rabbits	Bone wax	Bone wax significantly reduces the ability of cancellous bone of rabbits to clear bacteria
Wilkinson	1981	Surgical bone lesions in rabbits	Bone wax, GF	Gelatin foam paste is a good alternative to bone wax for the control of bone bleeding, and it seems not to impair bone healing
Ibarrola	1985	Experimental defects in both tibias of rats	Bone wax, cellulose, GF	All materials inhibited healing when left in situ. Bone wax inhibited osteogenesis. Cellulose reduced bone repair and caused inflammation. GF was completely resorbed, and healing was complete at 120 days
Alberius	1987	Cranial bone lesions in rabbits	Bone wax	Bone wax markedly impairs bone regeneration
Voormolen	1987	Cerebral lesions in rabbits	MFC, ORC	MFC establishes hemostasis faster, and it is resorbed faster than ORC
Haasch	1989	Osseous defects created in rat tibias	MFC	MFC doesn't impede bone healing
Finn	1992	Surgical defects in iliac crest of dogs	Bone wax, GF, ORC, MFC	MFC, ORC, and GF may be adequately used in iliac bone procurement, whereas bone wax seems to be contraindicated
Raccuia	1992	Rat model employing a standardized renal injury	OC, MFC, positively charged collagen, fibrin glue	MFC is the best overall hemostatic agent in microvascular surgery

found that bone wax almost completely inhibited bone healing. They suggested that the use of bone wax should be contraindicated in surgical procedures requiring bone fusion [19]. Brightmore found that bone wax formed a physical barrier to bone healing in sternotomized goats, causing absorption of cancellous bone and inhibiting osteogenesis [7]. Geary and Frantz studied experimental rib fractures in dogs. They found that fractures treated with bone wax allowed the formation of the same amount of calcified callus as untreated lesions, but fracture union was prevented by interposition of wax particles in the first group. Furthermore, they noted a foreign reaction to bone wax, with monocytes, giant cells and phagocytes [15] (Table 3).

Effects of bone wax on bacterial clearance have been studied by Johnson and Fromm. They penetrated iliac crest cancellous bone of rabbits, with or without *Staphylococcus aureus*, followed by placement of a cylinder of bone wax or stainless steel rod. The site of inoculation was excised and cultured 10 days later. A positive culture was found in 80% of animals whose bone was implanted with bone wax and bacteria, and in 40% of animals with steel rod and bacteria. No positive cultures were found in the bacteria-only, bone-wax-only and steel-rod-only groups. The combination of bacteria with a foreign body created by bone wax or a steel rod was significantly different from the other groups, showing that bone wax significantly reduced the ability of cancellous bone of rabbits to clear bacteria [24].

Larocca and Macnub used GF sponge as a scaffolding for fibroblasts over a laminectomy site in dogs [25]. Wilkinson and colleagues studied GF paste's effect on bone healing and osteogenesis in 1981. They evaluated either the hemostatic or osteogenic effects on surgical bone lesions in rabbits of both gelatin paste and bone wax. Thirty rabbits received four trephine craniotomies and four lumbar laminectomies, alternatively treated with either gelatin paste or bone wax. The mean intraoperative blood loss was similar in both groups. At 1 week postoperatively, histological examination of the fracture site showed no differences, but at 4 weeks only the gelatin-treated site specimens were satisfactorily processed with new bone formation and no foreign body reaction. At 6 weeks, the force required to fracture the bone at the trephination sites was similar for both groups. They concluded that gelatin foam paste is a good alternative to bone wax for the control of bone bleeding and that it seems not to impair bone healing [51].

The effects of bone wax, cellulose and gelatin on bone healing were microscopically evaluated by making exper-

imental defects in both tibias of rats. Hemostatics were placed and left in situ in the right tibias, whereas they were removed after 10 min. from the left side. All three materials inhibited healing when left in situ. Bone wax inhibited osteogenesis. Cellulose reduced bone repair and caused inflammation. Gelatin was completely resorbed and healing was complete at 120 days [20]. MFC did not impair bone formation in rat tibias in the Haasch study of 1989 [16]. Alberius et al. studied the effect of bone wax on rabbit cranial bone lesions. The lesion rim covered by bone wax presented a slight tissue reaction and a markedly impaired bone regeneration [3].

In 1987, Voormolen et al. conducted an experimental study in rabbits in which cerebral lesions were made and filled with oxidized regenerated cellulose (not in fibrillar form) and collagen fleece. In this study, bleeding times were evaluated and histological studies were realized. Results showed lower bleeding times for microfibrillar collagen, with a quicker resorption rate than for traditional oxidized regenerated cellulose. Voormolen concluded that collagen fleece established faster hemostasis than oxidized cellulose and that it was resorbed faster than oxidized cellulose [48].

Rybock et al. compared hemostatic properties of MFC versus GF in suction-evacuation lesions of the canine cortex. MFC was found to be faster and more effective than GF in achieving hemostasis. Histological evaluation at 2 months, 4 months and 6 months postoperatively didn't show any difference in regard to the amount or type of tissue reaction to the two agents. They concluded that MFC appeared to be as good as, or better than, GF, because it is absorbable; doesn't lead to major tissue reaction; doesn't swell significantly; and is quickly effective even in the presence of coagulation disorders. Also, smaller quantities of MFC remain in the wound after excess material is removed [37].

Wagner in 1996 quantitatively compared six commonly used topical hemostatic agents in terms of their ability to mediate platelet aggregation, deposition and activation in a series of in vitro tests. He presented an overall activity ranking of the materials used: collagen>gelatin>oxidized regenerated cellulose [49]. The efficacy of four topical hemostatic agents (oxidized cellulose, microfibrillar collagen powder, positively charged modified collagen and single donor heterologous fibrin glue) was compared in a rat model employing a standardized renal injury. Fibrin glue was by far the most effective agent in controlling hemostasis. The collagen materials, though effective, required a longer time to control bleeding and did not differ from one another statistically in their activity. Microfibrillar collagen was showed to be the best overall hemostatic agent in microvascular surgery [34].

It has been shown that Avitene does not impede bone healing in osseous defects created in rat tibias. MFC, bone wax, GF and ORC were compared by Finn et al., concerning their effects on osseous regeneration. They researchers made surgical defects in the iliac crest of four dogs. Two months later, radiographic and histologic examination showed new bone formation in the presence of MFC, ORC, and GF. Residual material incorporated in bone was noted in MFC and GF sites. Bone wax showed a marked foreign-body reaction and lack of bone reformation. They concluded that MFC, ORC, and GF might be adequately used in iliac bone procurement, whereas bone wax seems to be contraindicated [12].

Complications

Most complications are due to mechanical compression of neural structures, due to the blind application of local agents into closed bone compartments or due to the natural swelling of those products. Other complications are sustained by the antigenic action of those products, which even if with a low rate, are possible. Bone healing is always slowed by all the reported hemostatics.

Brodbelt et al. presented three cases of paraplegia after thoracic surgery during which ORC had been used during thoracotomy for hemorrhage control. The ORC was later found to have passed through the intervertebral foramen, causing spinal cord compression. They stated that in all intraspinal and perispinal procedures, the over-liberal use of ORC should be avoided, and attempts made to remove all excess ORC once adequate hemostasis is obtained [8]. Iwabuchi first, and later Cherian, have reported similar cases in 1997 and 1999 [9, 21]. The manufacturer warns of encapsulation of fluids.

Bone wax is known to cause adverse effects such as allergic reaction, intracranial granuloma, epistaxis, and granulomatous infection. A case of iatrogenic quadriplegia has been reported by Cirak. In this case neurological deficit might have been caused by either direct compression from bone wax or by epidural bleeding by detachment of epidural veins [10].

Katz and colleagues reported two cases with bone wax granulomas of the orbit as a remote surgical complication in a large orbital surgical series. In one case, intraoperative cultures grew *Staphylococcus aureus*, showing that bone wax may act as a nidus for infection [22]. Seven cases of bone wax granuloma have been reported in women who underwent foot surgery. At re-operation, soft granulation tissue was resected. Microscopically, in all cases, a marked foreign body reaction was seen [5]. Sorrenti et al. found a definite foreign-body giant cell reaction to bone wax in 12 patients treated by elevation of the tibial tubercles. Giant cells eliminated bone wax particles from the site, culminating in a fibrous reaction [42].

Verborgt reported a case of a retroperitoneal tumor as a late complication of the use of bone wax in harvesting iliac crest. The tumor needed surgical removal 19 years later. Microscopically, a bone wax granuloma was diagnosed [47]. Wolvius reported a case of foreign body granuloma in a cranial defect [52].

Robicsek et al. used radioactive bone wax on the cut sternum. There was evidence of radioactive material in peripheral lung, indicating that bone wax may embolize. They concluded that embolization occur in clinical conditions and may give rise to secondary pulmonary complications [36].

In order to avoid bone wax complications, alternative materials have been developed. Orgill et al. reported their experience with a polyethylene glycol/microfibrillar collagen composite (PEG/MFC) that has inherent hemostatic qualities, is biodegradable, and is compatible with bone repair. The composite was placed in cranial defects of New Zealand white rabbits. Hemostasis and healing were compared to unfilled defects and defects filled with bone wax. Both PEG/MFC and bone wax stopped bleeding. The former was resorbed in 8 h, and the microfibrillar collagen was resorbed over 2 months, eliciting only a minor inflammatory response during the first month. Defects filled with the PEG/MFC composite showed similar amounts of bony regeneration, as did unfilled control defects. At 4 weeks, healing bone accounted for 43%, (+/-13%) in those treated with PEG/MFC and 47% (+/-19%) defect area in untreated holes. By contrast, less than 1% of the area was bone in defects filled with bone wax. They concluded that PEG/MFC composite provided excellent bony hemostasis and did not inhibit bone growth [31].

An experimental, biodegradable polymer ceramic composite combined with recombinant human transforming growth factor beta (rhTGF-beta 1) has been presented by Schmitt and colleagues. The polymer/rhTGF-beta-1 combination was introduced into calvarial defects in rabbits to evaluate biodegradability, biocompatibility, hemostasis control, and bone promotion. Evaluations consisted of clinical examinations, standardized radiography, radiomorphometry, as well as histology and histomorphometry. Radiomorphometric data indicated that standard-size defects treated with the wax-like polymer alone and the polymer plus 2.0 µg of TGF-beta 1 were significantly more radiopaque than control sites at both 6 weeks and 12 weeks. Histomorphometric data revealed that the amount of new bone was significantly greater at 6 weeks in the polymer plus 2.0 µg of TGF-beta 1 and in the control group than in the polymer alone. Moreover, at 12 weeks, there was significantly more new bone in the control than in either the polymer alone or the polymer plus 2.0 µg of TGF-beta 1. They speculate that the incomplete biodegradation of the polymer ceramic composite contributed to the radiopacity and may have retarded osseous regeneration. The bone-wax-like polymer material was biocompatible and acted as a hemostatic agent [39].

When Gelfoam was used in laminectomy operations, multiple neurologic events were reported, including but not limited to cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence. Toxic shock syndrome has been reported in association with the use of Gelfoam in nasal surgery, as warned by the producer.

MFC is of bovine origin and capable of producing a variety of allergic reactions. It has no bacteriostatic properties and can enhance an infection. It interferes with normal wound healing of soft tissue and bone. Therefore, it should be removed from the site of application before closing. It is believed to increase adhesion formation around neural structures. Its swelling rate is lower than other hemostatics; but it still occurs, so compression complications could also happen.

Conclusions

Local agents are largely used to reduce blood loss in spine surgery. Although many new materials are presented each year, the best hemostatic agents have been the same for several decades. Using local agents for chemical hemostasis is not free of risk of complications. Consequently, the spine surgeon should be aware of these and choose the appropriate product for each procedure, following directions for use and using only if strictly necessary.

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The use of fibrin sealants in spinal surgery

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Abstract Advances in anaesthesiology and intensive care therapy as well as improved instrumentation have been responsible for the rapid development of spinal surgery during the past 15 years. Pathological lesions of the spinal column often demand partial or complete resection of the vertebral body, which in turn requires its replacement. The extraordinary vascular supply of the vertebral body and of the spinal canal often results in profuse bleeding in the environs of sensitive structures such as the spinal cord. Electrocoagulation is of limited use, for fear of causing thermal injury. While preoperative embolisation can considerably reduce the tendency to bleed in such instances, bleeding from the epidural venous plexus may be unavoidable, e.g., in spondylitis and tumour surgery. In such instances, fibrin sealants have proved to be an excellent means of controlling diffuse bleeding. Fibrin sealants have also proved to be effective in controlling diffuse bleeding during cervical disc surgery, which occasionally necessitates preparation and identification of the vertebral artery. The resulting spectrum of applications of fibrin sealants are presented here.

Keywords Collagen matrix · Fibrin sealants · FloSeal matrix · Haemostasis · Spine surgery

Introduction

In the last 20 years, there has been rapid progress in the area of spinal surgery. Without advancements in the fields of anaesthesiology, intensive care medicine and the creation of special implants and instrumentation systems for the spine and a much better knowledge of the anatomical and fundamental biomechanical principles of the spine construct, the developments of modern-day spinal surgery could not have been achieved.

The concept of spinal surgery today centres on the treatment and correction of defects in the posterior and anterior parts of the spinal column, where malformations and instabilities can develop and where even the spinal cord and nerve roots can be affected. In the treatment of the more frequent disorders, spinal surgery involves the correction of congenital malformations such as scoliosis, kyphosis, hemivertebra, wedge-shaped vertebra and, especially, malformations at the craniocervical junction.

A further large group of disorders comprises degenerative changes or maladies of the spine. In the cervical spine area these include degenerative changes in the cervical disc, with marked reactive bony changes, such as uncovertebral arthrosis, or slipped cervical discs (with increasing frequency) and spinal stenosis. Similar changes in the area of the lumbar spine, such as degenerative lumbar scoliosis in older people, ventral or lateral spinal stenosis or spondylolisthesis frequently require surgical treatment.

Another large group of spinal surgical maladies comprises bone and soft-tissue destruction and deformities resulting from trauma, infections and tumour manifestations and those associated with systemic diseases such as rheumatoid arthritis.

Adequate operative measures to restore the function of the spine can be jeopardized by serious complications owing to its complex anatomy. The spinal cord and its branching nerve roots pose one important challenge, and the peculiar system of blood circulation poses another. As we know, the spine is constructed in segments and, corre-

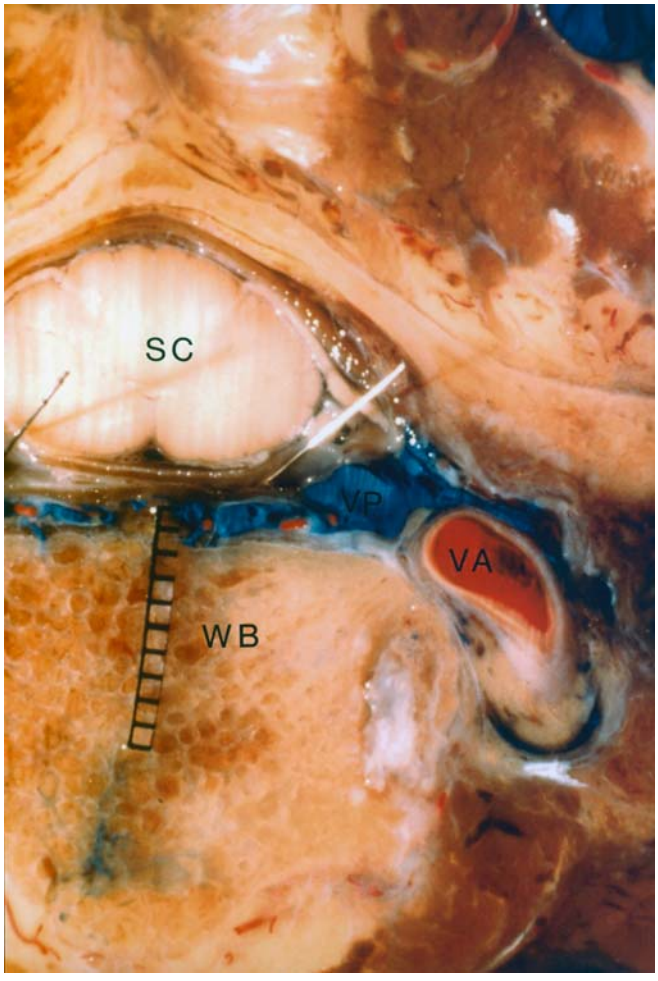

Fig. 1 Anatomical cross-section of the middle area of the cervical spine. Illustration of the blood circulation of the vertebral artery (*VA*) and the intraspinal and intraforaminal plexus of veins (*VP*). (*SC* spinal cord, *WB* vertebral body). (Kindly provided by Prof. Lang, Institute of Anatomy, Würzburg, Germany)

spondingly, the blood circulation is also segmental in nature, comprising an arterial and venous ring system. Figures 1 and 2 impressively show the great extent to which the spinal canal is supplied with blood vessels and the epidural plexus with veins.

It is easy to understand that an injury to this plexus of vessels can lead to extensive bleeding, confronting us with considerable problems in terms of haemostasis. Within a short time, the loss of blood can be considerable and become life threatening. The intraspinal and the intraforaminal courses of these vessels pose the main problem in surgical treatment.

In the cervical spine area, special attention must be paid to the vertebral artery. Care must be taken to protect this important artery and to carry out haemostasis of the deviating branches, as well as of the easily injured plexus around it. In the operative treatment of many conditions – such as degenerative changes, tumours and inflammatory diseases – this artery should be exposed as a precautionary measure.

In the lumbar spine area, attention should be paid to the plexus of vessels in the spinal canal and in the foramen nervosa area.

Methods of haemostasis in spine surgery

Controlling intraoperative bleeding is extremely important in spine surgery. In the case of osseous bleeding and in-

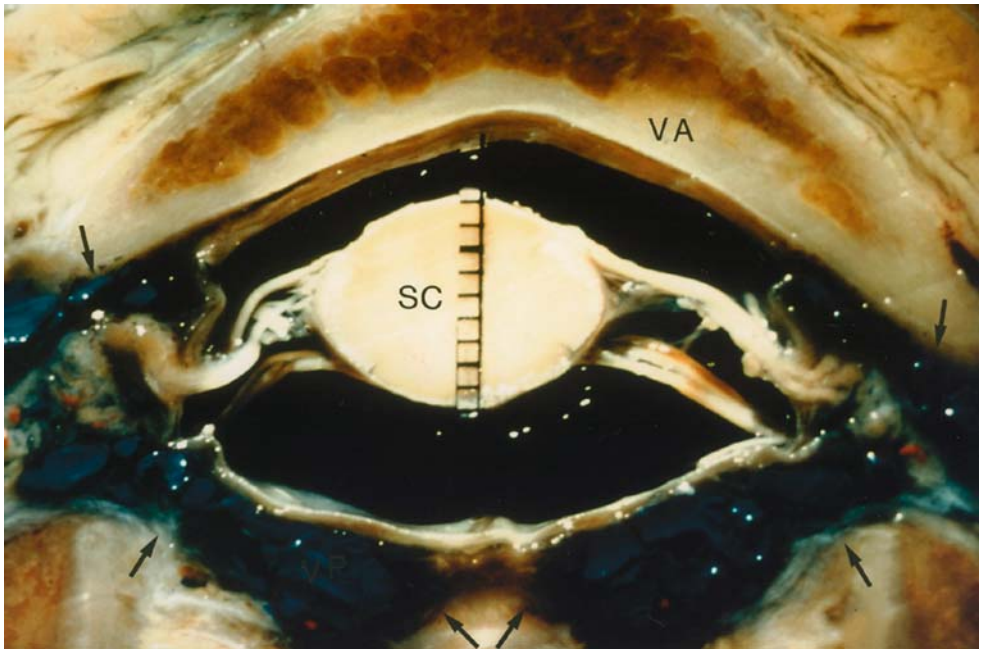

Fig. 2 Extent of the intraspinal plexus of veins (*arrows*) in the mid-thoracic spine area (*SC* spinal cord, *VA* vertebral arch) (Kindly provided by Prof. Lang, Institute of Anatomy, Würzburg, Germany)

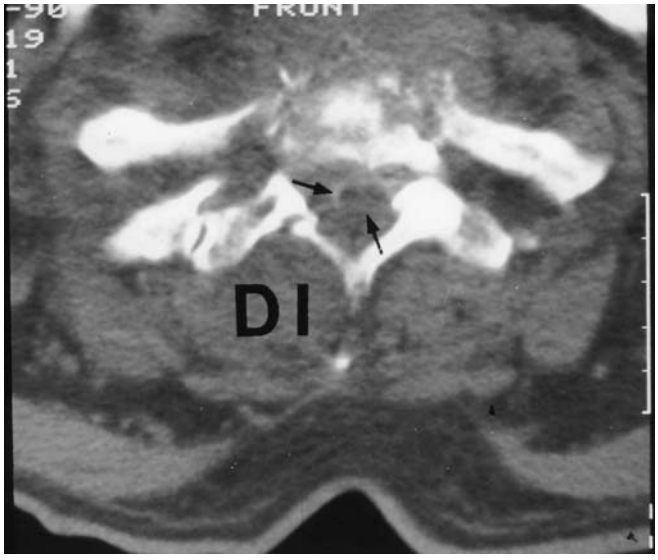

Fig. 3 Nonspecific spondylitis C7/T1 with an intraspinal abscess (*arrows*)

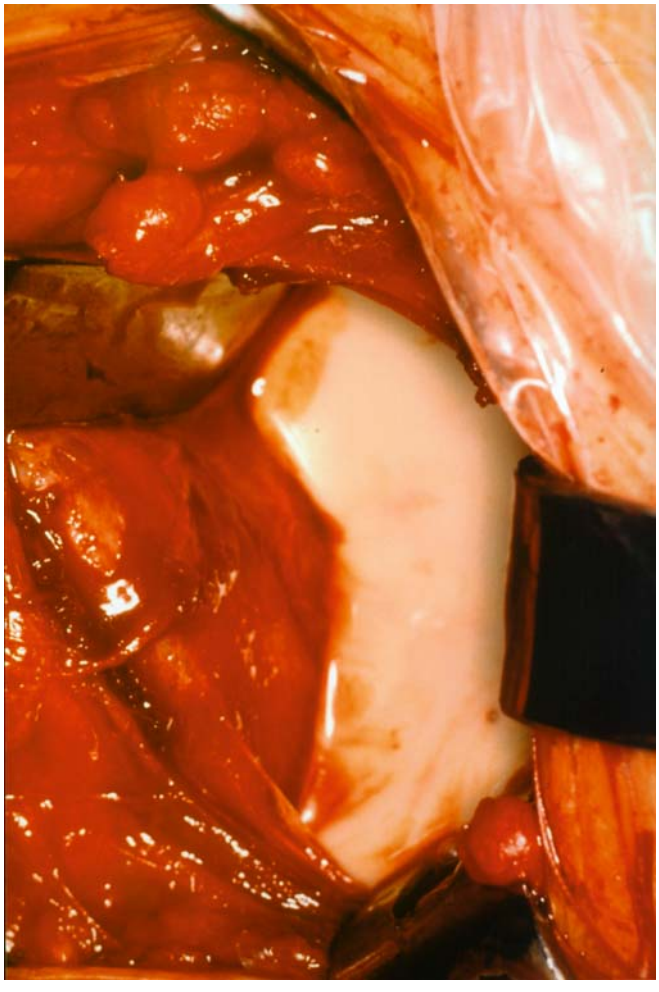

Fig. 4 Abscess-opening via an anterior approach

traspinal or epidural vascular bleeding, quick and safe haemostasis is mandatory to ensure adequate visualization and safe preparation so as to avoid damaging nerves and spinal medulla. In addition, quick and safe haemostasis reduces the duration of surgery. Efficient control of bleeding is also a prerequisite for the realization of the planned therapeutic procedure, i.e., the result of surgery, and can thereby reduce perioperative morbidity.

To reduce the risk of bleeding, the preoperative methods available to us are selective or superselective embolisation [7, 11, 21], as in the case of hypervascular pathologies (tumour surgery). Intraoperatively, in turn, we have the option of placing ligatures around segmental vessels, although this method or pericentesis is hardly ever an option for local spinal bleeding. When confronted with the intraspinal and intraforaminal plexus of veins, we suture where possible but frequently with great difficulty, because of the acute lack of space. As for electric bipolar coagulation and microcoagulation, it may lead to thermal injuries of nerve structures and is not very efficient against parenchymal or diffuse haemorrhagic oozing.

For the local management of intraspinal/intraforaminal and perivascular bleeding, gelatin and collagen sponges were developed and are often used in combination with thrombin preparations [5, 19, 25]. The use of resorbable fibrin sealant, also referred to as fibrin glue or fibrin tissue adhesive, as a natural or synthetic haemostatic agent has become widely established in all areas of surgery [3, 6, 7]. This applies to vascular or cardiac surgery for sealing anastomosis [10, 13], as well as to neurosurgery [15, 16] for percutaneous dural fistula occlusion [1, 9, 14, 22] and for cavity sealing, in reconstructive bone surgery and general surgery of parenchymal organs. As early as in 1993, Vaguero [33] pointed out that the use of fibrin glue was not associated with any additional induction of intraspinal scar tissue formation.

Our indications for use of fibrin sealant in spinal surgery include:

1. Haemostasis [3, 6, 16, 27]
   (a) Perivascular vessels (e.g., vertebral artery)
   (b) Intraspinal vessel systems (especially venous)
   (c) Diffuse and widespread bleeding from tumours or infected osseous or soft tissues, including rheumatoid manifestations of the spine
2. Suture reinforcement in combination with autologous tissue or collagenous material [7, 8]
   (a) Suturing of dura or dura reconstruction (Figs. 6, 7)
   (b) Suturing of blood vessels
3. Cavity sealing [16, 26, 27]. The closure of remaining cavities or layers prone to complications, mostly in transoral spinal surgery (soft palate, back wall of the pharynx, etc.)
4. Sanitation/fusion of osseous defects (in combination with spongiosa) [2, 17, 18, 28, 32]
   (a) Formation and stabilization of spongy bone grafts to avoid dislocation and damage to surrounding nerve structures [27]

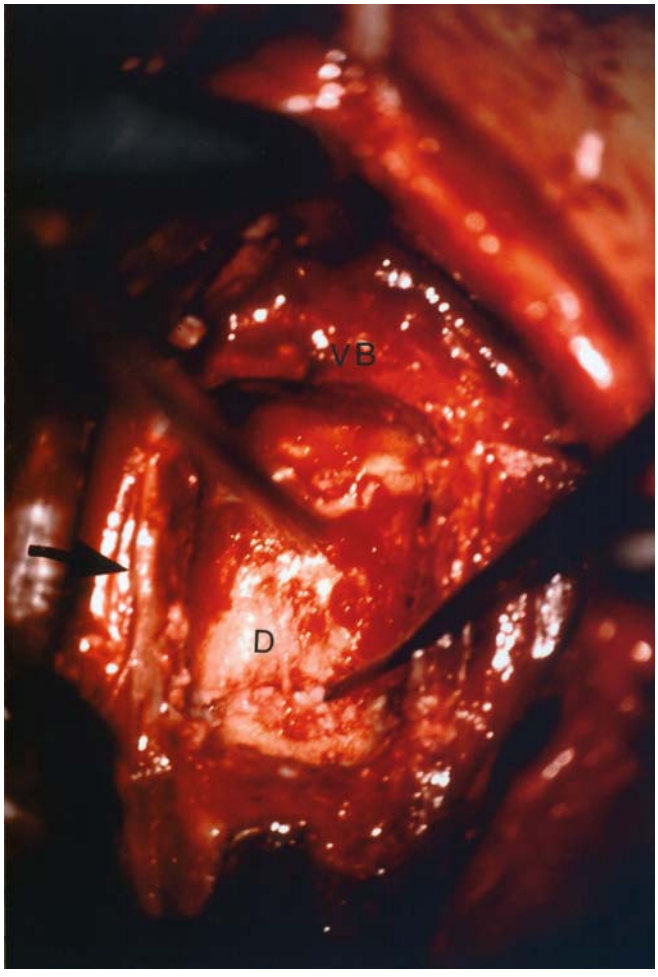

Fig. 5 Debridement with corporectomy and clearance of spinal canal (*VB* vertebral body, *D* dura with remainder of the infectious membrane). *Arrow:* vertebral artery with venous plexus

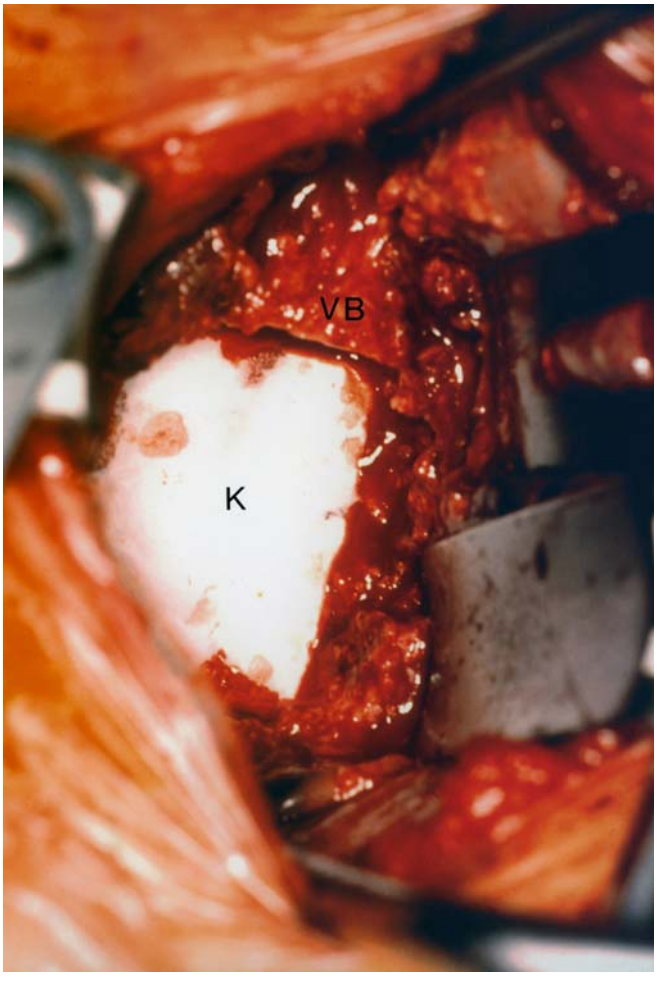

Fig. 6 Haemostasis with help of fibrin glue and antibiotic-impregnated collagen for an additive local therapy against infection (Genta-Coll resorb) (*VB* vertebral body, *K* collagen matrix)

(b) Reduction of blood loss at multilevel posterior corrective spinal fusion (scoliosis surgery) [32]

5. As a transport medium for the application of antibiotics to inflammatory processes or spaces where infection is likely to occur, or in combination with both antibiotics and spongiosa [4, 12, 19, 20]
6. Haemostasis and local infection therapy in combination with a collagenous material impregnated with antibiotics [19, 24, 28]

Fibrin sealant and collagen matrix are ideal haemostats that can be used simultaneously as drug carriers. For the treatment of infections of the vertebral column, a resorbable collagen carrier impregnated with antibiotic has been available since 1986 as a drug carrier in order to achieve high local concentrations of the bactericidal agent, in addition to systemic antibiotic treatment [19]. Our experience – more than 400 cases, with an infection-free healing rate of more than 97 % [28, 29, 30] – shows that this therapy has proved its worth in "one-step" surgery involving radical débridement and abscess removal with autologous-bone defect repair and instrumentation. Diffuse bleeding is an additional problem frequently associated with the surgical treatment of infections of the vertebral column. Consequently, the collagen carrier, in combination with fibrin sealant, may prove highly useful for haemostasis, apart from its antibiotic treatment effect. We use an equine collagen impregnated with gentamycin (Genta-Coll resorb) [24].

Nonetheless, the use of collagen sponges, alone or combined with fibrin adhesive, to achieve haemostasis can be problematic and ineffective. The expansion of collagen sponges can compress and damage surrounding nerve structures. At the same time, removal of the sponges to prevent compression frequently leads to persistent if not worsening bleeding. A new haemostatic agent can offer major advantages in this regard – it is a high-viscosity gel combining collagen-derived granules and topical thrombin (FloSeal). Studies showed [5, 8, 10, 23] that this

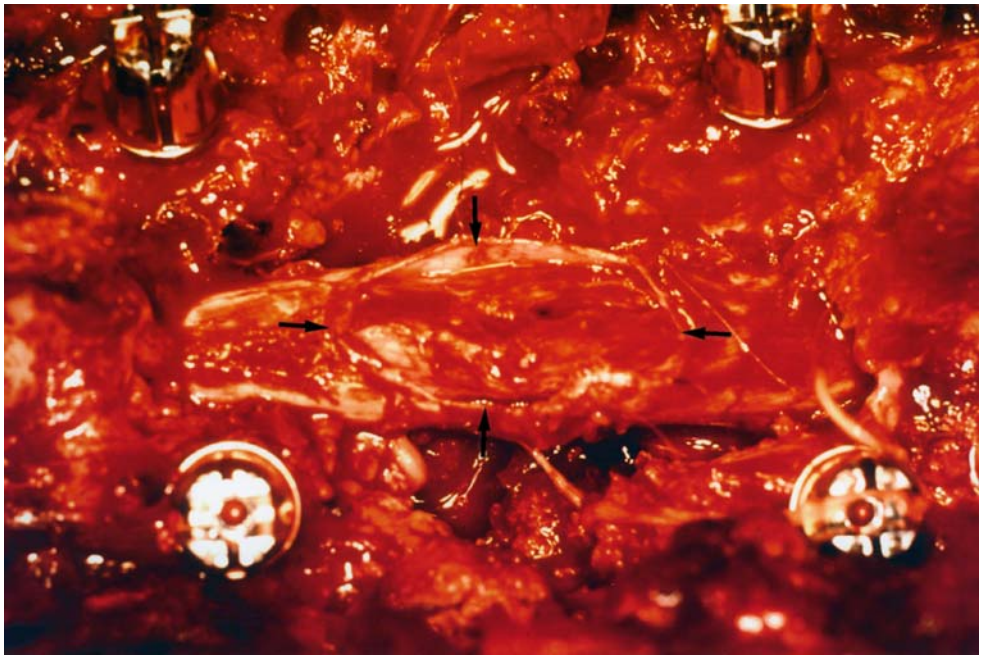

Fig. 7 Intraoperative exposure of the distraction injury. Depicted is the status after bony decompression. The *arrows* show an extensive tear of the dura and tearing out of the nerve root L1. The transpedicular screws for dorsal stabilization are in place

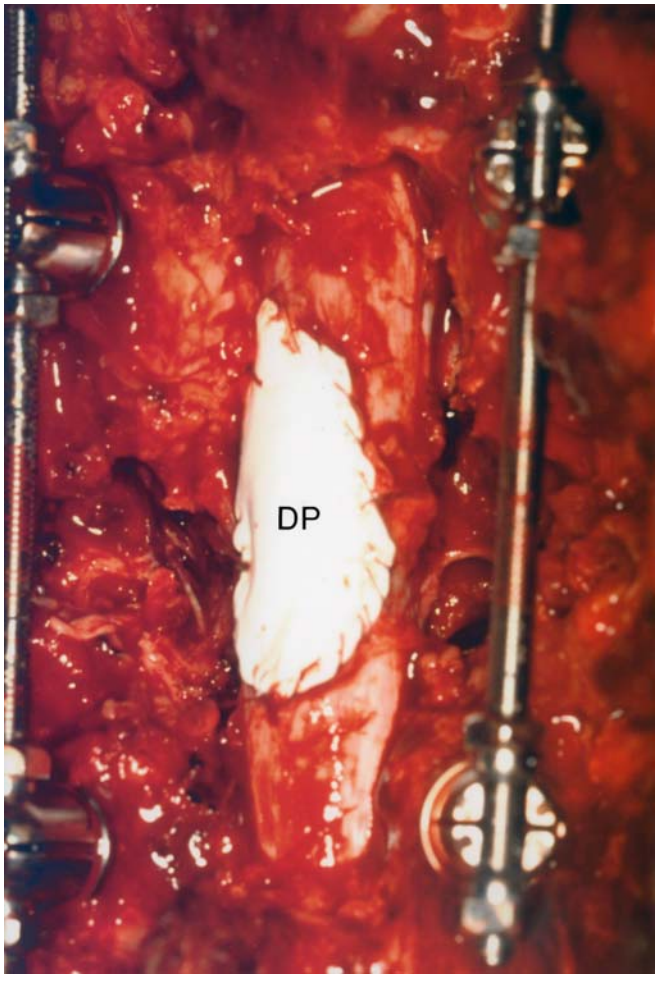

Fig. 8 After closing the dura with a patch (*DP*), the instrumentation is completed. Finally, the dura suture is secured with fibrin adhesive and covered with a fat-tissue graft

gelatin-based haemostatic sealant is significantly more effective, in less time, than other haemostyptic agents (Gelfoam + thrombin combination), and that it provides considerably more durable haemostasis. Another advantage of FloSeal is that, after application in the spinal or foraminal space where resulting compression could damage nerve structures, FloSeal can be irrigated away while maintaining haemostasis.

Our own clinical experience shows that the additional use of this product in the vicinity of the spinal cord and nerve roots is an efficient means of creating a dry and clear operating field, enhancing the safety of the operation while reducing its duration. FloSeal may also help to significantly reduce overall blood loss in major or multilevel surgical procedures and, particularly, in tumour surgery. In 1990 Tredwell [32] reported a major reduction in perioperative blood loss (approximately 25%) during multilevel dorsal fusion in scoliosis surgery, when a fibrin sealant was used for fusion to cancellous bone. Shortened operating times and the prevention of haematoma formation both serve to reduce perioperative and postoperative morbidity and, as a result, lead to better outcomes and cost savings.

Conclusion

Efficient and safe haemostasis, in the spinal canal and around the neuroforamen, is a prerequisite for successful spinal surgery. It facilitates the avoidance of intraopera-

tive complications, reduces the need for blood transfusions and prevents postoperative haematoma formation and its concomitant risks, wound healing disorders and infections. Given the increase in procedures involving older patients, these considerations continue to take on even greater importance. Indeed, modern spinal surgery without these products for haemostasis is hard to imagine.

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The use of local agents: Surgicel and Surgifoam

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Abstract There are various electrical, mechanical and chemical methods used to achieve haemostasis in spine surgery. Chemical haemostatic agents are often preferable to bipolar cautery in intraspinal procedures, because these products control bleeding without occluding the vessel lumen and cause no thermal injuries to adjacent structures. A topical haemostat is the often the technique of choice to control bleeding from bone and to diffuse capillary and epidural venous oozing. This paper focuses on technical aspects of the application of absorbable porcine gelatine and regenerated, oxidised cellulose. These haemostats have been used in neurosurgical intraspinal procedures for more than 30 years; however, new application forms like Surgicel fibrillar and Surgifoam powder imply different handling options, which are discussed in this paper.

Keywords Haemostats · Spine · Absorbable porcine gelatine · Regenerated oxidised cellulose · Intraspinal surgery

Introduction

Achieving haemostasis during surgical procedures within the spinal canal is of paramount importance. Whereas bleeding of up to one litre may be tolerated within structures such as the abdominal cavity, bleeding of only a few millilitres within the spinal canal may cause devastating neurological damage. In addition, microsurgical approaches to intraspinal structures depend on clear visualisation of the most delicate structures: continuous bleeding may impede identification of eloquent and/or pathological structures. Mechanical methods of haemostasis such as direct pressure and ligature are not applicable in intraspinal surgery because of the depth at which the surgery is performed and the indispensability of structures. For most of this century, the mainstay of controlling intraspinal bleeding has been bipolar cautery, allowing precise coagulation of small vessels, and, compared to monopolar cautery, minimizing the dangerous spread of current to adjacent tissue. Intraspinal, intradural and intramedullary bipolar cautery, however, has severe drawbacks. The complete occlusion of the vessel lumen may compromise the perfusion of the neural tissue supplied by the cauterized vessel. In addition, dissipation of heat from the tips of the bipolar forceps may induce thermal injury to adjacent vascular and neural structures. Though bipolar cautery is most effectively used to occlude identifiable vessels, it has minimal efficacy in controlling the diffuse capillary bleeding that characterises most intraspinal pathologies. For these reasons chemical haemostatic agents are often preferable to bipolar cautery in intraspinal procedures. These products can control bleeding without occluding the vessel lumen and cause no thermal injuries to adjacent structures. When applied topically, these agents can effectively control diffuse capillary oozing.

General remarks

In the majority of intraspinal, extradural procedures, bleeding is caused by venous vessels. This low-pressure bleeding will eventually stop when the patient is repositioned in the supine position and the intraspinal counter-pressure exceeds the intravenous pressure. However, due to venous compression, dilated varicose intraspinal veins may be a source of continuous bleeding, thereby impeding visuali-

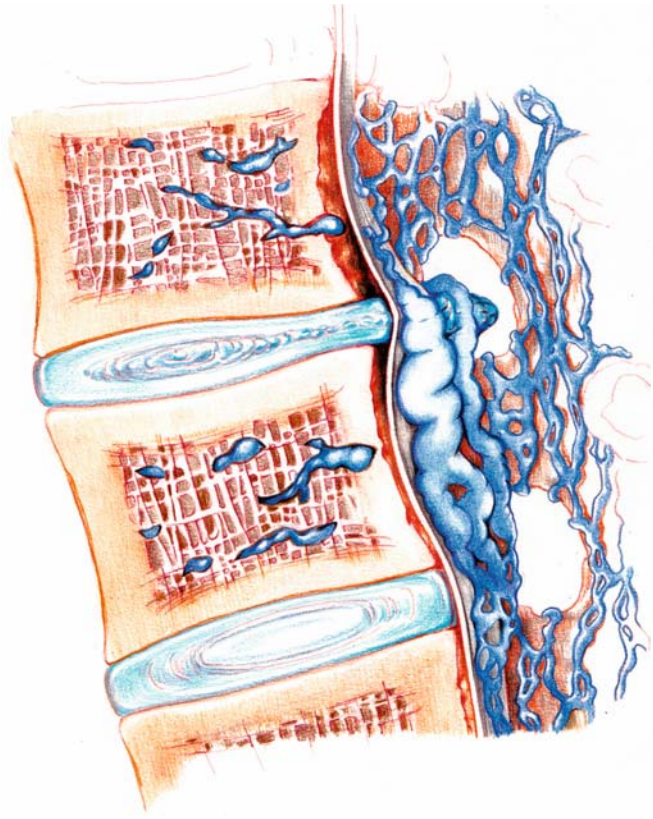

Fig. 1 Artist's rendition of the most common cause for troublesome bleeding during microsurgical intraspinal procedures. Mass effect of disc protrusion causes venous compression, which leads to dilated varicose intraspinal veins. These veins are the source of continuous bleeding, impeding visualisation of eloquent structures and can even cause severe blood loss

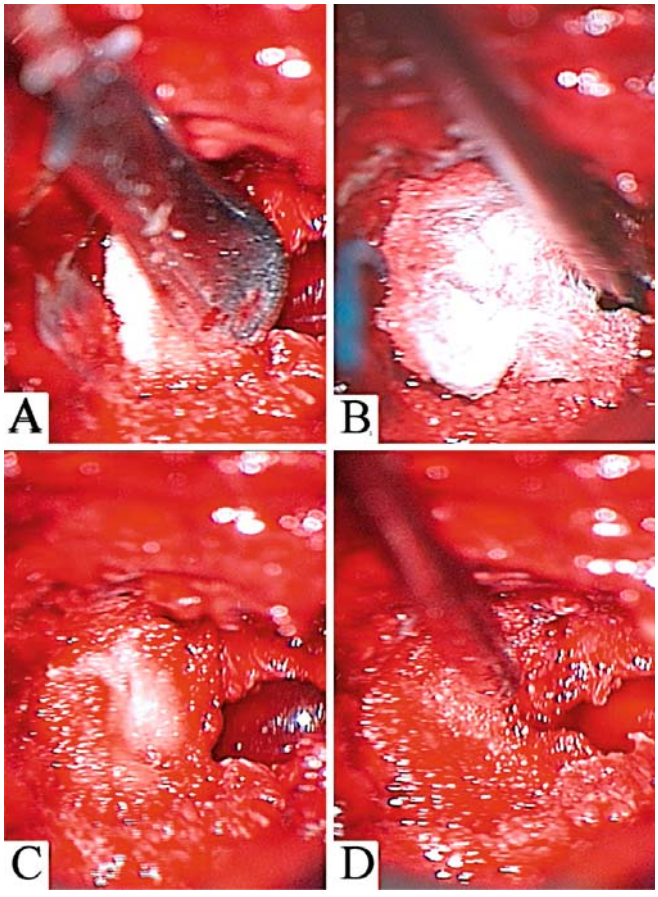

Fig. 2 **A** Application of Surgifoam powder to control bleeding from oozing bone after partial laminectomy; **B** Surgifoam powder is easily applied on the oozing surface using a dissector and molded into the bone after covering it with wet cottonoid patty; **C** bleeding will stop almost immediately; **D** residual Surgifoam powder may be removed by topical suction or irrigation

sation of eloquent structures and causing severe blood loss (Fig. 1). A topical haemostat is the technique of choice as an adjunct to diathermy, to bone wax placed on bleeding bone and to the conventional clamping and tying of bleeders. Arterial bleeding, which is usually not manageable with application of haemostats, is only rarely encountered during most intraspinal extradural procedures.

This paper will focus on the application of absorbable porcine gelatine and regenerated oxidised cellulose. The favourable chemical properties of these haemostats have been reviewed elsewhere [2].

Given the plethora of a complicated intraoperative situation, we will discuss the most commonly encountered indications for haemostats during a standard intraspinal procedure: bleeding from bone and epidural venous oozing.

Bone

Most intraspinal procedures involve a more or less extensive removal of bone. As bone is chipped away, the remaining bone and tissue tends to ooze. Bone wax is commonly used to stop bleeding from oozing bone. Though widely used, bone wax has some disadvantages. Because of its consistency it is often difficult to mold wax to the contours of the bleeding areas using a dissector. Recently, Surgifoam powder (absorbable porcine gelatine, also: Spongostan powder) has been introduced into the European market. This haemostat forms a paste that can be spread or shaped to conform to irregular surfaces to stop bleeding fast. In contrast to bone wax, Surgifoam powder is easily moulded on the irregular surfaces of chipped bone. We prefer to apply a pea-sized portion of Surgifoam powder on the oozing surface and mould it into the bone after covering it with wet cottonoid patties (Fig. 2). Bleeding will stop almost immediately. Residual Surgifoam powder may be removed by topical suction or irrigation.

Epidural oozing. Dissection of the dura from the lamina causes epidural venous oozing (Fig. 1). This can be a particular nuisance since many of the intraspinal approaches

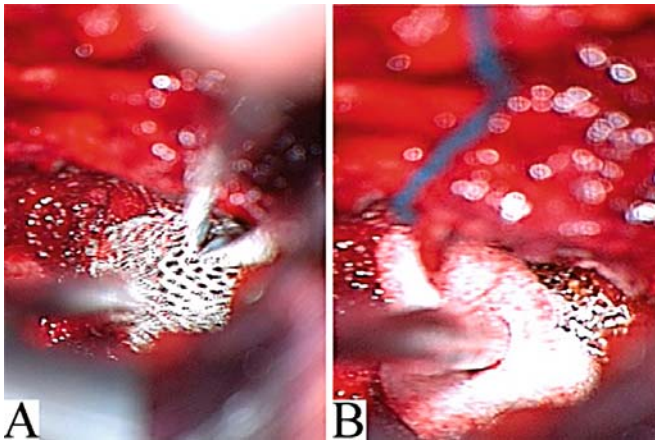

Fig. 3 **A** A small piece of Surgicel is shaped on the bleeding surface by bipolar forceps and suction device; **B** dislodgement by the suction device is best prevented by placing a cottonoid patty on the Surgicelstrip and manoeuvring the haemostat into the desired position

are typically performed through small incisions or under a microscope and even a small amount of oozing can obstruct the surgeon's view. The use of bipolar cautery is limited, since dissipation of heat from the tips of the bipolar forceps may induce thermal injury to adjacent nerve roots or neural structures. Though commonly used, the application of absorbable gelatine sponges in this setting has severe drawbacks. Blood-soaked gelatine tends to stick to surgical instruments. Furthermore, gelatine sponges don't form a tight bond with the source of bleeding and are, therefore, very easily dislodged. The introduction of regenerated oxidised cellulose (Surgicel) offers superior handling characteristics as compared to gelatine sponges. It is supplied as a knitted strip that can be easily trimmed to any size. Cut into small pieces, Surgicel conforms well to shapes, is easily manipulated and does not stick to instruments. The best way to prevent dislodgement by the suction device is to place a cottonoid patty on the Surgicel strip, thus enabling the surgeon to manoeuvre the haemostat, with the tip of the suction device, into the final position (Fig. 3). Surgicel fibrillar is supplied as a layered, three-dimensional wafer with a consistency resembling cotton. Since the layers are peeled off in the desired amount, controlled placement of custom-sized pieces is facilitated. In contrast to gelatin sponges, Surgicel fibrillar remains pliable and can be reshaped within the wound. If necessary and safe, bipolar cautery can additionally be directly applied to the fibrillar surface to produce more effective haemostasis. Interestingly, Surgicel fibrillar allows for a direct application of suction, obviating the need for the overlying cottonoid patty (Fig. 4). This is most comfortable for microneurosurgical, intraspinal procedures in which the rather bulky cottonoid patty significantly obscures the surgeon's view. Similar to the application of gelatine sponges, Surgicel can swell and should be removed from the site of application, when haemostasis is achieved.

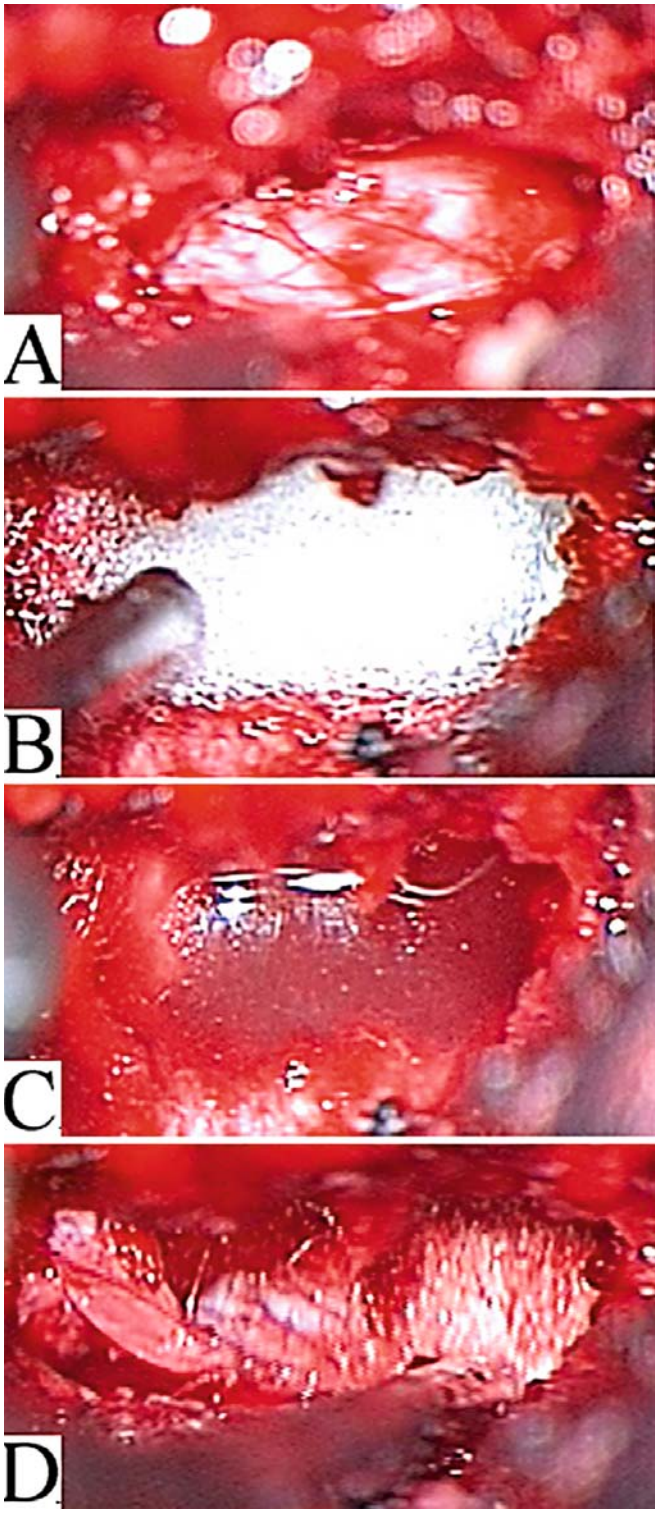

Fig. 4 **A** During microsurgical nerve-root decompression, severe venous oozing may be encountered; **B** a custom-sized piece of Surgicel fibrillar is placed on the nerve root; **C** after irrigation Surgicel fibrillar remains pliable and can be reshaped within the wound, allowing a direct application of suction; **D** this obviates the need for the overlying cottonoid patty

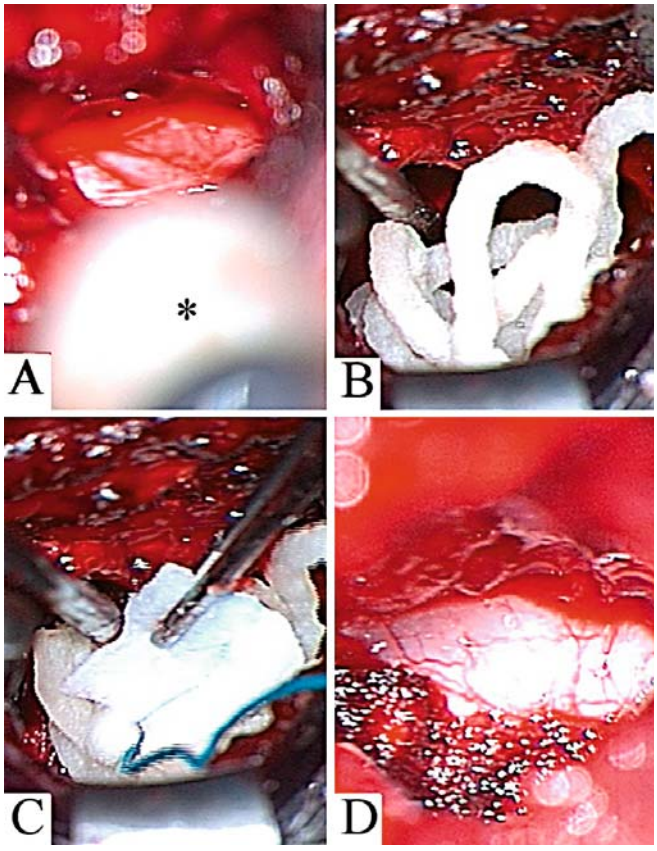

Fig. 5 **A** Example of intraspinal application of Surgifoam powder using a *syringe*;* **B** and **C** a cottonoid patty is used to mold the paste gently into the bleeding surface; **D** Surgifoam powder is easily removed using the suction device, revealing the target structures while haemostasis is achieved

The consistency of Surgifoam powder enables the surgeon to spread this haemostat into the contours of the bleeding surface, even using a syringe (Fig. 5). To achieve quick and effective haemostasis, the bleeding surface is covered with Surgifoam powder. A cottonoid patty is used to mold the powder gently into the bleeding surface. An outstanding feature of Surgifoam powder is that the paste which covers the target structures can be easily removed using the suction device, enabling the surgeon to proceed, while leaving the residual haemostat in position (Fig. 5).

Discussion

For decades absorbable porcine gelatine and regenerated oxidised cellulose have been used in intraspinal surgery. The superior handling characteristics of both haemostats make them most effective for the control of bleeding during microsurgical procedures. In our opinion they should be used primarily when bipolar cautery is either ineffective or dangerous. There are, however, complications associated with the intraspinal application of haemostats.

There are several reports of paraplegia after thoracic surgery during which oxidised cellulose had been used during thoracotomy for haemorrhage control and was later found to have passed through the intervertebral foramen, causing spinal cord compression [3, 5]. It is therefore recommended, that in all intraspinal and perispinal procedures, over-liberal use of Surgicel should be avoided, and attempts should be made to remove all excess Surgicel once adequate haemostasis is obtained. Similar to the complications associated with the use of oxidised cellulose, there are several reports of severe neurological deficits due to the intraspinal application of absorbable gelatin sponges [1, 4, 6]. If gelatine sponges are not handled properly, they can engorge, thus causing a mass effect. Therefore, care must be taken to avoid placing a large mass of sponge in a closed space, such as the spinal canal. Though Surgifoam powder consists of absorbable gelatine, its technical properties make it unlikely to cause mass effects. However, residual Surgifoam powder should be removed by topical suction or irrigation.

Although topical haemostats are widely used, there are only a few reports on the postoperative CT or MR characteristics of these products. In fact, oxidised cellulose granulomata may mimic tumour recurrence [9] or postoperative abscess [7, 10] on both CT and sonography when a patient undergoes imaging early in the postoperative period [11]. Oto described the appearance of oxidised, regenerated cellulose on postoperative MR imaging with a short relaxation time on T2-weighted images, resulting in low signal intensity in the early postoperative period. The author concluded that MR imaging may be helpful in differentiating Surgicel from an abscess and, therefore, in preventing unnecessary attempts at re-operation [8].

Conclusions

Despite these complications, the use of absorbable porcine gelatine and regenerated, oxidised cellulose as haemostats in intraspinal surgery must be considered safe and beneficial. However, the appropriate use of haemostats requires a certain understanding of their advantages, limitations and the nature of complications associated with their application.

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A new simplified technique for producing platelet-rich plasma: a short technical note

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Abstract A possible strategy to promote the wound-healing cascade in both soft and hard tissues is the preparation of an autologous platelet-rich plasma (PRP) to encourage the release of growth factors from activated platelets. In this process, PRP combines the advantage of an autologous fibrin clot that will aid in hemostasis as well as provide growth factors in high concentrations to the site of a tissue defect. The PRP preparation can be used as a biological enhancer in the healing of fractures and lumbar fusions. The local application of growth factors seems to promote initiation and early maturation of bone formation. Autologous bone or bone substitutes can be added to this mixture to increase the volume of grafting material. A simplified technique utilizing a commercially available separation system (GPS – Gravitational Platelet Separation System) is described. This system provides a less costly alternative to other previously described augmentation techniques and also presents a patient-friendly and operator-safe alternative. Further experimental studies of the actual concentrations of the growth factors in the PRP samples are necessary in order to validate the platelet concentration and growth-factor activation by laboratory evidence. In further prospective clinical trials, the safety and efficacy of PRP, in combination with autologous bone or bone graft substitutes, must be evaluated.

Keywords Platelet concentrate · Growth factors · Bone healing · Platelet-rich plasma · GPS

Introduction

Autologous platelet-rich plasma (PRP) is increasingly used in almost all fields of surgery for the clinical treatment of a variety of soft and hard tissue applications, most notably in accelerating bone formation and in the management of chronic nonhealing wounds [1, 13, 15, 24]. The use of PRP combines the advantage of an autologous fibrin clot that will aid in hemostasis as well as the provision of growth factors in high concentrations to the site of a bone defect or a region requiring augmentation after platelet release.

Bone formation at the site of a fracture or at the site of grafting is initiated by a process of fibrin clot formation, platelet aggregation, and degranulation. Platelet granules contain a variety of physiologically active substances, such as catecholamines, serotonin, calcium ions, adenosine triphosphate (ATP), albumin, fibrinogen, osteonectin, osteocalcin, various clotting factors, and the locally active growth factors, such as PDGF, TGF-β, IGF, FGF, and EGF [12]. With a better understanding of the various biological factors that initiate, maintain, and regulate the complex process of osteogenesis, new strategies can be followed to manipulate the biological environment of the site of bone formation and to enhance bone fusion.

For bone defects, PRP can be mixed with autologous bone or with bone graft materials [8, 9]. PRP is then delivered to the recipient bed along with autologous or bovine thrombin and placed in the graft site. The fibrino-

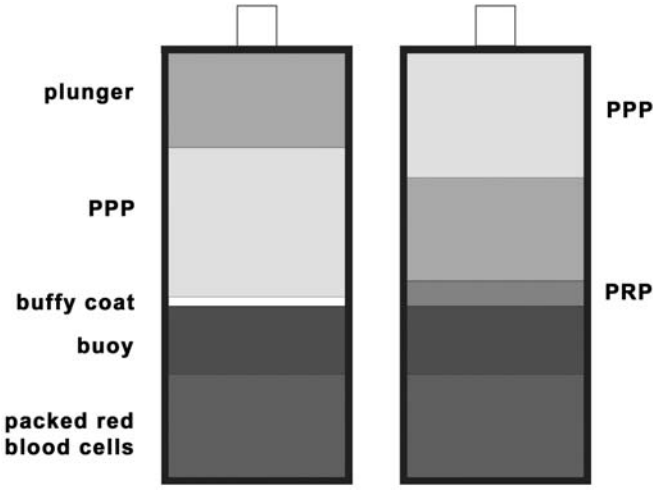

Fig. 1A, B Schematic view of the disposable GPS tube after centrifugation at 3,200 rpm for 12 min. The red blood cell fraction on the bottom of the tube is separated through a buoy from the buffy coat and the platelet-poor from the platelet-rich plasma (**A**). A plunger is manually pushed down and separates the platelet-poor from the platelet-rich plasma (**B**)

gen present in the PRP is activated and becomes cross-linked to form a fibrin network [16]. Thus, the graft is solidified and adheres within the defect.

The extraction of platelet concentrates through plasmapheresis is a process by which PRP is taken from the patient, and the remaining components of blood are delivered back into the body. With this technique, PRP can be produced at a concentration of 300% of normal blood levels [15, 22]. For practical and economic reasons, this procedure is generally only suitable within larger clinics or hospitals. For a broader and individual use of PRP, different platelet-concentration preparation systems are now commercially available. We describe a simple and disposable system for the preparation of PRP using the Gravitational Platelet Separation System (GPS).

Extraction of PRP

The Gravitational Platelet Separation System (GPS System, Biomet Merck Biomaterials, Darmstadt, Germany) is a simplified, commercially available technique for the ex-

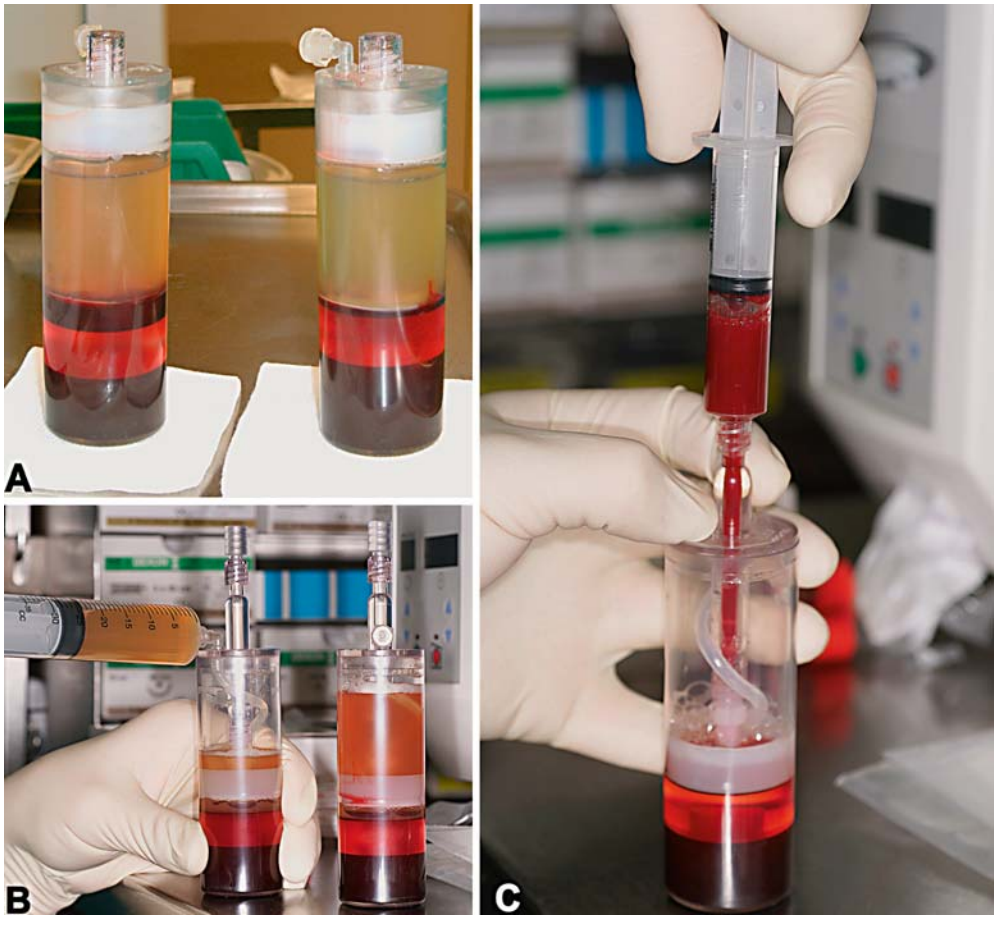

Fig. 2 A–C The GPS tube after centrifugation with the red-colored fraction of red blood cells on the bottom and the buffy coat above the buoy (**A**). The tube after the separation of the PRP, with a manually pushed down plunger (**B**) and the extraction of the PRP (**C**)

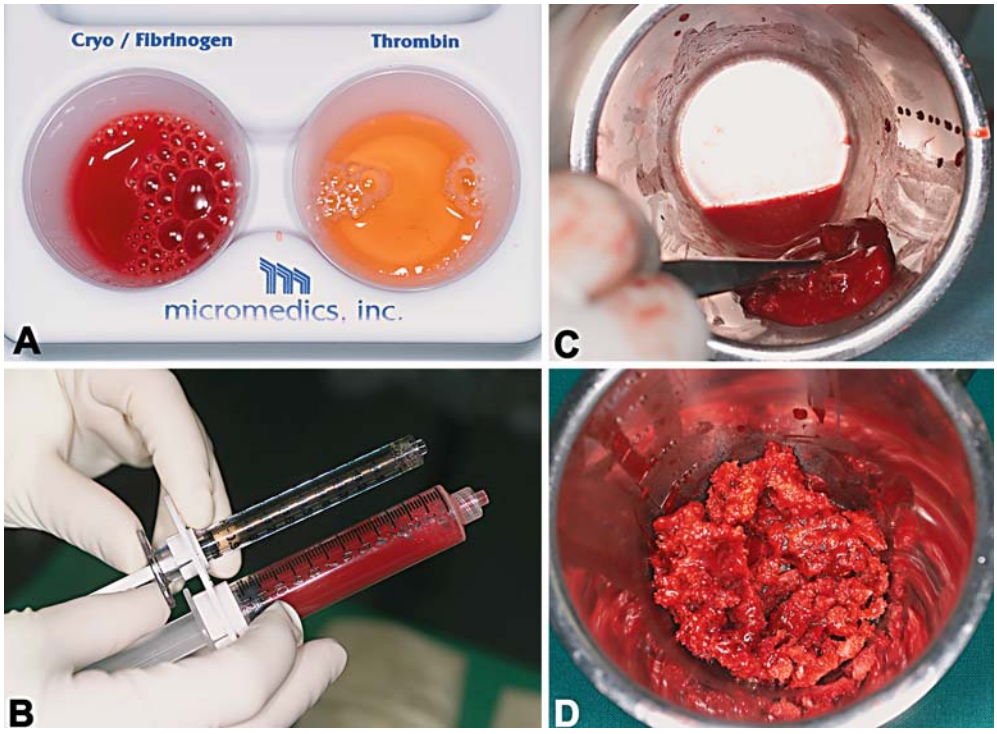

Fig. 3 A–D PRP and autologous thrombin solution on the operation table (**A**), aspirated in a double syringe in a 10:1 ratio (**B**), forming a clot after combination (**C**) and mixed with autologous bone (**D**)

traction of PRP. The system consists of a disposable GPS tube that is used together with a bench-top centrifuge. The preparation can be performed in the operating theater during the actual surgical intervention and takes about 30 min. First, 6 ml (1 ml=1 cm^3=1 cc) of Anticoagulant Citrate Dextrose Solution (ACD-A) is drawn into a 60 ml syringe, followed by 54 ml of whole blood. The sample is gently agitated to mix the anticoagulant thoroughly with the blood. Then, the blood is injected into the GPS disposable unit and centrifuged for 12 min at 3200 rpm using a standard electronically controlled bench-top centrifuge (Thermo, IEC International Equipment Company, Needham Heights, Mass.). Following centrifugation, the blood sample is separated in different blood fractions: the red blood cells form a red-colored fraction on the bottom of the tube separated through a buoy from the buffy coat and a whitish layer rich in white blood cells and platelets and the platelet-poor plasma (PPP), which contains autologous fibrinogen and is poor in platelets (Fig. 1). In the next step, a plunger is manually pushed down and separates the platelet-poor from the platelet-rich plasma (Fig. 2). The PPP is extracted through a separate luer-lock connection using a 30-ml syringe. Then the tube is vigorously shaken for 30 s, and the platelets are suspended in the remaining plasma. Through a second luer-lock connection the PRP is separately extracted in a 10-ml syringe. For sufficient clot formation, the PRP can now be used with autologous or bovine thrombin solution at a 10:1 ratio. Once the PRP is produced, it can be mixed with the preferred augmentation material, such as autologous bone or different bone substitutes (Fig. 3, Fig. 4).

Discussion

Platelet concentrates function as a tissue sealant and a drug-delivery system that contains a host of powerful mitogenic and chemotactic growth factors. Hemostasis is achieved through the formation of a fibrin clot that is initiated by the activation and aggregation of platelets. The clot is generated by the polymerization of fibrin from the monomer, fibrinogen, in the presence of calcium and thrombin. Platelet aggregation results in a platelet plug that is held in place by the clot and inhibits blood flow [14]. Beyond maintaining hemostasis, the fibrin clot then provides a matrix for the migration of tissue-forming cells and endothelial cells involved in angiogenesis and the remodeling of the clot into repair tissue.

Platelet α-granules have been shown to contain mitogenic and chemotactic growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulinlike growth factor (IGF) [21]. The effects of these growth factors on cell behavior and bone-healing sequences have been thoroughly studied [4, 5, 7, 11, 15, 20, 21].

Caplan has described three sites in bone containing undifferentiated stem cells that are capable of differentiating

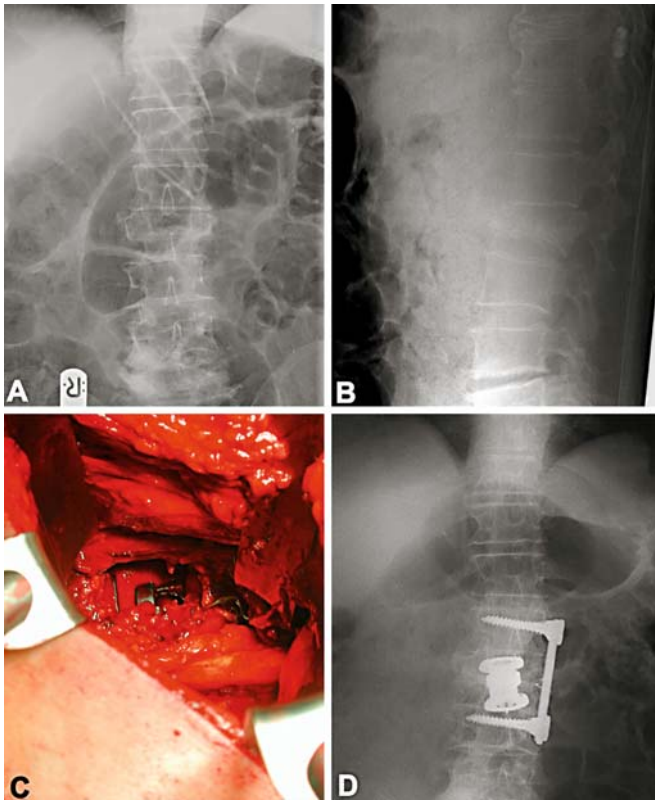

Fig. 4 A–D Example of a 62-year-old man who presented with a burst fracture of L2, with extensive loss of height in the vertebral body (**A**, ap view; and **B**, lateral view). The operation consisted of a retroperitoneal approach, partial resection of the fractured vertebral body, reduction by a distractable cage, and stabilization with a plate system. Autogenous bone was mixed with PRP (**C**, intraoperative site; and **D**, postoperative ap X-ray)

into osteoblasts: the marrow, periosteum, and the perivascular sheath [6]. PDGF and TGF-β have a chemotactic and mitogenic effect on these cells that causes them to multiply and secrete additional growth factors. In a rat tibial-fracture model, injections of TGF-β (4 and 40 ng) every other day for 40 days resulted in a dose-dependent increase in bone thickness [17]. Further, the 40 ng dose also increased mechanical strength [17]. Under the influence of other cytokines and local environmental conditions, such as pH, oxygen tension, and micromotion, these cells undergo a differentiation into osteoblasts or chondroblasts. Collagen and protein synthesis by osteoblasts is also stimulated by PDGF, but also requires the presence of IGF-I [7]. PDGF probably enhances the secretion of IGF-I by the osteoblasts and mesenchymal stem cells, which then accelerates the formation of a collagenous matrix [11]. PDGF also seems to enhance the activity of BMP in promoting cartilage and bone formation [10].

A major concern in the delivery of the growth factors to the site of bone healing has been their short half-lives in the systemic circulation [18]. PDGF has a half-life of about 2 min if injected intravenously, and TGF-β, in its active form, is also cleared from the bloodstream within a few minutes. Further, TGF-β acts only locally, with no influence on bone formation at sites distant from its application [19]. Furthermore, multiple growth factors are present at the same time at the site of bone formation and have a synergistic effect on each other [11]. A study about growth factor interactions concluded that TGF-β, IGF-II, and FGF modify the activity of other growth factors and cytokines and actually have a synergistic effect in combination [11]. This has led to the philosophy of providing multiple growth factors in the bone-cell microenvironment simultaneously to promote interactions between the factors that could be important for regulation of bone-cell proliferation. The mitogenic and chemotactic growth factors in platelets can provide a combination of multiple factors simultaneously, rather than individual factors, and accelerate the bone-healing sequences in order to mimic the natural process of osteogenesis as physiologically as possible.

Clinical experience in larger case series in the treatment of fractures of long bones is limited, as is experience with spine surgery. Prospective randomized trials comparing PRP with other bone-healing, accelerating substances are missing. Quantitative and qualitative measurements in maxillofacial surgery have shown that autologous bone grafts treated with PRP mature in two-thirds of non-PRP graft time, have a 1.6- to 2.6-fold higher radio-opacity, and are 70% more mature than untreated, naturally occurring bone at the site [15]. In a retrospective study, Lowery reported the use of autologous growth factors (AGF) in lumbar spinal fusions. Posterolateral fusion and instrumentation, with or without intradiscal fusion and laminectomy, was performed in 15 cases. Seven of these 15 patients had concomitant intradiscal fusion with titanium surgical mesh (TSM) or a femoral ring spacer with autograft. Posterolateral fusion was performed using a mixture of autograft and AGF concentrate activated by thrombin and coralline hydroxyapatite. In 4 cases, intradiscal fusion was performed without posterior fusion using HA dowels with autograft and AGF concentrate placed in carbon fiber cages or TSM. After a follow-up of a minimum of 6 months, bony fusion was confirmed intraoperatively in 5 of 19 patients. In the remaining 14 patients, radiographs showed solid or maturing fusion in all cases with no radiological or clinical evidence of pseudoarthrosis.

To our knowledge, no prospective studies have been performed using PRP. To prove the concept of using PRP in the treatment of nonunions in long bones and in lumbar fractures in combination with autologous bone augmentation, prospective pilot studies were performed at our institution. The preliminary results are promising, but further prospective comparative studies are necessary to validate the efficacy. These studies will also include a comparison with recombinant bone morphogenic proteins (BMP), which are used in the biological manipulation of the os-

teoinductive process [2]. In spine surgery, rhBMP-2 and rhBMP-7 have been used in clinical trials in different fusion models [2]. In a prospective, randomized, mulitcenter trial, posterolateral intertransverse arthrodesis in degenerative spondylolisthesis and lumbar stenosis was used to compare autograft and rhBMP-7 [23]. In other studies in degenerative disc disease and lumbar interbody fusion, autografts were compared with rh-BMP-2 [3]. If BMPs in these studies are effective and safe, further comparative trials with PRP are necessary and useful.

In conclusion, the GPS is a commercially available separation system for the preparation of PRP using a simplified technique. This system provides an alternative to other previously described augmentation techniques for accelerating bone healing and also presents a patient-friendly and operator-safe alternative. Compared to recombinant proteins and whole BMP extracts, PRP has the advantage that it can also act as a binding medium for bone autografts or granulated bone substitutes, making it easier to handle and place them into the graft site. The most significant benefit of using the PRP is its autologous nature, the fact that it is endogenously derived, and its easy availability. There are no issues about immunogenicity or transmission of infection. There are no known local or systemic side effects or adverse effects. The process is also considerably cost-effective compared to the use of purified or recombinant growth factors.

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Transfusion of post-operative shed blood: laboratory characteristics and clinical utility

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Abstract Increased awareness of the potential hazards of allogenic blood transfusion, such as incompatibility reactions, metabolic and immunologic disorders, or transmission of viral diseases, has led to an emphasis on allogeneic blood alternatives. For orthopaedic surgery, several autologous transfusion modalities have emerged as alternatives to allogeneic blood transfusion, avoiding its immunomodulatory effects. Among them, transfusion or return of post-operative salvaged shed blood has become popular in major orthopaedic procedures. However, although the effectiveness of this blood-saving method is well documented, several authors have questioned its safety and recommended the use of washed blood. Therefore, this review analyses the haematologic characteristics of unwashed filtered shed blood, including metabolic status and survival of red blood cells, the components of the haemostatic system, the content of fat particles, bacterial and tumour cells and the possibility of their removal, the content of inflammatory mediators, and the effects on the patient's immune system. From data reviewed in this paper, it can be concluded that post-operative salvage of blood seems to be an excellent source of functional and viable red cells without many of the transfusion-related risks and with some immuno-stimulatory effects. In addition, from our experience, post-operative re-infusion of unwashed shed blood after major spine procedures has proved to reduce post-operative homologous transfusion requirements and to complement pre-operative autologous blood donation, without any clinically relevant complication.

Keywords Post-operative salvaged blood · Spine surgery · Fat particles · Cytokines · Coagulation · Immune system · Effectiveness

Introduction

It is well known that the defence mechanisms provided by the immune system can be altered by traumatic injury, surgery and transfusions, and there is a growing interest for acquiring greater knowledge on the causes and mechanisms involved in the immunodepression induced by the anaesthetic-surgical procedure, since this increases the susceptibility to post-operative infection and tumour relapse after potentially curative surgery [15, 19, 62]. This interest further increases when it is seen that, in spite of current surgical techniques, of advances in anaesthetics and in the huge variety of anti-microbial agents, general and local infection continues to be one of the main causes of morbidity-mortality associated with traumatic injuries and surgery, increasing its incidence in those patients who have received allogeneic blood transfusions (ABT) [29, 61].

Patients undergoing orthopaedic surgery frequently receive ABT, and the results of two extensive studies including nearly 20,000 patients strongly suggest that peri-operative ABT in this surgery is associated with an increased risk of post-operative infection [5, 8]. The former was a retrospective study including 9,598 consecutive patients of over 60 years of age and having undergone surgery due to hip fracture. Fifty-eight percent of those patients received at least one ABT, and data analysis revealed that ABT was associated with a 35% increase in the risk of severe post-operative infection and a 52% increase in the risk of acquiring pneumonia. The increase was also dose-dependent [8].

In the later, 9,482 patients were studied who underwent elective orthopaedic surgery (EOS) of the knee or hip between September 1996 and June 1997. More than half of those patients (5,741) were included in a pre-operative autologous blood donation (PABD) program (average 1.7 U/patient), and of those, 9% (503) also received ABT, whilst 45% of the pre-deposited units were not used. The overall incidence of post-operative infections was 4.2%. However, when analysing the incidence of infections based on transfusions received, it can be seen that the patients who received ABT had 47% more post-operative infections than those not receiving them (7 compared to 3.68%, respectively; $p<0.001$), whilst there was no difference between those who received autologous blood and those that were not transfused (4 compared to 3%, respectively) [5].

This greater incidence of post-operative complications, in conjunction with other adverse effects both acute and chronic, have prompted the review of transfusion practice and the search for a series of alternative measures such as autologous transfusion, the final objective of which is to reduce to a minimum both the exposition to ABT and the ABT-associated risks [26, 34, 43, 59].

Auto-transfusion in orthopaedic surgery

PABD has been reputed as one of the most safe and effective transfusion therapies, being considered the "gold standard" in auto-transfusion. Thus, the analysis of the results obtained in 11 studies carried out in Spain and six studies carried out overseas with a total of 10,500 patients subjected to EOS of the knee, hip or spine has demonstrated that PABD has an average effectiveness, measured as the percentage of patients that avoid ABT, of 90%, although with an average yield, measured as the percentage of units donated that are transfused, of 62% [45]. Nevertheless, it should be taken into account that this over-collection of units is lower in Europe (10–15%) [53] than in the United States (40–50%) [26], being around 20% in Spain [45]. In addition, PABD may have problems of overtransfusion, is associated with higher rates of clerical errors, is not without infectious risks, and allogeneic transfusion may still be required (break-through transfusion) [5, 26, 45]. Moreover, because the possible role of blood storage on transfusion-induced immunomodulation [40], PABD might be accomplished as close to the operation date as possible, hence demanding a tight surgical program and limiting the number of units to be collected.

In regard to spine surgery, PABD can be safely used not only in adults but in adolescents as well [9, 42, 47, 51, 57]. In this clinical setting, adjuvant treatment with epoetin alpha (EPO) seems to facilitate the collection of the requested PABD units and results in higher peri-operative haematocrit levels [24, 41, 58].

Intra-operative cell salvage (ICS) and post-operative autologous transfusion (PAT) completely avoid the problem of blood storage. During surgery, the intra-operatively salvaged blood is processed to obtain a red cell concentrate ready for transfusion. This procedure has very few complications, the most normal being dilution coagulopathy when a large volume of processed blood is being transfused. However, in spine surgery, the effectiveness of ICS is controversial, and its selective use for operations with high intra-operative blood loss is recommended [1, 9, 10, 11]. Recently, a new automated, specifically designed device (OrthoPAT, Haemonetics), which recovers 80% of red cells from intra-operative blood loss, has been marketed, and both its clinical effectiveness and the quality of the yielded product are under evaluation by our group (unpublished data).

PAT consists of recuperation and re-infusion of shed blood from post-operative draining, total knee arthroplasty being the operation where it has been used the most. There are a number of devices for collecting post-operative shed blood, the principal differentiating characteristic being the existence or not of a washing process for the salvaged blood. When the ICS is not used, PAT is normally performed by using devices that recuperate and re-transfuse shed blood to the patient as unwashed filtered shed blood (USB).

With regard to clinical results, although there have been series published against the procedure, the re-infusion of USB has been shown to be effective in reducing the requirements for ABT [45]. In addition, a meta-analysis of the effectiveness of cell salvage in minimising peri-operative allogeneic transfusion concluded that, in orthopaedic surgery, devices producing either washed or unwashed cells decreased the frequency of exposures to allogeneic blood to a similar degree when compared with a control [30]. Regarding spine surgery, the addition of PAT can considerably reduce PABD requirements and/or complement ICS in both adult and adolescent patients undergoing instrumented spine fusion where the post-operative blood lost is substantial [4, 21, 52, 57, 56].

Controversy on the use of USB

Although the effectiveness of the return of USB after orthopaedic operations is well documented, several authors

Table 1 Some haematologic, metabolic, biochemical and immunological characteristics of post-operative shed blood in comparison with pre-operative venous blood in patients undergoing lumbar spinal surgery. Data are the mean ± SE of 20 determinations. *MCF* median corpuscular fragility, *f* fresh, *i* incubated, *ATP* adenosine triphosphate, *DPG* diphosphoglycerate, *PFHB* plasma-free haemoglobin, *GOT* glutamate-oxaloacetate aminotransferase, *GPT* glutamate-pyruvate aminotransferase, *LDH* lactate dehydrogenase, *CK* creatin kinase, *IL* interleukin, *TNF* tumour necrosis factor

	Pre-operative venous blood	Post-operative unwashed shed blood
Erythrocytes (10^6/μl)[a]	4.7±0.4	3.0±0.2**
MFC*f* (NaCl%)	0.406±0.01	0.422±0.01
MFC*i* (NaCl%)	0.498±0.01	0.486±0.01
ATP (μmol/g Hb)	3.5±0.8	4.3±0.7
DPG (μmol/g Hb)	16.1±2.6	11.5±2.6
D-glucose uptake (nmol/min g Hb)	6.53±0.55	12.10±0.11**
Haematocrit (%)	41.3±3.2	28.5±1.8**
Haemoglobin (g/dl)	14.2±0.3	9.6±0.8**
Leukocytes (10^3/μl)	6.8±1.6	6.7±0.6
Platelets (10^3/μL)	186±71	63±5
PFHB (mg/l)	49±8	2029±146**
Haptoglobin (mg/dl)	160±34	101±14
GOT (U/l)	26±3	1857±231**
GPT (U/L)	15±2	314±67**
LDH (U/l)	293±29	7452±662**
CK (U/l)	62±13	58791±2168**
IL-1β (pg/ml)	4.6±1.1	10.7±1.5*
IL-6 (pg/ml)	2.5±1.1	1335±49**
TNFα (pg/ml)	ND	ND

*p<0.05
**p<0.01
[a]All data taken from references 27 and 33
ND: not detected

have questioned the safety of this blood-salvaging method, because USB is diluted and may be contaminated with fat particles, bone fragments, free haemoglobin, activated coagulation factors, fibrin degradation products or inflammatory mediators, and programs set an upper limit on the volume of USB to be reinfused [3, 6]. In the following paragraphs, we will discuss these points of controversy in relation, where possible, to the USB salvaged after elective spinal surgery (ESS).

Haematologic and biochemical characteristics of USB

The haematologic characteristics of USB, recuperated in the first 6 post-operative hours of ESS using the ConstaVac CBC II (Stryker, USA) blood collection canister, were studied in 28 consecutive patients undergoing instrumented spinal fusion (SF), comprising 2–4 levels with or without decompression of the neurologic elements by microsurgery [56]. As shown in Table 1, USB samples contained lower erythrocyte and platelet counts, haemoglobin and haematocrit than blood drawn from the patient in the pre-operative period, with similar figures being reported previously [6, 52]. However, their erythrocytes showed no significant morphological abnormalities, presented a normal osmotic fragility and maintained a normal energy metabolism. In this regard, intra-cellular concentrations of adenosine triphosphate (ATP) and diphosphoglycerate (DPG) in USB erythrocytes were found to be higher than those of banked blood erythrocytes [44]. Taken together, these results seem to show that these red cells are not significantly damaged, keep all their functionality, and have a viability comparable to those from pre-operative and intra-operative blood collection [14, 50].

Measurement of PFHB has been used as an index of haemolysis and, certainly, its levels in USB were above the normal limits (Table 1). However, it has been previously reported that if USB is reinfused up to 15% of the total blood volume [6] or 1,000 ml [3], there seems to be enough circulating haptoglobin to bind PFHB, avoiding possible renal damage [4]. The increased serum concentrations of K^+, glutamate-oxaloacetate aminotransferase (GOT) and lactate dehydrogenase (LDH) in USB also suggest a degree of haemolysis, whilst increased levels of glutamate-pyruvate aminotransferase (GPT) and creatin kinase (CK), as well as partially those of LDH, are most probably due to enzyme release from muscle during surgery [56]. High levels of these enzymes were measured during the first post-operative week in patients undergoing SF, with a similar but more pronounced pattern being observed in patients receiving USB [56]. Therefore, caution should be taken when the serum levels of these enzymes are used for diagnosis at this time.

Fat particle content of USB

From a micro-rheological point of view, both the total blood and the erythrocytes of USB show a greater filterability through 5 μm polycarbonate membranes (which would be

equivalent of passing through a capillary bed) than the patient venous blood, which could be attributed to the practical absence of fibrinogen and a reduction in the number of leukocytes in USB [12, 13]. On the other hand, blood stored in a bank or processed with a cell saver shows a far less filterability than the blood from the patient [36]. Nevertheless, USB plasma shows less filterability than venous blood [13], which is attributable to contamination with several types of particles, among which are fat.

Return of fat probably increases the risk of fat embolism syndrome, which is mostly associated with acute lung injury. Thus, an effective, reliable, low-cost method of monitoring fat particle content in USB would be useful in ensuring that shed blood that is returned to the patient is not contaminated with fat. Usually, fat content in shed blood was measured in Nile red-stained samples with flow cytometry or fluorescence microscopy, which is an expensive and complex methodology [6, 28]. On the other hand, fat particle removal has been accomplished by either filtration [28, 35] or the use of cell salvage devices that wash and concentrate autologous RBCs [7, 35].

Very recently, we have validated a new method, far more simple and faster than the flow cytometry, based on the use of the different hematologic cytometers, that allows for detecting fat particles in USB and verifying their elimination by the use of several leukocyte filters (Pall RC100, PureCell, LeukoGuard, Sepacell, BioR, Imugard IIRC) [46, 49]. Also, there is data that supports the efficiency of these filters in the elimination of tumour cells and bacteria [16, 48], although other authors recommend washing and irradiating the blood [27].

Haemostatic alterations induced by re-infusion of USB

USB contains certain activated coagulation factors as well as degrading products of the fibrinogen so that its reinfusion could lead to a coagulopathy. In fact, compared to blood drawn from patients before the surgery, USB shows high levels of fibrinogen degradation products, tissue factor antigen, plasmin/antiplasmin complexes and D-Dimers, which indicates a certain degree of fibrinolysis, and low levels of alpha2-antiplasmin, antithrombin-III, Factor V, Factor VIII, Protein C and plasminogen [6, 20, 38, 39, 52]. Nevertheless, when analysing the evolution of the levels of these proteins in samples obtained from the patients at 1 and 24 h after re-infusion, a trend to normalisation was seen, except for the fibrinogen [6, 20], and no alterations were detected in standard coagulation times [52, 56]. For this reason, it was not surprising that in 13 studies with nearly 700 patients undergoing TKA, THA or SF, those who received a re-infusion of an average of 560 ml of USB did not experience clinically significant coagulopathy or increase in post-operative bleeding [44].

Inflammatory mediators in USB

With regard to the presence of inflammatory mediators, in several studies, an increase in serum levels was found of interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor (TNF-α) and anaphylatoxins in USB [45]. The use of a leukocyte filter between the wound and the drain blood container reduces IL-8 and TNF-α in drain blood, but at the same time triggers complement activation [2]. Nevertheless, in spite of the high concentration of certain proinflammatory cytokines in USB that produce a temporary increase in their circulatory levels after the infusion, 12–18 h later, no differences existed in the levels observed in the reinfused patients relative to the non-reinfused patients [56]. It should be remembered that these cytokines, which are also present in stored blood [33], induce the expression of adhesion molecules (ICAM-1, VCAM-1 and P-selectin) by the endothelial cells. These adhesion molecules specifically interact with the circulating leucocytes, facilitating adhesion to the endothelium and migration to the site of injury where they exert phagocytic and bactericidal (respiratory burst) effects [60]. Also, the leukocytes can strengthen platelet aggregation by means of the interactions between leukocyte P-selectin and platelet PSGL-1 [18]. On the other hand, the exposition of endothelial cells to an inflammatory stimulus also promotes the adhesion of circulating erythrocytes to endothelin [17]. All of this can give rise to alterations in micro-circulation, in conjunction with those that can directly induce anaphylotoxins [37], and we are conducting experiments to ascertain whether the temporary increase in cytokine levels that occurs after USB re-infusion induces changes in the expression of adhesion molecules by endothelium beyond that induced by cytokines released during surgery.

Reinfusion of USB and the immune system

Finally, with regard to cellular immunity, the ABT, even after being de-leucocyted, induces a depression of immunity measured by T cells, while these alterations have not been detected in patients receiving PABD [23, 31]. On the contrary, the influence of USB re-infusion is largely unknown. However, data from two recent reports seem to indicate a positive effect of USB on cellular immunity; namely, a significant increase in the production of reactive oxygen species by neutrophils [32] and in natural killer cell precursor frequency [25] in patients who received USB. This findings may support the hypothesis that this treatment may be another way of reducing post-operative infections after orthopaedic surgery. These results also support the previous clinical studies where infection rates after autologous transfusion were lower than after conventional treatment.

Table 2 Patient characteristics

	Group A[a]	Group B[a]	Group C
No. patients	31	28	64
Age (years)	48±2	52±3	51±2
Gender (M/F)	12/19	14/14	31/33
Haemoglobin (g/dl)			
Pre-operative	13.5±0.3	14.2±0.3	13.0±0.2
Post-operative	10.7±0.3	10.5±0.3	10.1±0.2
Operation length (h)	5.3±0.4	5.3±0.1	5.2±0.1
Hospitalisation (days)	9.6±1.4	8.4±0.5	9.1±0.5
Complications	4 (12.9%)	3 (10.3%)	4 (6.3%)*

All data are expressed as the mean ± SE (*n*)
*p<0.05
**p<0.01
[a]Data taken from reference 27

Table 3 Blood lost and blood units transfused. For data comparison, 1 U of pre-operative autologous blood donation (PABD) was consider to be equal to one allogeneic red cell concentrate, and the number of unwashed shed blood (USB) units were calculated according to the expression: Shed blood volume (ml) × shed blood haematocrit (%) / 400 (ml) × pre-operative haematocrit (%)

	Group A[a] (*n*=31)	Group B[a] (*n*=28)	Group C (*n*=64)
Blood lost (ml)			
Intra-operative	670±46	852±55*	959±50**
Post-operative	480±40	542±41	631±32*
Allogeneic blood (U/pt)			
Intra-operative	1.35±0.13	1.22±0.11	0
Post-operative	0.64±0.50	0.25±0.19*	0.28±0.08*[b]
Autologous blood (U/pt)			
PABD[c]	0	0	2.03±0.06**
USB	0	0.65±0.05**	0.77±0.03**
Overall transfusion (U/pt)	1.90 ± 0.22	2.13±0.19	2.98±0.11**

All data are expressed as the mean ± SE (*n*)
*p<0.05
**p<0.01
[a]Data taken from reference 27
[b]Eighteen units of RBC concentrate were administered to 12 patients
[c]Seven patients donated 3 U

Our experience in the use of post-operative USB reinfusion

Based in our previous experience with reinfusion of post-operatively salvaged USB in cardiac surgery [54] and after the evaluation of the quality of intra- and post-operatively salvaged USB in different types of orthopaedic surgery [44, 61], we decided to initiate a blood saving program in spine surgery introducing the use of USB recovered after the operation with the ConstaVac CBCII (Stryker). In this initial study, we included 28 consecutive patients undergoing lumbar spinal fusion in which post-operative shed blood was collected and reinfused (Group B). In comparison with a previous series of 31 patients (Group A), this procedure reduced allogenic blood requirements by almost 30% ($p<0.05$) without any increase in post-operative complications [56] (Tables 2 and 3). Despite these good results, it became evident that the exclusive use of post-operative USB was not enough to avoid ABT, and we decided to complement it with a short-time protocol of PABD. Eligible patients (Hb >12 g/dl) were asked to donate 2 U of autologous blood, the first one being donated 7–10 days before surgery (real PABD). The second unit was drawn the day before surgery, and the donated blood volume was replaced with saline (delayed normovolemic haemodilution).

Between 1999 and 2000, 64 patients undergoing instrumented lumbar spinal fusion were included in this new protocol (Group C). Despite a higher peri-operative blood loss due to an increase proportion of revision surgery, with this blood saving strategy, 80% of the patients avoided exposure to ABT (Table 3), and post-operative complications were reduced by 50% (Table 2). The use of erythropoietin in patients with Hb <13 g/dl might possibly prevent the decrease in Hb levels after PABD and reduce further the exposure to ABT. On the other hand, 96% of PABD units were transfused, and overall transfusion rate was higher than in group A, suggesting a tendency to a more liberal transfusion criteria when autologous blood is available [22].

Conclusions

The development of complex surgical procedures for the treatment of orthopaedic diseases have raised the demand for allogenic blood to a level that often exceeds supply. In addition, increased awareness of the potential hazards of allogeneic blood transfusion, such as incompatibility reactions, metabolic, and immunological disorders or transmission of viral diseases, has led to an emphasis on blood-saving techniques. Among them, reinfusion of salvaged shed blood has become popular in major orthopaedic procedures, including spine surgery, but this blood-saving technique is still controversial. However, in our experience, post-operative reinfusion of USB after major spine procedures has proven to reduce post-operative homologous transfusion requirements [56] and to complement PABD without any clinically relevant complication. Moreover, from data reviewed in this paper, it can be concluded that post-operative blood salvage seems to be an excellent source of functional and viable red cells without many of the transfusion-related risks and with some immuno-stimulatory effects.

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