Blood Conservation in Orthopedic Trauma

Suresh K. Nayar, MD and Babar Shafiq, MD, MSPT

Summary: In the setting of acute orthopedic trauma, blood management strategies are reactive rather than anticipatory, and patients may not receive the same options offered in elective surgery. There are several strategies for conserving blood, but it is not feasible for the orthopedic traumatologist to be familiar with the complexities of each method. Instead, practical options and those routinely offered at trauma centers should be considered. Evidence supports tolerable transfusion thresholds of hemoglobin concentrations of 7 and 8 g/dL for patients with and without history of cardiac disease, respectively. Cell salvage reduces the need for transfusions and produces modest cost savings in cases with blood loss exceeding 500 mL. Although researchers are still investigating the efficacy of tranexamic acid in orthopedic trauma, other large randomized controlled trials in the setting of general trauma, as well as in arthroplasty and spine surgery, have shown significant reductions in blood loss without increased risk of venous thromboembolism. Currently, little evidence supports the use of autotransfusion devices and biological adhesives in orthopedic trauma. Erythropoietin aids in blood conservation, but at an unacceptably high cost. Intravenously administered iron may help patients recover from postoperative anemia. There are few large, rigorous studies of blood management in orthopedic trauma; therefore, expert opinion, logical deduction, and practical reasoning are necessary to determine appropriate strategies on a case-by-case basis.

Key Words: blood conservation—cell salvage—orthopedic trauma—tranexamic acid—transfusion.

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In the past 2 decades, clinicians, payers, and administrators have shown increased interest in blood conservation programs, in part to avoid the risk of morbidity associated with allogeneic blood transfusions and to minimize costs. Blood conservation strategies are well documented in elective spine surgery[1,2] and hip and knee arthroplasty[3–10]; however, few studies have investigated their application in the setting of acute orthopedic trauma. Conventional blood management methods include blood product transfusions, fibrin sealants, pharmacologic agents, and various intraoperative techniques, each indicated at different points during the perioperative period (Fig. 1). This review will discuss the relevant literature for blood conservation in orthopedic surgery and highlight which blood conservation methods may be beneficial for orthopedic trauma patients.

From the Department of Orthopaedic Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD.

The authors declare that they have nothing to disclose.

For reprint requests, or additional information and guidance on the techniques described in the article, please contact Babar Shafiq, MD, MSPT, at editorialservices@jhmi.edu or by mail at Department of Orthopaedic Surgery, The Johns Hopkins University School of Medicine, 601 N. Caroline St., Fl. 5, Baltimore, MD 21205. You may inquire whether the author(s) will agree to phone conferences and/or visits regarding these techniques

METHODS

A systematic search using the key words, "blood conservation," "orthopedics," and "trauma" was applied to PubMed and adapted for Embase, The Cochrane Library, Scopus, Global Health, and World Health Organization Global Health Library and Regional Libraries to identify original research and review articles published in the last 3 decades. Abstracts from meeting proceedings or unpublished studies were excluded, and there were no exclusion criteria based on language. In total, 306 articles were identified. The abstracts were manually reviewed by the first author, yielding 61 that were also reviewed by the senior author and incorporated into this review.

RESULTS

Blood or Blood Product Transfusion

Transfusion Threshold

Restrictive transfusion is the key component in blood conservation. In trauma surgeries involving substantial blood loss, transfusions are often used to treat anemia. However, many patients can remain hemodynamically stable even when tachycardic without adverse outcomes. One study of 384 orthopedic and trauma patients reported overtransfusion rates as high as 25%.[11] The authors created evidence-based algorithms with various transfusion triggers depending on patient age, volume of blood lost, hemoglobin concentration, history of heart disease, and symptoms. Successful results when using such algorithms demonstrate that patients can tolerate lower hemoglobin concentration (<7 g/dL) in the absence of symptoms and complications.

A number of studies support lower transfusion thresholds. A retrospective study of 104 orthopedic trauma patients assigned to 2 groups by lowest hemoglobin concentration before first transfusion (<7 or ≥ 7 g/dL) showed no increased risk of postoperative complications in the lower threshold group.[12] In contrast, they found significantly higher risk of transfusion-related complications in a dose-dependent relationship. A dose-dependent increase in risk of cardiac, pulmonary, thromboembolic, and infectious complications is well documented in orthopedic spine patients who receive transfusions of >4 units of packed red blood cells.[13] In a small retrospective review of 64 intertrochanteric fractures, patients who were unintentionally transfused with blood in excess of total blood loss fared no better than those who were transfused with less than the total blood lost.[14] A large randomized controlled trial (RCT) of 2016 patients (aged above 50 y) with cardiovascular disease showed that a higher transfusion threshold (hemoglobin concentration of 10 vs. 8 g/dL) had no effect on death, ambulation at 60-day follow-up, or in-hospital morbidity.[15] Other authors have suggested thresholds of ≤ 8 g/dL for transfusion in the absence of symptoms.[16] The American Association of Blood Banks[17] and a recent Spanish consensus statement on transfusion[18] recommend restrictive transfusion criteria based on patient condition and medical

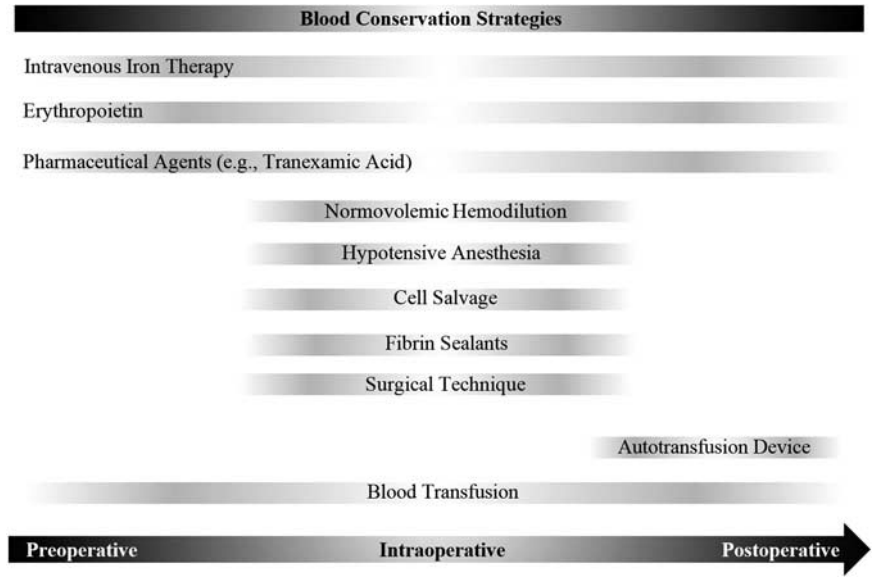

FIGURE 1. Conventional blood management methods throughout the perioperative period.

history. Combined recommendations consist of 4 guidelines to maintain hemoglobin concentrations of at least 7 to 8 g/dL in hospitalized, stable patients; >8 g/dL in patients with cardiovascular disease; 7 to 9 g/dL in critically ill, polytraumatized, and/or surgical patients; and 8 to 10 g/dL in critically ill, polytraumatized, and/or surgical patients with cardiac and/or central nervous system dysfunction. In each of these 4 groups, patients should receive no more than 1 unit of packed red blood cells at a time and be reassessed clinically, as well as have hemoglobin levels rechecked after receiving each unit.[19]

It is important to predict accurately which patients will require transfusion. A retrospective study of 1484 patients who sustained hip fractures reported the following predictors of transfusion within 72 hours of hospital admission: older age, female sex, lower hemoglobin concentration on hospital admission, type of surgical implant (cephalomedullary nail and dynamic hip screw more than hemiarthroplasty), and shorter time from admission to surgery.[20] These findings were corroborated by another study, which also identified longer operative time (> 85 min) and greater intraoperative blood loss (92 vs. 129 mL) as predictors of transfusion.[21]

Cell Salvage

Cell salvage is recommended when blood loss is expected to exceed 500 mL.[22,23] A review of the use of cell salvage in hip arthroplasty revision surgery reported a median reduction in blood transfusion of 4 units and a cost savings of £406 per patient.[22] Cell salvage has also been shown to reduce the rate of blood transfusion during knee arthroplasty in 100 patients from 80% to 16%.[22] Although cell salvage is viewed favorably by many arthroplasty surgeons, studies have shown mixed results regarding its efficacy and cost-effectiveness in orthopedic trauma.

One trauma study of 30 patients with pelvic fractures showed cell salvage to recover an average of 388 mL of blood and save £86 per case.[24] A retrospective study of 80 patients at a tertiary pelvic and acetabular reconstructive center also showed cell salvage to be cost-effective, particularly in associated-fracture types of injuries,[25] with a mean reduction of 1.4 units of blood transfused and a mean cost savings of $152 per case. Cell salvage has been shown to be useful in orthopedic spine trauma, as well.[26] In a retrospective study of 238 patients who required emergency surgery, 118 patients with similar risk of requiring perioperative blood transfusion received transfusions. Cell salvage was used in 53 patients, producing a 47% reduction in blood transfusion volume compared with estimates based on patient risk (mean, 743 ± 1191 mL vs. 1403 ± 1453 mL; $P < 0.008$) and a 45% absolute reduction in the number of patients who would have otherwise needed homologous blood.

In contrast, other studies have found no benefit of cell salvage. In a retrospective study assessing how surgical approach may affect cell saver utilization rates and blood return, no advantage was seen in 154 consecutive, routine cases of acetabular open reduction and internal fixation, especially when using a posterior Kocker-Langenbeck approach.[25] However, the authors concluded that cell salvage might be warranted for an anterior ilioinguinal approach if a large volume of blood loss is expected.[27] In this study, cell salvage was used in 23 of 65 cases (35%) using an anterior approach and 6 of 80 cases (8%) using a posterior approach. In a retrospective review of 186 patients with acetabular fractures, cell salvage was used in 32% of cases, recovering a mean of 345 mL of blood per case. The authors reported no effect on transfusion rates, and a mean charge increase of $1264 per case ($P < 0.0001$).[28] In 180 cases of single-level lumbar spine surgery, cell salvage had a negligible effect on transfusion rates and cost 56 times the accepted cost for 1 quality-adjusted life-year gained.[29]

In summary, no strong evidence exists to support widespread use of cell salvage in orthopedic trauma patients; however, it may reduce the volume of transfused blood, the number of patients needing transfusion, and costs. Further, cell salvage should be used on a case-by-case basis when substantial blood loss (> 500 mL) is expected, as may occur in open pelvic and acetabular surgery, as well as open femur repair or combined surgeries in the polytrauma patient.

Autotransfusion

Postoperative autotransfusion devices consist of a drain and pump and perform a similar function to intraoperative cell salvage. They have traditionally been used in arthroplasty and

other elective surgeries, and no studies have investigated the use of autotransfusion devices in orthopedic trauma patients. A small RCT of 74 patients who underwent knee or hip arthroplasty showed mean recovered blood volumes of 413 and 480 mL, respectively, with significant reductions in postoperative transfusion.[30] However, a 3-armed RCT (no drain, drain for 6 h, or drain for 24 h) of 575 patients showed no difference in allogeneic transfusion rates postoperatively in total knee or hip arthroplasty and median recovered blood volumes of 280 mL in knee arthroplasty and 500 mL in hip arthroplasty.[31] There were no significant differences in postoperative hemoglobin concentrations, length of hospital stay, or rate of adverse events.

Given the weak evidence supporting autotransfusion in arthroplasty and the lack of studies assessing its use in trauma patients, we do not recommend the routine use of autotransfusion devices in orthopedic trauma.

Pharmacologic Agents

Tranexamic Acid (TXA)

Perhaps the most promising and possibly underused antifibrinolytic agent in orthopedic trauma is TXA, a plasminogen inhibitor with high efficacy in hip and knee arthroplasty[6,16,32–38] and spine surgery[39] but with few well-designed, large studies assessing its use in orthopedic trauma.[40] Although there is currently little evidence to support its use in pelvic and acetabular trauma,[41] it may be recommended on a case-by-case basis.[42] The few studies that have assessed its use in orthopedic trauma have had positive results. In a RCT of 200 patients aged above 65 years who sustained intertrochanteric fractures, subfascial administration of 3 g of TXA resulted in a 43% reduction in transfusion rates with no difference in surgical site complications, medical complications [myocardial infarction, renal failure, respiratory infection, stroke, venous thromboembolism (VTE)], or mortality rate.[43] The clinical randomization of an antifibrinolytic in significant hemorrhage (CRASH)-2 trial assessing early (3-h) TXA use in 20,211 adult trauma patients in 40 countries (the largest TXA trial to date) found a reduction in all-cause mortality (14.5% vs. 16.0%; $P = 0.0035$) and death caused by bleeding (4.9% vs. 5.7%; $P = 0.0077$) with an incremental cost per life-year gained of $64.[44] Although these were general trauma patients, the results support further investigation of TXA use in orthopedic trauma patients.

Because it is an antifibrinolytic agent, TXA may pose a risk of VTE; however, large-scale trials have not found this. The CRASH-2 trial did not exclude patients at risk for thrombosis and showed significant reduction in the incidence of VTE events and arterial thrombosis.[44] A retrospective analysis of TXA use in hip and knee arthroplasty in >850,000 patients at >500 hospitals reported a 12% absolute reduction in allogenic or autologous transfusion rate with comparable rates of thromboembolic complications (0.6% with TXA use vs. 0.8% without) and acute renal failure (1.2% with TXA use vs. 1.6% without).[36] Similarly, a RCT of TXA use in 60 patients who underwent minimally invasive total hip arthroplasty and received TXA (n = 30) or placebo (n = 30) reported no VTE in either group.[34] A review of the safety of TXA reported that no RCT has shown an increased risk of thromboembolism with TXA use.[45] Finally, in another RCT of TXA use in total hip and knee arthroplasty (N = 2046) assessing chemical prophylaxis using aspirin, warfarin, or dalteparin, VTE incidence was also rare (< 0.52%).[46]

Although there are few published studies of TXA use in orthopedic trauma, there are 6 completed or ongoing trials registered with the National Institutes of Health. One study (University of Tennessee, NCT02080494) is investigating TXA use in fracture surgery around the hip and knee. Another study (Mayo Clinic, NCT01714336) has investigated TXA use in arthroplasty for acute femoral neck fractures in 128 patients (69 TXA, 69 placebo). Results show blood loss reduced by a mean of 305 mL ($P = 0.0005$) in those who received TXA. They found that fewer patients in the TXA group received transfusions (17% vs. 26%) ($P = 0.22$), and there were no differences in adverse events at 30 and 90 days. Three other studies are actively recruiting patients for TXA use in acetabular surgery (Carolinas Healthcare System, NCT02684851), topical application of TXA in femoral neck fractures (Queen's University, NCT01727843) and hip fractures (Rothman Institute, NCT02738073). The sixth study (Pfizer Investigational Site, Coimbatore, Tamil Nadu, India, NCT00824564) is complete and showed that TXA use in 82 femoral shaft fractures to be ineffective, with similar rates of intraoperative, postoperative, and total blood loss; transfusion; and VTE. These studies may provide insight to help determine the indications and effectiveness of TXA use in orthopedic trauma patients.

Erythropoietin (EPO) and Iron Supplementation

Over the past 2 decades, the use of exogenous EPO with or without supplemental iron has been debated; although it has been found to be effective, it is largely cost-prohibitive. Studies assessing EPO use with aggressive iron supplementation in nonelective hip fracture patients show that combination therapy can stimulate effective erythropoiesis.[23,47,48] A small study of 9 patients showed median red blood cell volume production of 398 mL, which is equivalent to 2 units.[48] Another cohort study of 196 patients with hip fractures showed that administration of EPO and intravenous iron compared with intravenous iron alone showed an absolute reduction in transfusion rates of 18%.[47] A systematic review of RCTs showed a decreased rate of transfusion in patients receiving EPO for orthopedic surgeries [odds ratio, 0.36; 95% confidence interval (CI), 0.24-0.56].[49] Another review analyzing EPO and iron use in various types of surgery found significant reduction in transfusion rates, with a number-needed-to-treat ranging from 3 to 6.[50] The authors also found an increased rate of embolism in spine patients who received only mechanical antithrombotic prophylaxis. However, most of the studies included in these 2 reviews were of elective procedures, and their results may not be generalizable to the acute trauma setting. Finally, a literature review analyzing iron use alone to treat postoperative anemia in the first week after major orthopedic surgery concluded that oral iron therapy was ineffective but intravenous iron therapy was effective.[51]

Although EPO effectively reduces transfusion rates as outlined above, it has consistently been shown to be cost-ineffective. A Canadian meta-analysis showed that EPO use alone in orthopedic surgery cost ~825 times the acceptable cost for quality-adjusted life-year gained.[52] A RCT of EPO use in total hip and knee arthroplasty showed significant reductions in transfusion (from 29% to 19%) but at a cost of €7300 per avoided transfusion.[53] In a retrospective study of nearly 5000 general trauma patients, the authors assessed anemia treatment guidelines with and without EPO use. They found no increased transfusion rate after discontinuing EPO administration at their hospital. They also found no significant difference in hospital or intensive care unit length of stay, and they reported a cost savings of >$170,000 per fiscal year.[54] Whereas the cost of

TABLE 1. Blood Conservation Interventions in Orthopedic Trauma

Interventions	Level of Evidence*	Grade of Recommendation
Blood product transfusions		
Autotransfusion	II	Insufficient evidence
Cell salvage†	II-III	Fair evidence
Lower transfusion thresholds	I-II	Good evidence
Pharmaceutical agents		
Erythropoietin	I, III	Not recommended‡
Fibrin and thrombin sealants	I, III	Not recommended
Iron supplementation§	III-V	Fair evidence
Tranexamic acid‖	I-II, V	Good/fair evidence
Operative practice		
Hypotensive anesthesia¶	V	Insufficient evidence
Normovolemic hemodilution	V	Not recommended
Surgical approach	III and V	Poor evidence

*Level I, randomized control trial; level II, prospective cohort study; level III, retrospective cohort study or case-control study; level IV, case series; level V, mechanism-based reasoning, expert opinion.

†When blood loss is expected to be >500 mL.

‡Not recommended because of prohibitive cost.

§Intravenous therapy. No evidence for oral therapy. For treatment of postoperative anemia.

‖Efficacy shown in large studies in trauma, arthroplasty, and spine surgery. Smaller studies assessing use in orthopedic trauma.

¶For acetabular fractures.

EPO is prohibitive, intravenous iron supplementation may help correct postoperative anemia at a more acceptable cost.

Fibrin and Thrombin Sealants

Fibrin and thrombin sealants are biological adhesives, often in gel or spray form, that aid in tissue sealing and hemostasis. There is currently no substantial evidence supporting the use of biological adhesives in orthopedic trauma, and there have been mixed results in other fields. For example, a review found favorable results in hip but not knee arthroplasty,[6] whereas another meta-analysis of 8 RCTs of 461 patients found a significant reduction in blood transfusions (risk ratio 0.47; 95% CI, 0.35-0.63) but not in total blood loss (weighted mean difference, −305 mL; 95% CI, −679 to 69 mL).[55] Another topical thrombin-gelatin hemostatic matrix (Surgiflo, Ethicon US, Somerville, NJ) produced no difference in blood loss or transfusion rate for 211 consecutive shoulder arthroplasty cases.[56] Fibrin and thrombin sealants, however, may have potential application in other nonemergent or elective orthopedic fields, including arthroplasty, cartilage preservation, spine, sports medicine, and orthopedic oncology.[57]

Hospital Standardization and Other Methods of Blood Conservation

There is a high degree of variability in blood management practices among surgeons, which is caused in large part by lack of standardized procedures across hospitals. For example, as described herein, transfusion guidelines are well established with strong evidence. Despite this, high variability in transfusion rates among surgeons has been shown for total knee arthroplasty (5% to 64%) and total hip arthroplasty (4% to 87%).[58] Education initiatives have been successful at standardizing and reducing transfusion rates. A study implementing blood management protocols during a period of 5 years with >15,000 patients showed lower transfusion rates but consistent transfusion volumes per patient receiving transfusion.[59] This suggests that setting new transfusion policies can be adopted easily, but that administering appropriate transfusion volumes may require additional protocols.

Depending on their training and comfort levels, surgeons may adopt and modify intraoperative methods to conserve blood. For example, hypotensive anesthesia has shown some efficacy in patients with acetabular fractures, whereas routine use of normovolemic hemodilution is not recommended in cases of acute hip fracture.[23] Others have described alternate novel methods in reducing blood loss. It been shown in a knee arthroplasty study of 71 patients that when surgical drains are clamped postoperatively for 2 hours following no intraoperative bleeding control, operating times can be reduced without additional need for transfusion compared with careful intraoperative hemostasis.[60] Finally, a modified and less invasive lateral surgical approach to total hip arthroplasty produced significantly less blood loss with similar clinical outcomes in 55 patients.[61]

RECOMMENDATIONS AND CONCLUSIONS

A number of strategies to reduce blood loss and transfusions exist during the perioperative setting in orthopedic trauma. Unfortunately, many studies of blood conservation offer low levels of evidence and contradictory findings. However, practical options available to the traumatologist include the following: accepting higher transfusion thresholds, using cell salvage when substantial blood loss is anticipated, and using TXA when indicated. These recommendations are shown in Table 1 according to the level of evidence and grade of recommendation. Further, institutions should develop and implement strategies for blood conservation to reduce variability in surgeon practices and to optimize patient outcomes.

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