A Review Paper

Minimizing Blood Loss in Major Spinal Surgery: A Review of the Current Literature

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Severe loss of blood during spinal surgery is a major concern because of its impact on patient health, length of surgery, and added surgical costs. To control blood loss during surgery, surgeons across all fields often use techniques, such as meticulous hemostasis, bipolar cautery, application of bone wax, and packing of exposed wounds. For surgeries that involve significant portions of the spinal cord, spine surgery teams may even consider operating on the thoracic spine and lumbar spine simultaneously in order to reduce blood loss.

If blood loss remains excessive after these techniques have been exhausted, postoperative blood transfusion may be warranted. Two types of transfusions may be performed: autologous, in which the patient donates his or her own blood before surgery for transfusion back into the body after surgery; and allogeneic, in which blood is donated by another person. Surgeries that involve significant blood loss may require transfusion of both autologous and allogeneic blood.

Studies have shown that patients transfused with allogeneic blood have higher infection rates, longer hospital stays, more consecutive days of fever, and a postoperative reduction in natural killer cells.[1] These findings have motivated surgeons to ask that patients donate their own blood before surgery in the event that blood transfusion is required.

Autologous blood donation, however, has its own limitations. Autologous blood can be donated only 35 to 42 days before surgery for adequate red blood cell (RBC) survival and donation is limited in patients with anemia, patients of advanced age, and patients with unacceptable hematocrit and hemoglobin concentration.[1] In a study of wasted autologous donated blood in scoliosis patients, a required transfusion was 9 times more likely in those who predonated blood than in a control group of patients who did not predonate. Bess and colleagues[2] found that 51% of predonated blood either was discarded or had an unacceptable hematocrit level (>30).

Therefore, the economics of blood loss and transfusions also must be considered. Not only does dealing with blood loss during surgery increase time spent in the operating room, but the cost of transfusion is significant enough to be taken into consideration. In a study of patients who underwent adult lumbar fusion surgery, mean costs were $270 per person for autologous transfusion and $250 per unit transfused for allogeneic blood.[3] Another study showed that, based on the level of severity of spinal surgery, the cost of transfusion can vary by $1043.[4]

In addition, given the anatomy of the spine, bleeding results primarily from damage to large veins, and, therefore, patients may continue to bleed after surgery.[5] In these scenarios, blood reinfused after surgery may not be sufficient as patients may continue to bleed afterward. Trying to avoid these complications, investigators have developed several approaches to maximize blood salvage and minimize blood loss perioperatively. In this article, we describe the mechanisms of these techniques and present data from studies that have evaluated their effectiveness and safety.

Cell Saver

Intraoperative autologous transfusion techniques, created with the intention of reducing the need for preoperative blood donation, have proved to be highly successful in cardiovascular surgery.[3] In one such method, Cell Saver, blood lost during surgery first is collected, anticoagulated, and filtered and then centrifuged to separate RBC and plasma components. Then, the RBCs are washed with a crystalloid solution and reinfused into the patient after surgery.[6]

Despite the success of Cell Saver in cardiovascular surgery, questions have arisen as to whether this method is efficacious during major spinal surgery. In a retrospective study of 102 cases of posterolateral fusion with pedicle instrumentation, Reitman and colleagues[3] found a 38% blood recovery rate with use of Cell Saver, reducing the need for postoperative transfusion. However, the mean cost of Cell Saver was $512 per patient compared with $270 for autologous transfusion for patients in the control group. This increased cost derived from the fixed cost of using Cell Saver and from increased mean time spent in the operating room for the Cell Saver group.

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Am J Orthop. 2010;39(12):E130-E134.

Another retrospective study, of 188 patients who underwent consecutive instrumented lumbar laminectomy and fusion, found a significant increase in number of postoperative blood transfusions, both autologous and allogeneic, for patients in the Cell Saver group compared with the control group. The Cell Saver group received a mean of 1.21 units of autologous blood and 1.6 units of allogeneic blood, whereas the control group received 0.73 unit and 0.87 unit, respectively.[7]

Therefore, intraoperative blood salvage alone may not be cost-effective or successful in reducing the need for postoperative transfusions. Other measures must be taken.

Hypotensive Anesthesia

Anesthetic techniques have been used successfully in reducing blood loss during surgery. During use of hypotensive anesthesia, intravenous vasodilative agents are used to reduce vascular tone and cardiac output. This method reduces the amount of blood lost during surgery simply by reducing blood flow in general. In 1983, Malcolm-Smith and McMaster[8] showed that hypotensive anesthesia may be useful in controlling bleeding during posterior fusion for scoliosis. During surgery, 21 patients were infused with hypotensive anesthesia and 23 patients were infused with normotensive anesthesia for control. Results showed mean total blood loss of 1058 mL for hypotensive patients and 2544 mL for normotensive patients. Hypotensive patients were transfused a mean of 2.2 units of blood and normotensive patients a mean of 4.9 units, demonstrating a 55% reduction in blood transfusion. Another retrospective study, of patients undergoing spinal fusion and Harrington-rod instrumentation, yielded similar results.[9]

A major concern regarding hypotensive anesthesia is risk for spinal cord injury due to reduced spinal cord blood flow. Phillips and Hensinger[10] hypothesized that an insult to the spinal cord could be more likely to cause neurologic deficit under these conditions. However, the patients in the 2 studies[8,9] showed no signs of complications in either the brain or the spinal cord. In addition, several investigators have demonstrated that spinal cord blood flow can be autoregulated independently of systemic blood flow under controlled hypotension.[10]

A second possible side effect of hypotension is the development of perioperative ischemic optic neuropathy (POION) during surgery. Although this complication is very rare in spinal surgery, with previous studies citing incidence rates between 0% and 0.12%,[11] the condition is debilitating and is still a cause for concern. In 2005, a retrospective study of 14,102 patients who underwent spinal surgery at Johns Hopkins University identified 4 cases of POION (0.028%). These patients experienced loss of vision in 1 eye—characterized by loss of color vision, visual field defect, and relative afferent pupillary defect.[11] Although the cause of POION is unclear, it is thought to be related to compromised blood flow to the optic nerve. The Johns Hopkins study reported that the 4 affected patients experienced anemia, hypotension, or both, during surgery. Other possible risk factors were prone position, long procedure times, and significant intraoperative hydration. Therefore, surgeons should take these risk factors into consideration before performing surgery with the patient under hypotensive anesthesia.

It generally is accepted that surgeons and anesthesiologists should aim for mean arterial blood pressure of 50 to 60 mm Hg to provide safe and adequate hypotension during spinal surgery in healthy patients.[12] In a 1999 randomized trial performed on 235 elderly patients, mean intraoperative arterial blood pressure reduced to as low as 45 to 55 mm Hg was equally as safe as the less hypotensive group's mean pressure of 55 to 70 mm Hg with respect to short- and long-term risks.[13]

Normovolemic Hemodilution

Another technique used to reduce transfusion requirements during surgery is to lower hematocrit before surgery, thereby reducing excess RBC loss. In normovolemic hemodilution (NH), a volume of autologous blood is removed immediately before surgery and replaced with warmed isotonic crystalloid solutions.[14] Every milliliter of blood removed is replaced with 2 to 4 mL of solution in order to prevent hypotension and hypovolemia; amount of blood removed is based on preoperative hematocrit level.[14] After surgery, the blood is reinfused.

In a 1999 study of adolescents who underwent spinal fusion, Copley and colleagues[15] found that NH reduced the need for postoperative blood transfusion. Seventy-nine percent of patients in the control group required transfusion, but only 37% of patients with NH. There was no significant difference between these 2 groups in postoperative hemoglobin level or hematocrit level. In another study, involving lumbar laminectomy with posterolateral fusion, Epstein and colleagues[16] found that 52 (76%) of 68 enrolled patients did not require allogeneic transfusion—an increase over the 60% previously reported in the literature.[17] In addition, NH was found to not increase length of surgery.[16]

Erythropoietin

Contrary to the logic of NH is the logic of administering erythropoietin, a hormone that promotes erythropoiesis. This process accelerates maturation of proerythroblasts into reticulocytes, stimulates the synthesis of hemoglobin, and promotes differentiation of reticulocytes into mature RBCs.[18] The goal of administering erythropoietin before surgery is to maximize preoperative hemoglobin concentration, and, thereby, safely maximize the quantity of blood available for any needed autologous blood transfusion.[19] In anemic patients who have difficulty producing adequate autologous blood, erythropoiesis stimulation may be very beneficial because of its ability to maximize patient hematocrit before surgery.[18]

The efficacy of erythropoietin in spinal surgery was confirmed in a 2004 study that compared 250 patients who underwent complex spinal surgeries with and without administration of recombinant human erythropoietin (rHuEPO), a biosynthetic form of human erythropoietin with the same biochemical structure and biochemical effect.[18] Patients were given 600 IU/kg of rHuEPO subcutaneously weekly over 3 weeks and on the day of surgery. These patients had a significant increase in the amount of donated blood and reduction in the need for allogeneic transfusion. These results confirmed those of a 2002 study, in which, rHuEPO patients had statistically higher hematocrit levels during preoperative autologous donation and perioperatively.[20] These patients had a 71% reduction in the likelihood of receiving allogeneic blood transfusion compared with control.

The disadvantages of rHuEPO therapy include side effects and cost. Side effects may include hypertension, myocardial infarction, angina, and deep venous thrombosis, though previous literature showed that these effects were not increased compared with control groups.[21] The cost of the epoetin alfa dose regimen, a specific type of rHuEPO, is approximately $400 per injection, or a total of $1600.[20]

Thrombotic Agents

To understand the mechanism of thrombotic agents, we must have a firm understanding of the human blood coagulation pathway, intrinsic and extrinsic. Both pathways ultimately converge on a common pathway that involves thrombin enzymatically acting on fibrinogen to form fibrin monomers, which polymerize to form the blood clot. Because of its role at the end of the clotting cascade, thrombin compares favorably with other hemostatic agents, including collagen and gelatin, as its action is less vulnerable to clotting factor deficiencies.[22] On the basis of this mechanism, thrombin has been used as a topical agent directly applied to bleeding sites during surgery.

One such agent is Floseal, a combination of gelatin matrix and topical thrombin, both of bovine origin. When applied to a bleeding site, the gelatin granules swell on exposure to blood and reduce blood flow through a tamponade effect.[22] The blood then is exposed to thrombin, which converts fibrinogen to fibrin and ultimately forms the clot in conjunction with platelets. The body then resorbs Floseal in 6 to 8 weeks, which is consistent with normal wound healing.[22] Unlike other products of its kind, including Tisseel, Hemaseel, and CoStasis, which require an initially dry surface for use, Floseal does not work in the absence of bleeding.[22]

In a multicenter, multispecialty, prospective, randomized clinical trial, Oz and colleagues[22] showed that Floseal may be safe and effective in restricting bleeding during major surgeries. Their study included 309 patients who underwent cardiac (93), vascular (89), or spinal (127) surgery. Success was measured as bleeding-site hemostasis within 10 minutes. Results of the study showed that patients who received Floseal had a 96% overall success rate (98% spinal surgery success) and control patients who received a thrombin-soaked gelfoam had a 77% success rate (90% spinal surgery success). In addition, median hemostasis time was 2.8 minutes in the Floseal group and 8 minutes in the control group.

Eighty-eight adverse events were reported in 36 patients in the Floseal group and 71 adverse events were reported in 32 patients in the control group. Of these events, only 2 in the Floseal group (mediastinal bleeding, cough) and 2 in the control group (leukocytosis, postoperative bleeding) were reported to have a possible relation to the hemostatic agents involved. The remaining adverse events were determined to be unrelated to the hemostatic agents.[22]

Given their action on fibrinogen, Floseal and other thrombotic agents are ineffective in patients who are fibrinogenemic (reported incidence, 1 in 1,000,000[22]). The retail cost of Floseal in 2004 was cited to be $85.[23]

As mentioned, Floseal and several of its counterparts consist of bovine thrombin (bThrombin), which has raised concerns regarding antigenicity and the potential for antibodies directed at the thrombin to be harmful. The antibodies are thought to be able to cross-react with human endogenous coagulation proteins and lead to alterations in coagulation laboratory parameters, hypersensitivity reactions, or severe bleeding or thrombosis.[24,25] Recombinant human thrombin (rhThrombin) was created to reduce these risks. Its amino acid sequence, structure, and biology are identical to those of bovine thrombin. The efficacy of rhThrombin versus bThrombin was evaluated in a double-blinded study of 401 patients who underwent vascular, spinal, and hepatic operations.[24] Success was measured as bleeding-site hemostasis within 10 minutes. Results of the study showed success rates of 95.4% (rhThrombin) and 95.1% (bThrombin). One month after treatment, however, only 1.5% of the rhThrombin patients developed antiproduct antibodies to the thrombin, compared with 21.5% of the bThrombin patients, which suggests that rhThrombin is significantly less immunogenic than bThrombin. In addition, postoperative laboratory results were similar and as expected for both groups.

The safety profiles of the rhThrombin and bThrombin groups were similar as well, with nearly 100% of patients experiencing at least 1 adverse event, possibly related to the thrombin, within the 1-month follow-up.[24] Side effects included thromboembolic events, cardiac events, hypersensitivity, and postoperative wound infections.

A similar study, by Doria and colleagues,[25] yielded similar results. The investigators compared the efficacy of bThrombin and plasma-derived human thrombin and found comparable hemostasis times and safety profiles but a difference in immunogenicity profiles between the groups. Testing positive for at least 1 of the 4 antibodies

assayed were 12.7% of patients in the bThrombin group but only 3.3% of patients in the plasma-derived human thrombin group. No patients in the human thrombin group developed seroconversion for antibodies to any human antigens.

Antifibrinolytics

At the end of the clotting cascade is plasmin-mediated fibrinolysis, which dissolves the fibrin clot. Antifibrinolytics, such as aprotinin, aminocaproic acid, and tranexamic acid, have been used during surgery to slow this process. Aprotinin is a naturally occurring, nonspecific serine protease inhibitor that inhibits plasmin, kallikrein, and several other anticoagulatory enzymes. Although the exact mechanism of hemostasis is unclear, aprotinin is believed to work by inhibiting the intrinsic coagulation pathway and fibrinolysis through kallikrein inhibition and plasmin inhibition, respectively. In one aprotinin regimen, patients received an initial dose of 2×10^6 KIU of aprotinin over 20 minutes immediately after anesthesia, and then 5×10^5 KIU/h until skin closure.[5]

Although aprotinin significantly reduces blood loss in major spinal surgery,[5,19,26] it was permanently discontinued for use in surgery in May 2008, after studies suggested increased risk for complications.[27] In 2007, Okubadejo and colleagues[28] reported study results suggesting that aprotinin may increase risk for acute renal failure in patients who undergo adult spinal deformity surgery. Of the 40 patients who received aprotinin in that study, 4 developed acute renal failure that required dialysis and 1 developed deep venous thrombosis. In comparison, of the 41 patients in the control group, 1 developed acute renal failure (presumed to be secondary to inadvertent gentamycin overdose) and 1 developed pulmonary embolus.

Aminocaproic acid and tranexamic acid also have been used to reduce blood loss during surgery—by blocking lysine-binding sites on plasmin, where the plasmin-fibrin complex usually forms, to begin degradation of the fibrin clot.[19] The actions of aminocaproic acid and tranexamic acid are similar, but tranexamic acid is said to be 10 times more potent than aminocaproic acid.[19] In one aminocaproic acid regimen, patients are infused with the drug at a rate of 100 mg/kg over 15 minutes directly after anesthesia, and then at 10 mg/kg/h throughout the procedure, until wound closure.[29]

Before aprotinin was discontinued, its efficacy was compared with that of aminocaproic acid in numerous studies, and aprotinin was found to be more effective in reducing blood loss. In one study, Urban and colleagues[26] randomized 55 anteroposterior thoracolumbosacral fusion patients into control, aminocaproic acid, and aprotinin groups. Mean blood loss was 5181 mL for control patients, 4056 mL for aminocaproic acid patients, and 3628 mL for aprotinin patients. Only aprotinin significantly ($P<.01$) reduced perioperative blood loss.

Nevertheless, in another study, which compared 28 aminocaproic acid patients with 31 similar patients used as controls, aminocaproic acid again did not significantly affect intraoperative blood loss but did significantly reduce postoperative drainage.[29] Mean postoperative blood loss was 498 mL (SD, 179 mL) for aminocaproic acid patients and 764 mL (SD, 284 mL) for control patients ($P = .014$), making mean total perioperative blood loss 1391 mL (SD, 212 mL) for aminocaproic acid patients and 1716 mL (SD, 513 mL) for controls ($P = .036$). The investigators stated that aminocaproic acid may have reduced postoperative bleeding through increased fibrinogen levels, which enhanced clotting.

Although aminocaproic acid has not proved to be as effective as aprotinin, the safety profile and cost of aminocaproic acid make it seem the better choice of drugs. Aminocaproic acid is much less expensive than aprotinin, with some studies citing aminocaproic acid at $40 per dose and aprotinin at $1000 per dose[30] and others claiming the cost of aminocaproic acid to be as low as $1.12 per patient.[29]

Conclusion

Although numerous techniques have been developed to reduce blood loss during major spinal surgery, none has proved to work better than any other, and there is no standardized system that all surgeons must follow. Before such a regimen can be instated, not only must the effectiveness of each blood salvage technique be evaluated, but the safety and cost-effectiveness must be considered as well. For example, though Cell Saver was found to effectively salvage blood in some studies, its cost may outweigh its effectiveness during surgery. Red blood cell augmentation through rHuEPO administration may reduce the need for allogeneic transfusion by 71%, but its own cost of $1600 is larger than the cost of allogeneic transfusion of $250 per unit, and its side effect profile may be even worse than the risks of allogeneic transfusion.

Research must be conducted to confirm the adverse side effect profiles of blood salvage techniques. In addition, more effort must be put into investigating the effectiveness and safety of combining multiple blood salvage techniques. More needs to be done to create a standardized blood salvage regimen for spinal surgery that is effective, safe, and cost-effective.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in regard to this article.

References

1. Keating EM. Current options and approaches for blood management in orthopaedic surgery. *Instr Course Lect*. 1999;48:655-665.
2. Bess RS, Lenke G, Bridwell KH, Steger-May K, Hensley M. Wasting of preoperatively donated autologous blood in the surgical treatment of adolescent idiopathic scoliosis. *Spine*. 2006;31(20):2375-2380.
3. Reitman CA, Watters WC 3rd, Sassard WR. The Cell Saver in adult lumbar fusion surgery: a cost–benefit outcomes study. *Spine*. 2004;29(14):1580-1584.

4. Blanchette CM, Wang PF, Joshi AV, Asmussen M, Saunders W, Kruse P. Cost and utilization of blood transfusion associated with spinal surgeries in the United States. *Eur Spine J.* 2007;16(3):353-363.
5. Lentschener C, Cottin P, Bouaziz H, et al. Reduction of blood loss and transfusion requirement by aprotinin in posterior lumbar spine fusion. *Anesth Analg.* 1999;89(3):590-597.
6. Halpern NA, Alicea M, Seabrook B, Spungen AM, McElhinney AJ, Greenstein RJ. Cell Saver autologous transfusion: metabolic consequences of washing blood with normal saline. *J Trauma.* 1996;41(3):407-415.
7. Gause PR, Siska PA, Westrick ER, Zavatsky J, Irrgang JJ, Kang JD. Efficacy of intraoperative Cell Saver in decreasing postoperative blood transfusions in instrumented posterior lumbar fusion patients. *Spine.* 2008;33(5):571-575.
8. Malcolm-Smith NA, McMaster MJ. The use of induced hypotension to control bleeding during posterior fusion for scoliosis. *J Bone Joint Surg Br.* 1983;65(3):255-258.
9. Patel NJ, Patel BS, Paskin S, Laufer S. Induced moderate hypotensive anesthesia for spinal fusion and Harrington-rod instrumentation. *J Bone Joint Surg Am.* 1985;67(9):1384-1387.
10. Phillips WA, Hensinger RN. Control of blood loss during scoliosis surgery. *Clin Orthop.* 1988;(229):88-93.
11. Chang SH, Miller NR. The incidence of vision loss due to perioperative ischemic optic neuropathy associated with spine surgery: the Johns Hopkins Hospital experience. *Spine.* 2005;30(11):1299-1302.
12. Urmey WF. Combined regional and general anesthesia for orthopedic spine fusion surgery. *Tech Reg Anesth Pain Manag.* 2000;4(2):101-105.
13. Williams-Russo P, Sharrock NE, Mattis S, et al. Randomized trial of hypotensive epidural anesthesia in older adults. *Anesthesiology.* 1999;91(4):926-935.
14. Epstein NE. Bloodless spinal surgery: a review of the normovolemic hemodilution technique. *Surg Neurol.* 2008;70(6):614-618.
15. Copley LA, Richards BS, Safavi FZ, Newton PO. Hemodilution as a method to reduce transfusion requirements in adolescent spine fusion surgery. *Spine.* 1999;24(3):219-222.
16. Epstein NE, Peller A, Korsh J, et al. Impact of intraoperative normovolemic hemodilution on transfusion requirements for 68 patients undergoing lumbar laminectomies with instrumented posterolateral fusion. *Spine.* 2006;31(19):2227-2230.
17. Moran MM, Kroon D, Tredwell SJ, Wadsworth LD. The role of autologous blood transfusion in adolescents undergoing spinal surgery. *Spine.* 1995;20(5):532-536.
18. Colomina MJ, Bago J, Pellise F, Godet C, Villanueva C. Preoperative erythropoietin in spine surgery. *Eur Spine J.* 2004;13(suppl 1):S40-S49.
19. Bess RS, Lenke LG. Blood loss minimization and blood salvage techniques for complex spinal surgery. *Neurosurg Clin North Am.* 2006;17(3):227-234.
20. Shapiro GS, Boachi-Adjei O, Dhawlikar SH, Maier LS. The use of epoetin alfa in complex spine deformity surgery. *Spine.* 2002;27(18):2067-2071.
21. de Andrade JR, Frei D, Guilfoyle M. Integrated analysis of thrombotic/vascular event occurrence in epoetin alfa–treated patients undergoing major, elective orthopedic surgery. *Orthopedics.* 1999;22(1 suppl):S113-S118.
22. Oz MC, Rondinone JF, Shargill NS. Floseal Matrix: new generation topical hemostatic sealant. *J Card Surg.* 2003;18(6):486-493.
23. Methiasen RA, Cruz RM. Prospective, randomized, controlled clinical trial of a novel matrix hemostatic sealant in children undergoing adenoidectomy. *Otolaryngol Head Neck Surg.* 2004;131(5):601-605.
24. Chapman WC, Singla N, Genyk Y, et al. A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis. *J Am Coll Surg.* 2007;205(2):256-265.
25. Doria C, Fischer CP, Wood CG, Li PM, Marra S, Hart J. Phase 3, randomized, double-blind study of plasma-derived human thrombin versus bovine thrombin in achieving hemostasis in patients undergoing surgery. *Curr Med Res Opin.* 2008;24(3):785-794.
26. Urban MK, Beckman J, Gordon M, Urquhart B, Boachie-Adjei O. The efficacy of antifibrinolytics in the reduction of blood loss during complex adult reconstructive spine surgery. *Spine*. 2001;26(10):1152-1156.
27. Manufacturer removes remaining stocks of Trasylol [press release]. Silver Spring, MD: US Food and Drug Administration; May 14, 2008. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116895.htm. Accessed October 12, 2010.
28. Okubadejo GO, Bridwell KH, Lenke LG, et al. Aprotinin may decrease blood loss in complicated adult spinal deformity surgery, but it may also increase the risk of acute renal failure. *Spine.* 2007;32(20):2265-2271.
29. Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL, Blakemore LC. The effect of Amicar on perioperative blood loss in idiopathic scoliosis: the results of a prospective, randomized double-blind study. *Spine.* 2004;29(3):233-238.
30. Munoz JJ, Birkmeyer NJ, Birkmeyer JD, O'Connor GT, Dacey LJ. Is aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery?: a meta-analysis. *Circulation*. 1999;99(1):81-89.