CURRENT CONCEPTS REVIEW

Perioperative Blood Management Strategies for Patients Undergoing Total Hip Arthroplasty: Where Do We Currently Stand on This Matter?

Konstantinos Vrontis, MD[1]; Georgios Tsinaslanidis, MD[2]; Georgios I. Drosos, MD, PhD[3]; Themistoklis Tzatzairis, MSc[4]

Research performed at Department of Orthopaedic Surgery, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Greece

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Abstract

Total hip replacement (THR) has proved to be a reliable treatment for the end stage of hip osteoarthritis. It is a common orthopaedic procedure with excellent results, but is associated with significant blood loss and high rates of allogeneic blood transfusion (ABT). The potential complications and adverse events after ABT, combined with the ongoing research, have resulted in multimodel, multidisciplinary blood management strategies adoption, aiming to reduce the blood loss and transfusion rates. Many reviews and meta-analyses have tried to demonstrate the best blood management strategies. The purpose of this study is to review any evidence-based blood conserving technique, dividing them in three stages: preoperative, intraoperative and postoperative.

Level of evidence: III

Keywords: Anemia, Blood loss, Blood management, Total hip arthroplasty, Tranexamic acid, Transfusion

Introduction

Total hip replacement (THR) has proved to be a reliable and efficient treatment procedure for the end stages of arthritic hip pathology. It provides pain relief, improves mobility and restores function (1). However, this procedure is associated with substantial blood loss; it has been calculated around 1,500 mL including the hidden blood loss (2) .

Different rates of allogenic blood transfusion (ABT) after total joint arthroplasty (TJA) have been reported with a 12% to 87% range (3, 4).

During the decade 2000-2009, a study examining the countries' trend line in the usage of blood transfusions in total knee and hip arthroplasty in the USA reported ABT rates of 12.4% and 19,1% respectively (5).

ABT is associated with transfusion reactions and "specific" complications or adverse events including prolonged hospital stay, increased cost and increased rates of surgical site infections (6-9).

An observational study of 2,087,423 patients undergoing primary THR from 2000 to 2009 (identified in the Nationwide Inpatient Sample in the USA) showed increased ABT rates which was further associated with surgical complications, adverse events, longer hospital stay and increased total cost (4).

During the last decade, the establishment and adoption of Patients' Blood Management (PBM) programs, combined with the widespread research regarding the predictors or risk factors for blood loss after TJA resulted in significant reduction of ABTs in patients undergoing TJA, with reported rates being less than 10% (10-13).

PRE-OPERATIVE

a. Pre-operative evaluation for anemia

According to the World Health Organization (WHO),

Corresponding Author: Konstantinos Vrontis, Bank of Cyprus Oncology Center, Acropoleos Ave 32, Strovolos, Nicosia, Cyprus
Email: velerevrondiscon@hotmail.com

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anemia is defined as having hemoglobin (Hb) <13 g/dL in men, <12 g/dL in nonpregnant women, and <11 g/dL in pregnant women (14). In an attempt to revise traditional WHO anemia definition, it has been suggested that the desirable pre-operative Hb value, in patients undergoing major surgical procedures, should be ≥13 g dl^{-1} for both genders (15).

The prevalence of pre-operative anemia in patients scheduled for elective orthopaedic surgery, according to recent reports is between 10.8% and 17%, with iron deficiency being the main cause in about half of the patients (16-18). A European study (PREPARE study) found that pre-operative anemia is associated not only with heightened postoperative complication rate, however with intraoperative transfusion risk as well, when it comes to patients that were scheduled for elective orthopaedic procedures (16). It was also found that patients' blood management measures such as iron status evaluation and strategies to avoid transfusion are still underused in Europe (16). A recent Australian article revealed that in anaemic patients, who were due to have elective orthopaedic surgery, with iron deficiency, the treatment was effective in improving the pre-operative haemoglobin and reducing perioperative transfusion rates (17).

The Network for Advancement of Transfusion Alternatives (NATA), created clinical guidelines on how to detect, investigate and manage anemia preoperatively in elective surgeries in orthopedics. These included the following (a) measurement of hemoglobin (Hb) within a period of 28 days before the scheduled surgery, (b) aim for a normal Hb level based on the normal range established by the WHO criteria, (c) if anemia is diagnosed, the evaluation should include nutritional deficiencies, chronic renal failure and/or chronic inflammatory disease, (d) any nutritional deficiencies identified must be corrected, and (e) if there is a negative workup for nutritional deficiencies, or have already been corrected but anemia persists, erythropoiesis-stimulating agents can be used for. (19) Treatment of pre-operative anemia is beyond the scope of this article.

b. Antiplatelet agent medication

A significant amount of patients that have been scheduled for surgery also suffer from cardiovascular diseases and they are on antiplatelet medication. It is estimated that within 5 years after stent implantation, an approximate rate of 5-25% of patients with coronary stents may require non-cardiac surgical procedure (20).

According to the 2016 ACC/AHA (American College of Cardiology/American Heart Association) guidelines, non-cardiac surgeries should be delayed for at least 6 months after drug eluting stent (DES) placement and 30 days after bare metal stent (BMS) placement in case that the risk of stent thrombosis is greater than the risk of delaying surgery (20).

The main concern regarding the use of antiplatelet agents is the high risk of bleeding that may occur during total hip arthroplasty. It has been suggested that a surgery like total hip arthroplasty should be avoided during the first year since a 5- to 10-fold increase in acute stent thrombosis has been reported (22). After the operation, patients should continue with aspirin (21).

Aspirin

Precipitous discontinuation of aspirin is associated with a "rebound" effect while surgical interventions can increase coagulation. Therefore, perioperative discontinuation of aspirin therapy is associated with a considerable raise of major adverse cardiac events (MACE) (22-23).

Recent population-based cohort studies, including large number of patients, have shown that in long-term users, discontinuation of low-dose aspirin in the absence of major surgery or bleeding was associated with an increased risk (>30%) of cardiovascular events (24).

From an anesthesiologist's point of view, there is an increased risk of neurological complications in the presence of abnormal bleeding status, spinal or epidural hematoma. To this end, it is clear that a safe neuraxial technique can be safely performed in patients on aspirin therapy (25).

The two main concerns from the surgeon's perspective are hematoma formation and bleeding. A meta-analysis on how low-dose aspirin affected the risk of perioperative bleeding showed a 50% upsurge of bleeding complications in patients receiving aspirin (26). There was only one double-blinded randomized trial on the association of perioperative bleeding and low dose aspirin (75mg) in non-cardiac surgical procedures. This indicated that in high-risk patients on low dose aspirin, undergoing non-cardiac surgery, there was a perioperative reduction of MACE without causing an increase in bleeding complications. However, the study was not powered to evaluate bleeding complications (23).

A consensus between the Italian cardiac, surgical and anaesthesia societies that was published in 2014, suggest the continuation of aspirin during total hip arthroplasty (27). According to 2016 ACC/AHA (American College of Cardiology/American Heart Association) guidelines, low-risk patients, in terms of cardiovascular events, should stop aspirin 7 to 10 days before surgery (enough time for the platelet pool to be replenished). For high risk patients, it is suggested that aspirin should be continued during the whole perioperative period (28).

$P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, prasugrel) - Dual anti-platelet therapy (DAPT)

Clopidogrel and ticagrelor should be discontinued at least five days and prasugrel at least seven days prior to surgery unless there is a high risk of thrombosis (29). A significant number of patients may have an indication for dual anti-platelet therapy (DAPT) after coronary intervention or myocardial infarction. DAPT comprises of a combination of an oral inhibitor of the platelet P2Y12 and aspirin.

It is recommended that elective non-cardiac surgical procedures should be delayed until the completion of the full course of DAPT (30). In the majority of the clinical situations, aspirin should not be discontinued because it provides an advantage that overweight the bleeding risks

(27, 31). If P2Y12 inhibitor therapy has been halted prior to surgery, it should be restarted as soon as promptly (within 24 h) (32, 33). The ideal time for restarting P2Y12 inhibitors post-surgery should ultimately be decided via a multidisciplinary discussion prior to the operation and traced in the patient file (30).

c. Pre-operative blood donation (POBD)

Retrospective cohort studies in large number of patients during the past decade reported that the risk of ABT decreased when POBD was used in patients who underwent total hip arthroplasty (10). Nevertheless, during the same period, the POBD rate was decreased (5). In addition, similar studies revealed that during the current decade the use of POBD has declined and hasn't been included in patients' blood management programs (11-13). According to the authors, this strategy's drawbacks include the induction of phlebotomy-induced anemia, unnecessary costs, and potential complications related to reinfusion (12).

A recent study suggests that topical TXA is equivalent to POBD in anemic patients with similar transfusion rates. Furthermore, TXA showed to be more efficient in non-anemic patients as it reduced transfusion rates when compared to POBD (34).

d. Transfusion protocols

ABT is associated with several transfusion reactions (6, 7). In TJA patients, it is also associated with an increase in surgical complications, including surgical-site infection, length of stay and increased total cost (4, 35, 36).

Transfusion protocols are part of PBM programs in surgical patients, describing the indications for ABT, including transfusion trigger, symptoms of anemia and comorbidities. The so-called "transfusion trigger" is the Hb verge value at which the physician choose to transfuse the patient. Recent data have shown that restrictive strategies, with transfusion trigger (Hb level) between 7g/dl and 8g/dl, are safe with no increase in patients morbidity and mortality and are associated with a reduction of transfusions compared to outdated transfusion strategies (transfusion trigger of Hb 9-10 g/dl) (37, 38).

As a reference, a stringent transfusion trigger point 7 g / dl is recommended, whereas a higher threshold (8 g / dl) is suggested for patients undergoing cardiac or orthopedic surgical procedure and those with pre-existing cardiovascular disease (39, 40).

Patients should be transfused one unit at a time, and the patient's Hb should be checked before each unit transfused, unless there is ongoing bleeding or a large blood loss that needs correcting (39, 40). In case of an ongoing blood loss not responding to resuscitation measures, appropriate actions should be undertaken (39, 40).

INTRA-OPERATIVE

a. Type of anesthesia

Major lower extremity orthopaedic surgeries like THR can be performed with either neuraxial or general anaesthesia. Evidence from several comparative clinical studies show conflicting results concerning mortality, morbidity and outcomes after THR and TKR. A retrospective study, using a large national sample of patients, suggests that neuraxial anesthesia for primary THR and TKR is associated with superior perioperative outcomes compared to general anesthesia (41). On the other hand, a recent systematic review showed limited evidence to suggest that neuraxial anaesthesia is associated with improved perioperative outcomes for THR and TKR (42).

In patients who underwent THR, retrospective studies including several thousand patients have found that general anesthesia is more commonly performed, although it is associated with worse perioperative outcomes including complications (43, 44). Furthermore, when general anesthesia was compared to regional anesthesia, it seems that resulted in increased blood loss and blood transfusion rates (10, 43).

b. Hypotensive epidural anesthesia

Hypotensive epidural anesthesia (HEA) was developed decades ago and it combines epidural anesthesia and low blood pressure resulting in reduced intra-operative blood loss in operations like THR (45).

There is evidence that HEA results in less intraoperative blood loss than hypotensive total intravenous anesthesia, or spinal anesthesia during THR. Furthermore, recent article suggests that administration of TXA combined with HEA managed to reduce blood loss and transfusion requirements when that was compated with HEA alone (46-48). Nevertheless, it seems that HEA is not widely used in orthopaedic surgeries (49).

c. Acute normovolemic haemodilution

Acute normovolemic haemodilution (ANH) is a blood conservation strategy used in the operating theater by anesthesiologists. During this technique, two units of patients' blood were withdrawn through one of the venous cannulae and preserved into a collection bag holding anticoagulant. As blood is drained, crystalloid or colloid fluid is infused, in order to maintain hemodynamic stability. The collected units of blood then, are being transfused back to the patient when hemoglobin decreases post-operatively (50).

There is little evidence regarding the use of ANH in THR. Two comparative studies with a small number of patients have shown that ANH is effective in reducing the ABT and is more effective than nitroglycerin-induced hypotension in reducing allogeneic blood transfusion requirement in THR, without significant metabolic changes (51, 52).

Furthermore, results regarding ANH in surgery are controversial. A recent meta-analysis found that although there is evidence that ANH is effective in reducing ABT there are still concerns about its true efficacy (53).

d. Antifibrinolytic agents

Antifibrinolytic agents such as tranexamic acid (TXA), Epsilon-aminocaproic acid (EACA) and Aprotinin, have been widely used in order to minimize the intraoperative blood loss in total joint arthroplasty.

TXA represents a synthetic derivative of the amino acid

lysine, which inhibits the interaction between plasmin and fibrin by binding to plasminogen. TXA has been the most commonly used agent in the last decade. In addition, TXA can be administered either intravenously (IV), locally, orally, or combined. Recent meta-analyses have shown that TXA is efficient in reducing the blood loss and the transfusion rate, and also safe without increasing the complications (54-56). Furthermore, recent reports support the use of TXA post-operatively (57). Although it is clear that TXA is efficient and safe, there is still no consensus on the best route of administration, dosage regimen or time of administration (58).

Epsilon-aminocaproic acid (EACA) represents an antifibrinolytic agent which acts by a similar mechanism to TXA. A retrospective clinical study in patients who underwent THR, found that EACA is comparable to TXA in THA for reducing transfusion rates while at a lower cost per surgery (59). A recent meta-analysis showed that intravenous EACA is effective and safe in THR and TKR without escalating the frequency of thromboembolic events (60). The authors stated that further studies should focus on the comparison of aminocaproic acid and TXA in arthroplasty procedures (60).

Aprotinin represents a non-lysine antifibrinolytic agent. Although a multicenter, randomized, double-blind, placebo-controlled study published in 2007 showed that aprotinin is safe and effective in decreasing blood transfusion in THR, there is no recent data concerning its use in THR. It is known that in 2008, the U.S (61). Food and Drug Administration prohibited aprotinin use because of associated postoperative complications, including cerebrovascular accidents and renal failure.

e. Intra-operative auto-transfusion or cell salvage

Intra-operative auto-transfusion (IAT) or cell salvage (CS) represents a method through which the blood loss during the arthroplasty is collected, filtered and washed in order to be reinfused back to the patient. Many devices have been developed since the 1960s in order to produce autologous blood ready to be reinfused. Although the use of CC in major orthopaedic operations significantly decreases intraoperative and postoperative ABT requirements, clinical studies regarding the use of CC in THR patients are limited (62, 63). However, CC seems to be a more efficient method compared to post-operative autotransfusion (PAT) when it comes to patients undergoing THR (64).

Nevertheless, the increase in cost and the lack of studies comparing the CC to other methods of patients' blood management, leads to the conclusion that further research is required to best establish when and how cell salvage should be exercised together with newer blood conservation methods (62, 65).

f. Surgical Approaches. Standard versus Mini-Incision approaches

THR can be performed using many different approaches; mini-incision or minimal-invasive approaches are performed through a less than 12 cm skin incision (65).

Direct anterior approach (DAA) and posterior mini-incision are the most commonly used mini-incision approaches but there is still no consensus concerning the advantages of the mini-incision approaches (66, 67). However, there are numerous studies that report statistically significant reduction in blood loss when DAA was compared to direct lateral approach. Furthermore, most of these articles advocated better early functional outcomes and less pain (68-71).

A recent meta-analysis found that limited incision THA was better than standard incision THA in four measures, including blood loss (421 mL versus 494 mL). In addition, there were no outcomes for which standard incision was better and no major difference was noted regarding the rate of complications (72). According to another meta-analysis, there is evidence that mini-incision posterior THA resulted in statistically significant decrease in blood loss (67).

g. Non pharmacological hemostatic agents
Topical fibrin sealants

Fibrin sealant (FS) is composed mostly of human fibrinogen and thrombin. These agents mimic the final steps of the physiological coagulation cascade to form a fibrin clot (73).

There are many studies that have evaluated the efficacy or safety of FS regarding the perioperative blood loss management in patients undergoing THA. Recent systematic reviews and meta analyses have shown that topical administration of FS was associated with a reduction of blood loss and transfusion rate without an increase in complications (74, 75).

Biopolar vs Monopolar sealant

Monopolar electrocautery represents a device which can be used for various modalities including cut, desiccation and fulguration. Through a pencil instrument, electrical current is delivered to cut tissue and cause blood coagulation. Perioperative temperatures can reach 300 degrees Celsius causing smoke and eschar formation. On the other hand, bipolar sealer combines radiofrequency energy and saline in order to provide hemostatic sealing of soft tissue (76). This combination allows the device to operate at nearly 100 degrees Celsius (77).

Although bipolar sealant is effective in reducing blood loss in other operations like spine and brain surgery, recent meta analyses have found that the use of bipolar sealer was not superior to standard electrocautery in patients undergoing primary THA in terms of blood loss and transfusion rate (77, 78).

Platelet rich plasma

Platelet rich plasma (PRP) is an autologous blood product with an increased concentration of platelets. PRP contains specific growth factors, which play a crucial role in the healing process and has been used in many fields including musculoskeletal conditions for more than 30 years (79, 80).

Although there is some evidence that PRP if effective in reducing the post-operative bleeding in TKR patients we found no reports concerning the PRP effect on blood loss in THR patients. On the other hand, a recent comparative systematic review of clinical and experimental data in

equine and human musculoskeletal lesions reported that the use of PRP in musculoskeletal lesions, although safe and promising, has still not shown strong evidence in clinical scenarios (81, 82).

h. Drainage

The closed-suction drains are used in many othopaedic procedures in order to evacuate any postoperative hematoma (83). Theoretically, the postoperative hematoma formation increases the postoperative swelling and pain, impairs the wound healing and increases the risk in surgical site infection. On the other hand, the use of drains increases the blood loss and potentially the transfusion rates by eliminating the tamponade effect. Furthermore, it may allow retrograde surgical site infection.

Systematic reviews and meta analyses showed that the routine use of drains in THR is not supported by the literature (84-86). No significant difference has been found in the incidence of hematoma formation, wound infections or wound healing problems between those allocated to drains and the non-drained wounds. On the other hand, the use of drains increased requirement in postoperative blood transfusion. Nevertheless, it is concluded that the accuracy of the meta-analysis is limited due to the heterogeneity between studies and it is suggested that high-quality randomized trials are needed to maximize the reliability of evidences (85, 87).

POST-OPERATIVE

a. Cryotherapy

The term refers to the use of means that induce low temperature to the skin surrounding the injury. Examination of nerve conduction velocity, skeletal muscle microcirculation and changes of the blood vessels under/in a cold environment over the years concluded that cryotherapy can deescalate local inflammatory response, oedema formation, and blood loss and cause anaesthetic effect post-surgery (87-89).

A recent systematic review has shown that cryotherapy was effective without increasing the risk of adverse effect in both THR and TKR patients in terms of decreasing the pain. It was also effective in decreasing blood loss in TKR but not in THR patients (90).

b. Post-operative auto-transfusion

The post-operative auto-transfusion (PAT) is the reinfusion of patients' blood collected in special reinfusion drains. This blood is usually filtered -or less commonly washed- before reinfusion.

Systematic reviews and meta analyses have found that PAT decreases the ABT rate in both THR and TKR patients (91-93). However, due to the poor methodological quality and the heterogeneity of the studies, it is not clear whether PAT decreases the complications rate, length of stay and total cost when compared to ABT (92).

The use of reinfusion drains has been questioned in clinical studies where TXA was used. A randomized controlled trial has shown that addition of TXA to a restrictive transfusion protocol, makes the use of a postoperative blood salvage system in patients undergoing primary hip and knee arthroplasty, unnecessary (94). Another randomized comparative study has shown that the use of TXA in both THR and TKR patients is more effective and provides cost savings compared with reinfusion drains (and PAT) as a blood management tool (95).

Discussion

Strategies that are currently supported by strong evidence

According to this review's findings, preoperative patients' evaluation and treatment of possible anemia is undoubtedly the first and probably the most important strategy that should be included in any PBM program in order to reduce the transfusion rate.

The use of TXA in THR is currently the most widely used nonsurgical agent regarding the decrease in blood loss and ABT transfusion rate.

In our opinion there is enough evidence not to use drains in THR, although it seems that further high-quality studies are needed.

Strategies that are currently supported by weak evidence

Although there is some evidence that neuraxial anaesthesia is associated with improved perioperative outcomes including a decreased blood loss, there is still need for further well-organized studies. Additionally, mini-incision posterior approach seems to be associated with less blood loss.

Other intra-operative interventions such as acute normovolemic haemodilution, intra-operative auto-transfusion or cell salvage and no pharmacological hemostatic agents (topical fibrin sealants, and platelet rich plasma) although they reduce the need for ABT, are not currently supported by strong scientific evidence and their cost is substantial. Furthermore, a very recent cost-effectiveness analysis has shown that TXA, when compared with no pharmacological hemostatic agent as well as with EACA, it is the most cost-effective strategy to minimize intraoperative blood loss in THR and TKR (96, 97).

Post-operative autotransfusion (PAT) seems to be a less "attractive" technique when compared to TXA, while TXA use during the post-operative period is supported by numerous studies.

Strategies that are currently not supported by enough evidence

On the contrary, the available data do not support the use of pre-operative blood donation, bipolar sealant, and cryotherapy in THR patients.

THR is a common orthopaedic procedure and is associated with a significant amount of blood loss. Significant outcomes of the consequent ABTs and/or anaemia which take place post-surgically include an increased length of stay, morbidity, cardiovascular risks and slow rehabilitation.

The aim of all blood saving methods is the cost-effective lessening of ABTs. The purpose of this review was to assess current evidence regarding the safety, cost-effectiveness

and efficacy on the different pre/intra/post-surgical management strategies for patients receiving THR. Numerous techniques have been described in order to minimize blood loss. However, there are controversial results in the literature. Our article is not a systematic review; thus, our main limitation is the "selection bias" of studies/articles that have been included. We acknowledge that there are numerous published articles that have not been included/analysed in our review. However, we tried to apply high qualitive criteria regarding the included studies rather than quantitive increase in our references.

Nowadays, blood management programs is a necessity. These programs should have a multimodel/ multidisciplinary approach and be structured on strong evidences aiming to minimize the blood loss and in the meantime be cost-effective. It's of paramount importance for every orthopaedic surgeon to understand each method separately and combine these methods to result in an individualistic blood saving model. Ultimately, it's crucial to emphasize the significance of a team approach (e.g. hematologist, orthopaedic surgeon, anesthesiologist) so as to attain the best outcomes.

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Konstantinos Vrontis MD[1]
Georgios Tsinaslanidis MD[2]
Georgios I. Drosos MD PhD[3]
Themistoklis Tzatzairis MSc[4]
1 Bank of Cyprus Oncology Center, Acropoleos Ave 32, Strovolos, Nicosia, Cyprus
2 George Eliot Hospital NHS Trust, Nuneaton, Warwickshire
3 Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Dragana, Greece
4 Whitechapel Rd, Whitechapel, London, UK

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