Management of Haemostasis in Spine Surgery

a report by

Marek Szpalski¹ and Robert Gunzburg²

¹. Co-ordinator, Surgical Departments, Iris South Hospitals, Brussels; 2. General Secretary, International Society for the Study of the Lumbar Spine (ISSLS)

Blood loss in spine surgery is an underestimated problem. It is an important concern in the performance of spinal surgery, not only in major deformity surgery but also in less extensive fusion procedures. The degree of blood loss varies enormously and is related to the complexity of the procedure, duration of surgery and co-morbid conditions. Extensive blood loss leads to greater transfusion needs and serious consequences for the patient’s haemodynamic equilibrium, and can cause devastating neurological damage because of the vicinity of major and highly fragile neurological structures. It is important to reduce bleeding in spine surgery in terms of the surgeon as well as the patient: reduced bleeding allows a better view of the surgical field, thereby increasing the surgeon’s control and shortening surgery time, which further decreases bleeding. This article will summarise the main haemodynamic and pharmacological techniques used to reduce bleeding in spine surgery.

Methods to Reduce Bleeding in Spine Surgery

Blood-sparing techniques can be divided into two groups: they aim at either decreasing the bleeding itself or decreasing the need for homologous transfusion. Several blood-sparing techniques are available to surgeons who treat complex spinal disorders; these techniques include haemodynamic methods and pro-haemostatic methods used either systemically or locally. Inhibiting fibrinolysis with antifibrinolytics offers evidence of bleeding prevention. Topical agents combining collagen, thrombin and fibrin have successfully demonstrated bleeding control. This article reviews the clinical effectiveness of several treatments of surgical wound management in spinal surgery.

Controlled Hypotensive Anaesthesia

Controlled hypotension has been shown to reduce blood loss and improve operating conditions during orthopaedic surgery. It is frequently advocated for spinal surgery, alone or in combination with haemodilution, and promising results have been published since the early 1970s.¹⁻⁴ Brodsky et al. found that blood flow was more strongly correlated to surgery duration than to blood pressure.¹² Kakiushi observed a correlation of intraoperative blood pressure to intraosseous but not arterial pressure in thoracic vertebral bodies.¹³

It has been shown that hypotensive anaesthesia does not decrease transfusion requirements compared with normotensive anaesthesia in scoliosis surgery.¹⁴ However, Malcolm-Smith and McMaster showed a 58% reduction in total blood loss for patients with idiopathic scoliosis.¹⁵ Although hypotensive anaesthesia may lead to complications¹⁶ and is contraindicated in some patients with hypertension or ischaemic disorders, the safety risk in spinal surgery is difficult to quantify. The risk of neurological damage in addition to direct injury may be worsened by ischaemic complications.¹⁷,¹⁸ The effect on spinal cord function during scoliosis surgery has also been questioned.¹ However, although electrophysiological monitoring may detect temporary alterations, hypotensive anaesthesia does not appear to increase the risk of neurological damage.¹⁹ Hypotensive anaesthesia can be safely combined with acute normovolaemic haemodilution.²⁰ Acute normovolaemic haemodilution is widely used in spine surgery with favourable results in both fusion surgery²¹⁻²³ and scoliosis surgery.²³,²⁴ Combined application of acute normovolaemic haemodilution and pre-operative autologous blood transfusion in spinal fusion patients eliminated the use of homologous blood transfusion.²⁶

Marek Szpalski is Chairman of the Department of Orthopaedic and Trauma Surgery and Co-ordinator of the Surgical Departments at the Iris South Hospitals in Brussels. He is also an Associate Professor at the Université Libre de Brussels and an Adjunct Associate Professor at New York University School of Medicine. Professor Szpalski holds six editorial positions and seven fellowships and has authored 70 international publications and 16 books, as well as delivering 117 international podium paper communications and chairing 19 congresses and 35 sessions as Chairman and/or Moderator at international meetings.

Robert Gunzburg is General Secretary of the International Society for the Study of the Lumbar Spine (ISSLS) and Past President of the EuroSpine Society. He is a Visiting Professor at the Free University of Brussels, and has occupied positions at Brugmann University Hospital, Royal Adelaide Hospital and Al Noor Hospital, Abu Dhabi. Dr Gunzburg holds seven editorial positions and fellowships, and has authored 90 international papers, 14 books and seven book chapters, as well as delivering 117 international podium paper communications and chairing 24 international congresses. He is Past Treasurer of the European Spine Society (ESS), the Belgian Association of Orthopaedics (BGB-VBO) and the Spine Society of Europe (ESE), and former European Representative for ISSLS. He graduated cum laude from the Catholic University in Leuven, acquired a diploma in Tropical medicine from the Pêns Leopold Institute for Tropical Medicine in Antwerp and gained his PhD from the Free University of Brussels.

E: robert@gunzburg.be
Many drugs have been used over time: anaesthetic agents, calcium (Ca) channel blockers, beta blockers, nitroglycerin, nitroprusside and opioids. As all of these drugs are administered intravenously and are associated with different side effects, Namazi proposed using a transdermal nitroglycerin preparation for the reduction of peri-operative bleeding.

**Local Vasocostrictrors**

Orthopaedic surgery studies have sought to minimise blood loss using locally applied vasocostrictrors, but no reduction in blood loss and transfusion needs has been reported. Local infiltration of paraspinal muscles with epinephrine and omipressin to reduce bleeding is widely used in spinal surgery. A relation between intraoperative blood loss and the quantity of injected epinephrine has not been observed. The literature is very scarce, especially in spinal surgery, and there is little evidence of true efficacy. Nevertheless, Kiss et al. have shown that epinephrine-augmented hypotensive epidural anaesthesia results in less intraoperative bleeding.

**Neuraxial Blockade**

Epidural anaesthesia is usually applied to provide adequate analgesia, depending on whether selective sympatholysis ensues. Inadequate dosage of analgesics may cause unpredicted blood pressure elevation and dynamics, resulting in massive bleeding events. Yoshimoto et al. described the effectiveness of pre-operative epidural anaesthesia in terms of stabilisation of hypotension and reduction of blood loss during lumbar spine surgery. Apart from pain control, the beneficial aspects of epidural blockade combined with normotensive anaesthesia regarding the reduction of blood loss have been described. Sympathetic blockade may induce vasodilatation in the pelvis and lower limbs, resulting in a reactive vasocostriction beyond the blocked level. Venous hypertension exerts its effect in the lumbar, but not in the cervical or thoracic, spine. It can therefore be used in the lumbar spine only.

A recent study evaluated the blood-sparing effect of intrathecal morphine in children undergoing elective spinal fusion. Significantly reduced blood loss with no difference in mean arterial pressure and reduction in post-operative opioid demand was observed in both high- and low-dose regimens.

**Systemic Pro-haemostatic Methods**

**Deamino-8-D-arginin Vasopressin**

Deamino-8-D-arginin vasopressin (DDVAP or desmopressin; Minirin®, Pfizer) is an analogue of the natural hormone vasopressin or antidiuretic hormone (ADH). It increases the release of factor VIIc and von Willebrand factor (vWF) from endothelial cells, along with a paradoxical increase of plasminogen activator and prostaglandins.

There is no consistent evidence for the effectiveness of DDVAP for widespread use in surgical bleeding control. Despite the successful use of DDVAP in patients with von Willebrand disease, congenital platelet disorders, renal failure, cirrhosis and long-term salicylate treatment, its effectiveness during spinal surgery has been controversial, as it is based on a small number of experimental studies. The incidence and severity of peri-operative side effects, mainly on urinary output, has been a particular matter of controversy. Furthermore, a Cochrane review did not find any evidence for surgical use of DDVAP outside patients with congenital bleeding disorders.

Kobrinsky et al. have reported a significant decrease in blood loss, transfusion requirements and use of analgesic agents in the post-operative period in patients undergoing posterior spinal fusion and Harrington rod placement; however, others do not confirm these findings. Neither Alanay et al. nor Guay et al. found any significant effect of DDVAP on blood loss in surgical interventions to treat idiopathic or congenital scoliosis. In neuromuscular scoliosis, which is often associated with coagulation abnormalities leading to severe blood loss, Theroux et al. showed that DDVAP significantly increased factor VIIc and vWF; nevertheless, blood loss remained unaffected compared with placebo. Letts et al. proposed monitoring bleeding time after a test dose of DDVAP a few days before surgery, as they concluded that DDVAP decreases bleeding only in some patients with idiopathic scoliosis.

**Aprotinin**

Aprotinin (Trasylo®, Bayer) inhibits a broad spectrum of serine proteases including plasmin, trypsin and kallikrein, chemotrypsin-activated protein C and thrombin. By stabilising the platelet membrane it also prevents pathological platelet activation and seems to decrease the inflammatory response by inhibiting bradykinin, interleukin and tumour necrosis factor (TNF).

Mangano et al. have shown that aprotinin administration is related to an increased risk of renal failure, myocardial infarction and stroke. In 2008, the Blood conservation using Antifibrinolytics in a Randomised Trial (BART) reported an increased risk of death associated with aprotinin. Consequently, aprotinin was suspended from marketing pending US Food and Drug Administration (FDA) review. However, topical aprotinin seems to exert antifibrinolytic action and stabilises fibrin sealing while avoiding the adverse events associated with its systemic use. Although bovine aprotinin is a component of topical fibrinic glues and topical administration was shown to significantly reduce blood loss and transfusion requirements in cardiac surgery, the safety profile of the topical preparations needs to be investigated in detail.

The use of aprotinin in spine surgery has been analysed in a few controlled studies. Urban reported a decrease in blood loss and transfusion requirements in adult fusion. Cole et al. and Okubadejo et al. showed similar results in children and adolescent deformity surgery. A dramatic reduction of blood loss during and within 24 hours after surgery, but no reduction in homologous transfusion, was reported by Lentschener et al. Amar et al. used aprotinin for major orthopaedic tumour surgery including spine surgery without observing an effect on blood loss reduction. There are conflicting results regarding the optimal dosing regimen.

**Tranexamic Acid and Epsilon-aminocaproic Acid**

Both tranexamic acid (TXA; Exacyl®, Sanofi-Aventis, and Cyclokapron®, Pfizer) and epsilon-aminocaproic acid (EACA; Hemocaprol, Amicar®, Lederle) are synthetic lysine analogues and prevent plasminogen- and thus plasmin-mediated fibrinolysis.

Recent studies have assessed the effectiveness of TXA in reducing bleeding and allogenic blood transfusion during various orthopaedic procedures, with variable results. In the field of spine surgery, TXA appears to reduce transfusion needs in scoliosis correction; specifically, it reduces intraoperative bleeding in paediatric scoliosis surgery, as shown in a randomised, placebo-controlled study, without added complications.
Shapiro et al. demonstrated that TXA significantly decreases intraoperative bleeding and the need for homologous transfusion in spinal fusions for Duchenne muscular dystrophy scoliosis. Other studies show that TXA is quite effective for reducing spinal bleeding during spine surgery. However, TXA does not seem to have an effect on bleeding in spinal metastasis surgery. In terms of the safety of TXA, there have been rare reports of allergic reactions to gelatin products but no cases of anaphylaxis have been described.

Collagen-based – Instat® (J&J), Cogen® (Baxter), Lystopryt® (B.Braun) and Hemoco® (Pilling-Weck)

Like gelatin products, collagen-based haemostats can be of bovine, porcine or equine origin and are available in different forms, such as sheets, powder or aggregates. They lead to thrombocyte adhesion and inhibition of fibrinolysis in the spinal canal. Many of these products have been shown to avoid epidural fibrosis. A randomised, placebo-controlled study demonstrated that the use of TachoComb® (Nycomed), which is a ready-to-use fixed combination of collagen coated with fibrinogen and thrombin, which all dissolve after contact with liquids, involves the lowest risk of epidural fibrosis in a rat model. A further development of TachoComb is TachoSil®, a ready-to-use combination of collagen coated with fibrinogen and thrombin.

Oxidised Cellulose-based – Surgicel® (J&J) and Curacel® (CuraMedical BV)

These products are not markedly different from other ‘sponge’ formulations and also exist in multiple formulations. Activation of the initial coagulation phase is caused by their surface effect. They also induce a moderate acceleration of fibrinogen polymerisation and seem to act as a caustic haemostat by decreasing pH. Numerous neurological complications have been reported for oxidised cellulose, severe neurological complications due to epidural migration and spinal compression in thoracotomy after use of cellulose haemostats have also been observed. These products should not be left in the spinal canal because of swelling and the risk of immune reactions, which may induce granulomas, pseudotumours or images of herniated disc recurrence. These reactions may also result in misleading pseudo-compression images on magnetic resonance imaging (MRI) examinations. It appears that even if used as a dural substitute, oxidised cellulose induces marked fibrosis in animal models.

Fibrin Sealants

Stimulating the formation of a fibrin clot, fibrin ‘glues’ initiate the final stage of the clotting cascade. Two major families can be distinguished: the combination of a fibrinogen component together with a thrombin/Ca2+ solution and, more recently, a collagen/thrombin component that uses the endogenous fibrinogen of the bleeding source.

Tissucol/Tisseel® (Baxter), Beriplast® (Behring), Hemaseel® (Hemacure) and CoStasis® (Cohesion Tech)

These two-component systems usually contain factor XII to accelerate the cross-linking of the clot. To inhibit fibrinolysis, some contain aprotinin and even plasminogen to control the reaction. The nature of the antifibrinolytic component is important: Quixil® (Omnix, J&J) contains TXA instead of aprotinin. This is especially important in spine surgery as it appears that TXA is neurotoxic, and fatal neurotoxic reactions have been reported in neurosurgery. Generally, they are applied with a syringe. Sprayable formulations are available to cover larger surfaces; however, on
Orthopaedic Surgery  Spine

wet and bleeding surfaces the adherence is poor. 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 limitations in the methodology. Fibroinogen of bovine origin may present a safety problem regarding spongiform encephalitis, and thus commercialisation of Biocoll® was stopped. CoStasis® combines the patient’s centrifuged plasma with bovine thrombin and has been reported to be effective in spine surgery, but it seems to be expensive, cumbersome and time-consuming.

**Haemostatic Matrices**

FloSeal® (Baxter)
The bicomponent medium of the second family of fibrin glues contains thrombin and a gelatin matrix. A tamponade effect of the swelling collagen granules restricts bleeding while the gelatin matrix provides the thrombin and a gelatin matrix. A tamponade effect of the swelling have been reported in spinal procedures.

Recothrom® (Bayer)
Recothrom® is the first FDA-approved recombinant plasma-free topical thrombin product. When applied with an absorbable gelatin sponge, it controlled bleeding within 10 minutes in 95% of surgical patients. Its efficacy and safety are similar to those of bovine thrombin, but it carries considerably fewer infectious and immunogenic risks than bovine-derived thrombin products. Topical bovine thrombin is highly immunogenic. Patients may develop antibodies against bovine thrombin, factor V and other plasma proteins, leading to thromboembolic or bleeding complications. In contrast, Recostrum application did not lead to antibody formation, abnormal coagulation laboratory results or bleeding events. As it does not use human blood sources there is no risk of any transmissible diseases, e.g. hepatitis and HIV.

**Summary and Conclusion**

Blood sparing in spine surgery is important, and a variety of blood-sparing agents have been described. However, evidence is often lacking or conflicting and controlled studies are rare. The daily routine use of all of these methods is limited and regular use of any blood-sparing method is infrequent. The problem of blood loss and blood sparing in spine surgery has not been approached as frequently and as thoroughly as in other areas of orthopaedics, such as knee and hip arthroplasty. As a result of this, evidence is scarce and available studies are often based on a small number of subjects and/or unsatisfactory methodology. Nevertheless, there seems to be acceptable evidence for haemodynamic methods such as hypotension and acute haemodilution. Evidence for antifibrinolytic drugs is often conflicting and varies according to the type of surgery and/or patients. Recombinant FVIIa shows promising results, but its use is hampered by its high cost. Fibrin glues and recombinant thrombin appear effective, although the realisation of controlled studies for these products is technically difficult, especially regarding end-points and objective assessment. Of these locally applied products, recombinant thrombin appears to have advantages related to the absence of immunogenic response.

**Acknowledgements**

The authors would like to thank Physicians World GmbH for its assistance in drafting the manuscript. Funding for medical writing support was provided by Bayer Schering Pharma.

35. Mesa-Ramos F, Mesa-Ramos M, Maquieira-Canosa C, et al., Predictors for blood transfusion following total knee...
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.

53. Levy JH, Pharmacologic methods to reduce perioperative 
54. Mangano DT, Tudor IC, Dietzel C, The risk associated with 
58. Urban MK, Beckman J, Gordon M, et al., The efficacy of 
45. Guay J, Reinberg C, Poitras B, et al., A trial of desmopressin to 
46. Kannan S, Meert KL, Mooney JF, et al., Bleeding and 
51. Levy JH, Pharmacologic methods to reduce perioperative 
52. Levy JH, Lammers I, The safety of desmopressin administered 
1987;107:446–50.