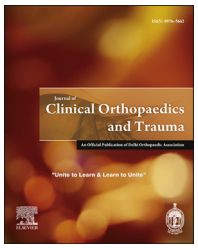
Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jcot



Review Article

Blood conservation strategies in orthopedic surgeries: A review

Balaji Sambandam M.S. Orthopaedics[a,*], *Sahil Batra M.S. Orthopaedics*[a], *Rajat Gupta M.S. Orthopaedics*[a], *Nidhi Agrawal D.A., D.N.B. Anaesthesia*[b]

[a] *Senior Resident, Lok Nayak Hospital, New Delhi, India*
[b] *Specialist Anesthesia, V.M.M.C. & Safdarjung Hospital, New Delhi, India*

ARTICLE INFO

Article history:
Received 7 November 2013
Accepted 13 November 2013
Available online 8 December 2013

Keywords:
Blood conservation
Orthopedic surgery
Tranexamic acid

ABSTRACT

In orthopedics management of surgical blood loss is an important aspect which has evolved along with modern surgeries. Replacement of lost blood by transfusion alone is not the answer as was considered earlier. Complications like infection and immune reaction due to blood transfusion are a major concern. Today numerous techniques are available in place of allogenic blood transfusion which can be employed safely and effectively. In this article we have reviewed these techniques, their merits and demerits.

In modern day orthopedic surgeries, apart from the complications directly related to fractures and implants, a surgeon faces numerous perioperative complications. These range from excessive intraoperative and postoperative blood loss, infection, poor wound healing, electrolyte imbalance to even acute renal shut down and shock. Surgeries in orthopedics being more invasive leads to more blood loss when compared to other surgical specialties.

Tumor surgeries, pelvic surgeries, arthroplasties particularly revision arthroplasties take a heavy toll on the hemodynamics. A study in University of California estimated that average blood lost during a primary hip replacement was 3.2 ± 1.3 units and in case of revision surgeries it was 4.0 ± 2.1 units.[1] In a similar study the estimated average blood lost during total knee replacement was 1000–1500 ml.[2] Amount lost will be more in uncemented arthroplasties because of the absence of the hemostatic action of bone cement.

"Blood for blood" is what we follow from age old times. But blood transfusion is not free of complications. Apart from the well known viral infections HIV, HBV and HCV the list of blood borne infections also includes syphilis, malaria and a variety of bacteria that can grow in 1–6° centigrade particularly coagulase negative Staphylococcus and Yersinia. Even deaths were reported from sepsis due to transfusion of Yersinia infected blood products.[3] Though not a true pathogen transmission of Creutzfeldt Jakob disease is also a possible complication. Furthermore we have a list of immunological complications viz. febrile reaction, allergic reaction, direct immune hemolytic reaction, transfusion related acute lung injury, immunomodulation, graft versus host disease etc.

American society of anesthesiologist[4] gave the following evidence based guidelines for blood transfusion in perioperative and postpartum settings-

1. Transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dl and is almost always indicated when it is less than 6 g/dl, especially when anemia is acute.

* *Corresponding author.*
E-mail addresses: balajinimrotz@gmail.com, balajisambandam@yahoo.com (B. Sambandam).
0976-5662/$ – see front matter
http://dx.doi.org/10.1016/j.jcot.2013.11.002

2. The determination of whether intermediate hemoglobin concentration (6–10 g/dl) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.
3. The use of single hemoglobin trigger for all patients and other approaches that fail to consider all important physiological and surgical factors affecting oxygenation are not recommended.
4. The indications for transfusion of autologous RBCs may be more liberal than allogenic RBCs because of lower (but still significant) risks associated with the former.
5. When appropriate preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution and measures to decrease blood loss (deliberate hypotension and pharmacological agents) may be beneficial.

Given below is a review on the techniques employed for blood conservation, their merits and demerits based on scientific evidences available. These techniques can mainly be divided into:-

A) Preoperative-
   a) Autologous blood donation
   b) Recombinant erythropoietin
B) Perioperative-
   a) Hypotensive epidural anesthesia (HEA)
   b) Platelet rich plasmapheresis
   c) Acute normovolemic hemodilution (ANH)
   d) Cell salvage (scavenging)
   e) Anti-fibrinolytics
   f) Fibrin sealants

1. Preoperative autologous blood donation

Patients who are about to undergo elective surgeries can donate their own blood before surgery, which can be stored for about 6 weeks and later used during and after surgery. Although cost involved in this procedure is almost same as that of allogenic transfusion many of the complications associated with allogenic transfusion can be averted. Donation can be done twice weekly and can be done up to 72 h before surgery. Initially it was considered as a gold standard technique to reduce allogenic blood exposure. A 3 year retrospective study by Goodnough et al showed that it reduced homologous blood transfusion from 41% in non autologous blood patients to 14% in autologous blood donors.[5] Later many studies though proved that it is not an ideal strategy for blood conservation.[6–8] Results of a meta-analysis done by Forgie et al showed that although it reduced allogenic transfusion rate, it increased the overall transfusion rate, the results being of no significance in the non anemic patients.[9] In one study out of 416 units donated only 47 have been used, the rest were discarded.[10] Hence its use has to be rationalized depending on the situation. It has several limitations and adverse effects. Number of units that can be donated is limited by age, sex, physical fitness and other co-morbid illness. By itself it can cause anemia increasing the chances for either autologous or allogenic transfusion. If the surgery is postponed there is a chance for wastage. Sometimes all the units harvested are not transfused resulting in wastage of precious blood. There are few problems with stored blood, the most common is infection from the commensals in skin of the donor and the paramedics who process them. A remote possibility of a mismatch transfusion due to human error is always there.

2. Recombinant erythropoietin

It is a hormone synthesized by recombinant DNA technology that mimics the human hematopoietic hormone erythropoietin. It is mainly used for treating anemia due to chronic renal failure and that occurs during cancer chemotherapy. Its use is now extended to improve the preoperative hemoglobin in elective orthopedic surgeries. Instead of postoperative transfusion or preoperative autologous blood donation, this hormone directly improves the hemoglobin of the patient. It has been observed in some studies that preoperative hemoglobin status is an absolute indicator for postoperative transfusion.[11,12] By improving the hemoglobin level, this hormone can avoid most of the transfusions in at least elective orthopedic surgeries. Usual schedule is a dose of 300 IU per kilogram (kg) of body weight per day for 10 days prior to surgery, the day of surgery and four days after surgery. An alternate schedule is 600 IU per kg body weight administered once weekly beginning three weeks before surgery, then a fourth dose on the day of surgery. Iron supplementation should be given along with the hormone. In one study conducted by Santoro et al among patients undergoing total knee and hip replacement, there was a significant decrease in transfusion rate and a significantly higher postoperative hemoglobin in patients who were given erythropoietin when compared to their controls, though there was no difference in the length of their hospital stay.[13] In a similar study conducted by Faris et al with a large group of patients undergoing major orthopedic surgeries patients who received erythropoietin needed significantly lesser blood transfusion. Also the group of patient who received a higher dose of the hormone needed still lesser transfusion than the group which received a lower dose of the same, though this was not statistically significant.[14] When the expected loss during a surgery is very large and acute this hormone can also be used to increase the harvest from autologous blood donation. Since autologous blood can be donated only within 6 weeks prior to surgery and anemia being a restricting factor, erythropoietin can be handy for this purpose. When autologous blood is collected the dosage of erythropoietin is 600 IU twice a week. Colomina et al did a study with 250 patients who underwent complex spine surgeries wherein all patients were made to donate autologous blood preoperatively. Patients who were given recombinant erythropoietin had higher hemoglobin values on the day of surgery, had more autologous blood donated and needed less allogenic blood transfusion when compared to the rest.[15] This hormone is relatively safe. However, due to rapid increase in red cell mass, there is a risk of increase in blood pressure in hypertensive patients. Hence it is to be avoided in patients with uncontrolled hypertension. Other side effects like cerebral convulsion, hypertensive encephalopathy,

thromboembolism and myocardial infarction occur only with long term therapy for chronic kidney disease and in blood doping in sports. Thus it is a safe and effective solution for severely anemic patients undergoing elective orthopedic surgery.

3. Hypotensive epidural anesthesia (HEA)

Reducing blood loss by lowering blood pressure using vasodilators or cardiac depressants during general anesthesia is not new. Hypotensive epidural anesthesia is a more recent development to achieve this purpose. To lower blood pressure epidural block is given to achieve a level of up to T4 dermatome. This creates a sympathetic block which causes vasodilatation and blocks cardiac accelerator fibers leading on to hypotension. To avoid the fall in heart rate, central venous pressure and cardiac output that occurs along with the fall in blood pressure epinephrine in low doses is infused. Several studies done in this technique showed significant reduction in the amount of blood loss and transfusion requirements.[16,17] Sharrock et al had done an extensive study in this technique over 8 years in over 800 cases of total hip replacements.[16] In additions to serving the purpose of lowering blood loss they observed a reduced risk of deep vein thrombosis in their patients. Deep vein thrombosis occurs because of loss of anticoagulants like antithrombin III due to consumption and hemodilution that occurs during surgical blood loss. Also the intravenous fluid which is given will cause hypothermia and vasoconstriction which in turn leads to stasis. By avoiding these factors the risk of deep vein thrombosis is reduced. Further epinephrine increases the skeletal muscle blood flow thereby avoiding stasis. Through this study they established the safety of this technique even in high risk patients with congestive heart failure, ischemic heart disease, hypertension, elderly and patients with spinal disease. Juelsgaard et al compared hypotensive epidural anesthesia with spinal anesthesia in patients who underwent total knee replacement. Total average blood loss in spinal anesthesia group with the use of tourniquet was 1826 ml, while in the hypotensive epidural anesthesia group without tourniquet was significantly lower, 1056 ml and so was the reduction in allogenic transfusion rate.[17] In a retrospective study, Sharrock et al also observed that hypotensive epidural anesthesia is safe even in chronic kidney disease and does not predispose them to acute renal failure.[18] In another study comparison was made between hypotensive epidural anesthesia and hypotensive total intravenous anesthesia in 40 patients who underwent total hip replacement.[19] Despite the same level of hypotension maintained in both the group hypotensive epidural anesthesia group had significantly lesser blood loss and needed lesser transfusion. They attributed this difference to the relatively more central venous pressure in general anesthesia group due to positive pressure ventilation and redistribution of blood in skeletal muscles and adipose tissue due by epinephrine used in the other group. Also by providing a dry surgical field better bone cement penetration and thereby better fixation of implants has been observed by Ranawat et al.[20] The most important complication of this modality is high epidural anesthesia causing respiratory failure by paralyzing cervical dermatomes. This occurs due to high dosage of the local anesthetic agent or in patients with previous lumbar surgery. Hypotensive epidural anesthesia is contraindicated in severe aortic or mitral stenosis, severe stenosis of carotid or vertebral artery and in patients with heart block. Apart from technical skill and meticulous monitoring an arterial catheter, central venous catheter and an infusion pump are the requirements for this technique, which is a small price paid to the immense benefits we derive.

4. Platelet rich plasmapheresis

Employed primarily in cardiothoracic by-pass surgeries, its scope can be extended into orthopedic surgeries. Coagulation abnormalities and hemorrhage are particularly common following cardiac surgeries because of the cardiac by-pass machine. Therefore transfusion of a platelet rich concentrate is very helpful postoperatively. Several studies in cardiac surgeries proved this technique to reduce allogenic blood transfusion.[21–24] Sawat et al were able to perform scoliosis correction in four Jehovah's witnesses with the help of platelet plasmapheresis and hypotensive anesthesia.[25] Similarly Ekback et al found this technique to be as effective as preoperative autologous blood donation in 40 patients who underwent total hip replacement.[26] They were able to totally avoid allogenic transfusion. Plasmapheresis is done 24 h before surgery or after induction of anesthesia. With the help of large bore catheters blood from the patient's body is transferred to the plasmapheresis machine. In a single cycle 200–300 ml blood will be withdrawn and will be subjected to centrifuge. This separates the blood into three components viz. RBCs, plasma and platelet concentrates. RBCs and plasma are retransfused into the patient's body at the same time. In addition to this, crystalloids and colloids are used to compensate for the volume lost due to platelet harvest. This cycle is repeated several times until the desired amount of platelet is collected. The platelet harvested will be equal to about 20–30% of the blood volume and this will be equal to five units of platelet concentrates. This is stored and transfused at the end of surgery. Most important complication is development of hypotension during plasmapheresis. This is due to volume loss that occurs, which should be managed effectively by volume replacement and inotropes if required. In one study conducted in cardiothoracic surgery hypotension was reported during transfusion of platelets.[27] This was attributed to the hypocalcaemia caused by the citrates used in storage of the components. The quality of the transfused platelets is a concern though. But a study using flow cytometry showed no change in the quality of platelets harvested by plasmapheresis.[28] Thus but for its cost it is an effective technique.

5. Acute normovolemic hemodilution(ANH)

ANH is a technique in which whole blood is removed from a patient, while circulating volume is maintained with acellular fluid. It is performed shortly before or shortly after induction of anesthesia. The procedure is carried by an experienced team inside the operation theater which usually takes around

20–35 min. Blood withdrawn from the patient is stored in the normal blood bags containing Citrate-Phosphate-Dextrose-Adenosine (CPDA) labeled for "autologous use only". The blood is fractionated into Platelet Rich Plasma (PRP) and Platelet Poor Plasma (PPP) so as to treat any coagulopathy caused by the hemodilution or by the replacement fluid. The rate of blood withdrawn does not matter as long as euvolemia is being maintained. The fluids used generally are Ringer-Lactate in the ratio of 3:1 or Hydroxyethyl starch in the ratio of 1:1, the latter one carrying the risk of a coagulopathy. The blood removed is only for use in the operating room and not to be used outside. The bags will be transfused back to the patient in the reverse order of which they were withdrawn, supposing that all the blood will be transfused back. For ANH to be maximally efficacious, surgical blood loss should be more than 70% of the patient's blood volume.[29,30] When the blood loss exceeds 90% of the patient's blood volume ANH alone may not be able to prevent exposure to allogenic blood, but it may reduce the number of allogenic units transfused.[31]

Volume of blood that can be withdrawn is calculated as follows

$$V = EBV \times (Hi - Hf)/Hm$$

Hi = Initial hematocrit; Hf = Target hematocrit; Hm = Average hematocrit= (Hi + Hf)/2; EBV = estimated blood volume (body weight × 65 ml for women and 70 ml for men).

Usually the harvest of blood can be done until a hematocrit of 20% or until the patient reaches the phlebotomy threshold. A total of not more than 2 L can be safely withdrawn from the patient depending on the preoperative hemoglobin, age and general build up of the patient. The end point of withdrawing of blood is tachycardia, the occurrence of which suggests the upper limit of the possible blood withdrawn. This technique stands out in that it provides fresh autologous blood products with adequate quantities of platelets, clotting factors and 2,3 DPG, capable of being used in emergency surgeries, being least costly. Unlike autologous blood donation there is no chance of mismatched transfusion due to clerical error as the stored blood never leaves the operation theater. Several studies in hip and knee arthroplasty,[32,33] spine surgery[34] and other non orthopedic surgeries[35–40] have demonstrated its effectiveness. Contraindications include severe anemia, impaired renal function, untreated hypertension, cardiac dysfunction, clotting disorders, bacteremia, severe pulmonary disease and in conditions in which increased cardiac output is desirable like coronary artery disease and aortic stenosis.

6. Cell salvage technique

Cell salvage is a technique in which the patient's own blood is used as self donation by collecting shed blood intraoperatively and in the postoperative drains through a collector container. The RBCs are washed and the washed RBCs are reinfused into the patient. A double drainage catheter system is usually used which is connected to a blood bag and a cell saver unit. Usually, only the blood shed in the first 6 h of the postoperative period is retransfused. There are studies to support that cell salvage connecting systems and retransfusion of the shed blood reduces the need for allogenic transfusion.[41–45] Strumper et al observed the rate of allogenic transfusion was reduced from 47% to 34% in the total hip arthroplasty group and from 18 to 6% in total knee arthroplasty group.[46] Goulet et al[47] reported that 60% of total blood transfusion would be substituted by intraoperative blood salvage using cell saver in orthopedic surgeries and Wilson et al[48] reported the decrease in the same as 47%. Cost is a major limiting factor for this technique and so the cost effectiveness of the technique is limiting its popularity. Slagis et al[45] and Naumenko[49] et al used a cell washer system which increased the expenses of the operation while Newman et al[42] and Zhao et al[50] reinfused unwashed blood which reduced the cost of the technique and found that fever episodes are significantly lower in comparison to the allogenic transfusion. It has also been even shown in many other studies that the unwashed and filtered blood is of satisfactory quality and safe to return.[51,52] When cell salvage was first introduced in 1970s it was complicated by hemolysis, air embolism and coagulopathy.[53] Processing salvaged blood removes platelet and coagulation factors. But coagulation usually remains unaffected unless blood loss exceeds 3 L.[54] Djaiani et al[55] reported that this technique increased the need for Fresh Frozen Plasma (FFP) transfusion but there are other studies which contradicts this.[56,57] A new technology that can reduce the risk of coagulopathy by extracting platelets and clotting factors from the cell salvage waste and making it available for retransfusion with salvaged RBCs is available now-a-days.

7. Pharmacological agents

Pharmacological agents can be used to achieve hemostasis during and after surgery by altering the delicate balance between blood clotting and fibrinolysis. During a surgical insult there is activation of the clotting mechanism. In order to check uncontrolled clot formation fibrinolytic mechanism also get activated simultaneously. Drugs used to reduce blood loss inhibit the fibrinolytic mechanism. Aprotinin, epsilon amino caproic acid and tranexamic acid are the three drugs in this group.

Aprotinin is bovine pancreatic trypsin inhibitor which inhibits trypsin and related proteolytic enzymes like chymotrypsin, plasmin and kallikrein. It inhibits fibrinolysis by its action on plasmin. Earlier this drug was used to reduce blood loss in many orthopedic and cardiac surgeries. But later this was banned as there was an increased risk of acute renal failure, myocardial infarction, heart failure, stroke and encephalopathy with its usage.

Epsilon amino caproic acid (EACA) is an antifibrinolytic drug which binds to the fibrin binding site of plasmin and blocks its action on fibrin, thus preventing fibrinolysis. Unlike aprotinin, this is a safe drug and studies have proved this to be as effective as the former.[58] Most of studies conducted with this drug are in cardiac surgeries but we do have some orthopedic studies. In a study conducted among 49 patients who underwent total hip replacement there was 27% reduction in total blood loss and 11% reduction in transfusion rates in the patients who were given EACA, compared to the control group.[59] Similarly in another study with 127 patients who

underwent total knee replacement the efficacy and safety of this drug was proved.[60] Though theoretically it can cause deep vein thrombosis, no increased risk had been observed in any of the studies conducted.

Tranexamic acid has the same mechanism of action as EACA, with comparable efficacy and safety at a lower cost. In high blood loss surgeries it is given intravenously at a dose of 10 mg per kg body weight, which can be repeated once or twice after 4 h. It is also available in oral formulation which can be used at a dose of 15–25 mg per kg body weight in prostatectomy, minor gynecological procedures, menorrhagia, epistaxis, haemophilia and hereditary angioneurotic edema. There are numerous studies with this drug that proved its efficacy.[61–63] Also a study conducted in our hospital showed this drug to be effective in reducing blood loss and transfusion in total knee replacement patients.[64] In addition to the usual intravenous route this drug can be used topically as demonstrated by Wong et al wherein 1.5 or 3 g of tranexamic acid in 100 ml of normal saline was applied to the joint surface for minutes at the end of surgery.[65] Though safe, it is better to avoid these drugs in patients with deep vein thrombosis and the patients with the risk of developing it as there is a rare possibility of this complication. Other rarely reported adverse effects are abdominal discomfort, chest pain, myocardial infarction, dyspnea, pulmonary embolism and hypersensitivity.

8. Fibrin sealants

These are surgical hemostatic and adhesive agents derived from plasma product. Safety from infection is ensured by careful selection of donors and employing many purifying techniques. Till date no infection has been reported with its use. It usually consists of fibrinogen, thrombin, factor XIII, an antifibrinolytic agent like aprotinin and calcium chloride. After thawing the frozen components, they are reconstituted at the time it is to be used. Clots similar to the natural blood clot, that can be degraded by the body's natural enzymes are produced. Earlier used mainly in soft tissue surgeries its use later expanded into orthopedic surgeries. This is applied to the actively bleeding cancellous bony surfaces to achieve hemostasis. This can be used as a hemostatic agent in orthopedic and other high blood loss surgeries, as a sealing agent in tympanoplasty, CSF fistula repair, premature rupture of membranes in pregnancy, bowel anastomosis, pleural surgeries etc., and as an adhesive in parenchymal surgeries. Significant reduction in blood loss and blood transfusion has been observed in several studies done in idiopathic scoliosis surgery, total knee replacement and total hip replacement.[66–68] Allergic reaction is the only known but rare complication. This is for topical use only as thromboembolic complication might occur on direct intravascular application. Spray devices employing high pressure regulators should not be employed to administer fibrin sealants as this is known to cause air embolism. Usually employed to control unexpected high bleeding this can be used routinely in high blood loss surgeries, thereby reducing allogenic blood transfusion.

The above eight are the techniques currently available to reduce allogenic blood transfusion. Due to the numerous disadvantages of allogenic blood and with so many alternatives available now-a-days allogenic blood transfusion is gradually losing its ground in orthopedic surgeries. Depending on the patient's profile, nature of surgery and the expertise available, suitable methods have to be chosen. In elective procedures involving severe blood loss preoperative autologous blood donation and preoperative erythropoietin can be used. In emergency procedures pharmacological agents, acute normovolemic hemodilution and fibrin sealants can be used. In tertiary care hospitals where the set up is available, platelet rich plasmapheresis or cell salvage techniques can be employed in isolation or in combination with any of the before mentioned techniques. Sometimes more than one technique has to be used. There is no single technique that is universal to all situations. Gradually increasing awareness and newer advances in these techniques will definitely decrease the popularity of allogenic blood transfusion in the near future.

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES

1. Toy PT, Kaplan EB, McVay PA, Lee SJ, Strauss RG, Stehling LC. Blood loss and replacement in total hip arthroplasty: a multicenter study. The preoperative autologous blood donation study group. *Transfusion*. 1992;32(1):63–67.
2. Keating EM, Meding JB, Faris PM, Ritter MA. Predictors of transfusion risk in elective knee surgery. *Clin Orthop Relat Res*. 1992;357:50–59.
3. Brecher ME, Hay SN. Bacterial contamination of blood components. *Clin Microbiol Rev*. Jan 2005;18(1):195–204.
4. Practice guidelines for blood component therapy. A report by the American society of anesthesiologist task force on blood component therapy. *Anesthesiology*. 1996;84:732–747.
5. Goodnough LT, Shafron D, Marcus RE. The impact of preoperative autologous blood donation on orthopaedic surgical practice. *Vox Sang*. 1990;59(2):65–69.
6. Billote DB, Glisson SN, Green D, Wixson RL. Efficacy of preoperative autologous blood donation: analysis of blood loss and transfusion practice in total hip replacement. *J Clin Anesth*. 2000 Nov;12(7):537–542.
7. Goldman M, Savard R, Long A, et al. Declining value of preoperative autologous donation. *Transfusion*. 2002;42:819–823.
8. Cohen JA, Brecher ME. Preoperative autologous blood donation: benefit or detriment? A mathematical analysis. *Transfusion*. 1995;35:640–644.
9. Forgie MA, Wells PS, Laupacis A, et al. Preoperative autologous blood transfusion decreases allogeneic transfusion but increases exposure to all red blood cell transfusion. Results of a meta-analysis. *Arch Intern Med*. 1998;158:610–616.
10. Reqis D, Corallo F, Franchini M, Rosa R, Ricci M,Bartolozzi P. Preoperative autologous blood donation in primary total knee arthroplasty: critical review of current indications. *Chir Organi Mov*. 2008 Jan;91(1):41–44.
11. Faris PM, Spence RK, Larholt KM, Sampson AR, Frei D. The predictive power of baseline hemoglobin for transfusion risk in surgery patients. *Orthopedics*. 1999;22(suppl l):s135–s140.

12. Nuttall GA, Santrach PJ, Oliver Jr WC, et al. The predictors of red cell transfusions in total hip arthroplasties. *Transfusion*. 1996;36:144–149.
13. Santoro JE, Eastlack RK, Mirocha JM, Bugbee WD. Impact of erythropoietin on allogenic blood exposure in orthopaedic surgery. *Am J Orthop*. 2007 Nov;36(11):600–604.
14. Faris PM, Ritter MA, Abels RI. The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American erythropoietin study group. *J Bone Joint Surg Am*. 1996;78:62–72.
15. Colomina MJ, Bago J, Pellise F, Godet C, Villanueva C. Preoperative erythropoietin in spine surgery. *Eur Spine J*. 2004;13(suppl 1):S40–S49.
16. Sharrock NE, Salvati EA. Hypotensive epidural anesthesia for total hip arthroplasty. *Acta Orthop Scand*. 1996;67:91–107.
17. Juelsgaard P, Larsen UT, Sorensen JV, Madsen F, Soballe K. Hypotensive epidural anesthesia in total knee replacement without tourniquet: reduced blood loss and transfusion. *Reg Anesth Pain Med*. 2001 March-April;26:105–110.
18. Sharrock NE, Beksac B, Flynn E, Go G, Gonzalez Della Valle A. Hypotensive epidural anaesthesia in patients with preoperative renal dysfunction undergoing total hip replacement. *Br J Anesth*. 2006;96:207–212.
19. Eroglu A, Uzunlar H, Ercives H. Comparison of hypotensive epidural anesthesia and hypotensive total intravenous anesthesia on intraoperative blood loss during total hip replacement. *J Clin Anesth*. Sep 2005;17(6):420–425.
20. Ranawat CS, Beaver WB, Sharrock NE, Maynard MJ, Urquhart B, Schneider R. Effect of hypotensive epidural anaesthesia on acetabular cement-bone fixation in total hip arthroplasty. *J Bone Joint Surg Br*. 1991;73-B:779–782.
21. Ferrari M, Zia S, Valbonesi M, et al. A new technique for hemodilution, preparation of autologous platelet-rich plasma and intraoperative blood salvage in cardiac surgery. *Int J Artif Organs*. 1987;10:47–50.
22. Giordano GF, Rivers SL, Chung GK, et al. Autologous platelet-rich plasma in cardiac surgery: effect on intraoperative and postoperative transfusion, requirements. *Ann Thorac Surg*. 1988;46:416–419.
23. Giordano Sr GF, Giordano Jr GF, Rivers SL, et al. Determinants of homologous blood usage utilizing autologous platelet-rich plasma in cardiac operations. *Ann Thorac Surg*. 1989;47:897–902.
24. DelRossi AJ, Cernaianu AC, Vertrees RA, et al. Platelet-rich plasma reduces postoperative blood loss after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1990;100:281–286.
25. Safwat AM, Reitan JA, Benson D. Management of Jehovah's Witness patients for scoliosis surgery: the use of platelet and plasmapheresis. *J Clin Anesth*. 1997 Sep;9(6):510–513.
26. Ekbäck G, Ryttberg L, Axelsson K, et al. Preoperative platelet-rich plasmapheresis and hemodilution with an autotransfusion device in total hip replacement surgery. *J Clin Apher*. 2000;15(4):256–261.
27. Shore-Lesserson L, Reich DL, DePerio M, Silvay G. Autologous platelet-rich plasmapheresis: risk versus benefit in repeat cardiac operations. *Anesth Analg*. 1995;81(2):229–235.
28. Ekbäck G, Edlund B, Smolowicz A, et al. The effects of platelet apheresis in total hip replacement surgery on platelet activation. *Acta Anaesthesiol Scand*. 2002 Jan;46(1):68–73.
29. Bryson GL, Alpacas A, Wells GA. Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. *Anesth Analg*. 1998;86:9–15.
30. Monk TG, Goodnough LT, Birkmeyer JD, et al. Acute normovolemic hemodilution is a cost-effective alternative to preoperative autologous blood donation by patients undergoing radical retropubic prostatectomy. *Transfusion*. 1995;35:559–565.
31. Matot I, Scheinin O, Jurim O, Eid A. Effectiveness of acute normovolemic hemodilution to minimize allogenic blood transfusion in major liver resections. *Anesthesiology*. 2002;97:794–800.
32. Oishi CS, D'Lima DD, Morris BA. Hemodilution with other blood reinfusion techniques in total hip arthroplasty. *Clin Orthop*. 1997;339:132–139.
33. Schmied H, Schiferer A, Sessler DI, Meznik C. The effects of red-cell scavenging, hemodilution, and active warming on allogeneic blood requirements in patients undergoing hip or knee arthroplasty. *Anesth Analg*. 1998;86:387–391.
34. Lim YJ, Kim CS, Bahk JH, Ham BM, Do SH. Clinical trial of esmolol-induced controlled hypotension with or without acute normovolemic hemodilution in spinal surgery. *Acta Anaesthesiol Scand*. 2003;47:74–78.
35. Monk TG, Goodnough LT, Brecher ME, et al. A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. *Anesthesiology*. 1999;91:24–33.
36. Monk TG, Goodnough LT, Pulley DD, Brecher ME. Acute normovolemic hemodilution can replace preoperative autologous blood donation as a standard of care for autologous blood procurement in radical prostatectomy. *Anesth Analg*. 1997;85:953–958.
37. Spahn DR, Zollinger A, Schlumpf. Hemodilution in elderly patients without known cardiac disease. *Anesth Analg*. 1996;82:681–686.
38. Spahn DR, Schmidt ER, Seifert B, Pasch T. Hemodilution tolerance in patients with coronary artery disease who are receiving chronic adrenergic blocker therapy. *Anesth Analg*. 1996;82:687–694.
39. Torella F, Haynes SL, Kirwan CC, Bhatt AN, McCollum CN. Acute normovolemic hemodilution and intraoperative cell salvage in aortic surgery. *J Vasc Surg*. 2002;36:31–34.
40. Wong JW, Torella F, Haynes S, et al. Autologous versus allogeneic transfusion in aortic surgery. A multicenter randomized clinical trial. *Ann Surg*. 2002;235(1):145–151.
41. Faris PM, Ritter MA, Keating EM, Valeri CR. Unwashed filtered shed blood collected after knee and hip arthroplasties. A source of autologous red blood cells. *J Bone Joint Surg Am*. 1991;73:1169–1178.
42. Healy WL, Pfeifer BA, Kurtz SR, Johnson C, Johnson W, Johnston R. Evaluation of autologous shed blood for autotransfusion after orthopaedic surgery. *Clin Orthop Relat Res*. 1994;299:53–59.
43. Gannon DM, Lombardi Jr AV, Mallory TH, Vaughn BK, Finney CR, Niemcryk S. An evaluation of the efficacy of postoperative blood salvage after total joint arthroplasty: a prospective randomized trial. *J Arthroplasty*. 1991;6:109–114.
44. Heddle NM, Brox WT, Klama LN, Dickson LL, Levine MN. A randomized trial on the efficacy of an autologous blood drainage and transfusion device in patients undergoing elective knee arthroplasty. *Transfusion*. 1992;32:742–746.
45. Newman JH, Bowers M, Murphy J. The clinical advantages of autologous transfusion: a randomized, controlled study after knee replacement. *J Bone Joint Surg Br*. 1997;79:630–632.
46. Simpson MB, Murphy KP, Chambers HG, Bucknell AL. The effect of postoperative wound drainage reinfusion in reducing the need for blood transfusions in elective total joint arthroplasty: a prospective, randomized study. *Orthopedics*. 1994;17:133–137.
47. Slagis SV, Benjamin JB, Volz RG, Giordano GF. Postoperative blood salvage in total hip and knee arthroplasty. A randomised controlled trial. *J Bone Joint Surg Br*. 1991;73:591–594.
48. Naumenko SE, Pokrovsky MG, Belavin AS, Danilenko AV, Kim SF. Blood preserving efficacy of reinfusion of drainage discharge in uncomplicated coronary heart bypass operation. *Thorac Cardiovasc Surg*. 2003;1:43.

49. Zhao K, Xu J, Hu S, Wu Q, Wei Y, Liu Y. Autotransfusion of shed mediastinal blood after open heart surgery. *Chin Med J*. 2003;116:1179–1182.
50. Allam J, Cox M, Yentis SM. Cell salvage in obstetrics. *Int J Obstet Anesth*. 2008;17:37–45.
51. Wang G, Bainbridge D, Martin J, Cheng D. The efficacy of an intraoperative cell saver during cardiac surgery: a meta-analysis of randomized trials. *Anesth Analg*. 2009;109:320–330.
52. Djaiani G, Fedorko L, Borger MA, et al. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. *Circulation*. 2007;116:1888–1895.
53. Niranjan G, Asimakopoulos G, Karagounis A, Cockerill G. Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on versus off-cardiopulmonary bypass: a randomised trial. *Eur J Cardiothorac Surg*. 2006;30:271–277.
54. Hussain S, Clyburn P. Cell salvage-induced hypotension and London buses. *Anaesthesia*. 2010;65:661–663.
55. Strumper D, Weber EWG, Drumpt RV, Bulstra S. Clinical efficacy of postoperative autologous transfusion of filtered shed blood in hip and knee arthroplasty. *Transfusion*. 2004;44:1567–1571.
56. Goulet J, Bray TJ, Timmerman LA. Intraoperative autologous transfusion in orthopaedic patients. *J Bone Joint Surg Am*. 1989;71:3.
57. Wilson WJ. Intraoperative autologous transfusion in revision total hip arthroplasty. *J Bone Joint Surg Am*. 1989;71:8.
58. Munoz JJ, Birkmeyer NJO, Birkmeyer JD, O'Connor GT, Dacey LJ. Is e-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery?: a meta-analysis. *Circulation*. 1999;99:81–89.
59. Harley BJ, Beaupré LA, Jones CA, Cinats JG, Guenther CR. The effect of epsilon aminocaproic acid on blood loss in patients who undergo primary total hip replacement: a pilot study. *Can J Surg*. 2002 June;45(3):185–190.
60. Camarasa MA, Ollé G, Serra-Prat M, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. *Br J Anaesth*. 2006 May;96(5):576–582.
61. Hippala S, Strid L, Wennerstrand M, et al. Tranexamic acid (cyclokapron) reduces peri-operative blood loss associated with total knee arthroplasty. *Br J Anesth*. 1995;74:534–537.
62. Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br*. 1996;78-B:434–440.
63. Jansen AJ, Andreica S, Claeys M, et al. Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. *Br J Anaesth*. 1999;83:596–601.
64. Gautam VK, Sambandam B, Singh S, Gupta P, Gupta R, Maini L. The role of tranexamic acid in reducing blood loss in total knee replacement. *J Clin Orthop Trauma*. 2013 Mar;4(1):36–39.
65. Wong J, Abrishami A, Beheiry HE, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am*. 2010 Nov 03;92(15):2503–2513.
66. Tredwell SJ, Sawatzky B. The use of fibrin sealant to reduce blood loss during Cotrel-Dubousset instrumentation for idiopathic scoliosis. *Spine (Phila Pa 1976)*. 1990 Sep;15(9):913–915.
67. Everts PA, Devilee RJ, Brown Mahoney C, et al. Platelet gel and fibrin sealant reduce allogeneic blood transfusions in total knee arthroplasty. *Acta Anaesthesiol Scand*. 2006 May;50(5):593–599.
68. Lassen MR, Solgaard S, Kjersgaard AG, et al. A pilot study of the effects of Vivostat patient-derived fibrin sealant in reducing blood loss in primary hip arthroplasty. *Clin Appl Thromb Hemost*. 2006 Jul;12(3):352–357.