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REVIEW

Perioperative blood management strategies for patients undergoing total knee replacement: Where do we stand now?

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Abstract

Total knee replacement (TKR) is one of the most common surgeries over the last decade. Patients undergoing TKR are at high risk for postoperative anemia and furthermore for allogeneic blood transfusions (ABT). Complications associated with ABT including chills, rigor, fever, dyspnea, light-headedness should be early recognized in order to lead to a better prognosis. Therefore, perioperative blood management program should be adopted with main aim to reduce the risk of blood transfusion while maximizing hemoglobin simultaneously. Many blood conservation strategies have been attempted including preoperative autologous blood donation, acute normovolemic haemodilution, autologous blood transfusion, intraoperative cell saver, drain clamping, pneumatic tourniquet application, and the use of tranexamic acid. For practical and clinical reasons we will try to classify these strategies in three main stages/pillars: Pre-operative optimization, intra-operative and post-operative protocols. The aim of this work is review the strategies currently in use and reports our experience regarding the perioperative blood management strategies in TKR.

Key words: Total knee replacement; Transfusion; Total knee arthroplasty; Blood loss; Autologous blood donation; Blood management; Perioperative; Tranexamic acid; Tourniquet; Haemodilution; Anaemia; Transfusion protocol

Core tip: Total knee replacement is one of the most common elective surgeries in orthopaedics. Blood loss during surgery is putting the patient at risk for a blood transfusion. A number of reviews and meta-analyses have tried to analyze the best blood conservation strategy. Our objective is to review any blood saving method/strategy into the preoperative, intraoperative and postoperative period and analyze their possible

combination. A zero allogenic blood transfusion rate with safe and cost-effective methods should be the aim and an achievable goal.

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INTRODUCTION

Total knee arthroplasty (TKA) is currently the most cost-effective and efficacious way for treating patients with end-stage knee osteoarthritis who suffer from severe pain, activity limitation and for whom conservative treatment is unsuccessful. Based on National registries, TKA is considered to be the most common major orthopaedic surgery performed worldwide[1]. It's really important to mention that the number of TKA surgeries performed each year increases and is projected to have a five to six-fold increase by 2030[2].

Blood loss during TKA is putting the patient at risk for a blood transfusion. It's reported that patients undergoing TKA may result in blood loss between 1000 mL and 1500 mL which necessitates subsequent allogeneic blood transfusion (ABT) in 10%-38% of them[3-7]. Thus, it becomes prudent to minimize the ABTs while trying to maintain hemoglobin (Hb) in a safe and efficient level to help patient's rehabilitation. Many strategies have been used in order to minimize blood loss including preoperative autologous blood donation (PAD), acute normovolemic haemodilution (ANH), autologous blood transfusion (ABT), intraoperative cell saver, drain clamping, pneumatic tourniquet application, and the use of tranexamic acid (TXA)[8-10].

Although many strategies and algorithms have been proposed for ABTs reduction there is not a consensus about the most efficient/successful combination[8,11]. This article will try to review the latest strategies, analyze the results and our experience regarding the use of TXA. Summarizing, these strategies can be divided in three stages: Pre-operative, intra-operative and post-operative (Table 1).

PRE-OPERATIVE

The main aim of blood management is to eliminate ABTs and prevent anaemia simultaneously. In order to avoid anaemia's clinical symptoms we need to preserve post-operative Hb values as higher as possible. Therefore, we highlight the significant effect of high pre-operative Hb on the requirement of ABT in TKA.

Detection of anaemia and iron deficiency treatment

Anaemia has been defined by the World Health Organization as an Hb concentration < 130 g/L for men, < 120 g/L for non-pregnant women[12]. Regarding patients undergoing TKA it's been reported that 8% to 21% of them were anaemic before the procedure[13,14].

Pre-operative assessment of patients should be performed at least 30 d (some reviews suggest at least 60 d) before the procedure in order to have enough time to investigate the cause and/or plan the required treatment[15-17]. In case of low Hb additional lab tests should be carried out including at least full blood count, serum ferritin, transferrin saturation index (TSAT), vitamin B12, folic acid, a marker of inflammation (*e.g.*, serum CRP) and a marker of renal function (*e.g.*, serum Creatinine) (Figure 1)[18]. Any other low Hb cause apart from iron deficiency anaemia (IDA) should be carefully investigated.

IDA is the main cause of low Hb. It's been reported that IDA counts up to 50% of the patients with Hb lower than 12 g/dL[19,20]. It's been suggested that patients undergoing TKA should meet WHO's criteria regarding the minimum pre-operative Hb. Otherwise, surgery should be postponed[15]. Furthermore, a recent, retrospective study demonstrated that preoperative anaemia (haematocrit < 25%) and ABTs are the two "evils" that increased the post-operative morbidity and mortality[21].

Adult patients with IDA who are candidates for TKA should be treated before the surgery. Either intravenous or oral iron therapy has been found to be effective in the treatment of pre-operative anaemia, meanwhile reducing the rehabilitation's duration[14,22]. Moreover, the superiority of intravenous iron therapy with respect to oral iron therapy has been reported[23]. A 3-wk duration, administration of intravenous iron, just before surgery seems to be the most efficient and safe treatment[24]. Additionally, oral iron may not be efficacious in patients with malabsorption such as coeliac disease[25].

Erythropoietin

Erythropoietin (EPO) is a great tool in correcting anaemia as it is an essential hormone for red blood cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells[26,27]. Its role in blood loss management has been thoroughly studied, showing a 60% reduction of ABTs in patients who received EPO compared to control group[28-30]. Three or four weekly subcutaneous injections (600 IU/kg) seems to be the most frequently used protocol with the best results[31-35]. Weber *et al*[36] reports a mean rise in pre-operative Hb of 1.9 g/dL in patients that received EPO. A big disadvantage of EPO is the really big cost which is being estimated to 1500 dollars per patient (4 weekly injections)[37]. For this reason, EPO use is being suggested when the patient has anemia and meets the criteria for blood transfusion, but declines a blood transfusion because of religious beliefs (*e.g.*, Jehovah's Witness), or the appropriate blood type is not available because of the patient's red cell antibodies[38]. Adverse events have been reported in 5% of patients that have been treated with EPO. These complications include deep venous thrombosis (DVT),

Table 1 Three pillars of patient's blood management and saving

Pre-operative	Intra-operative	Post-operative
Detection of anaemia and iron deficiency treatment	MIS and navigated MIS TKA	Compression and cryotherapy
Erythropoietin	Tourniquet	Limb position
Perioperative management of antiplatelet agents	Hypotensive epidural anesthesia	Post-operative cell saving
Transfusion protocol agreement	Acute normovolemic haemodilution	Drainage clamping
Pre-operative autologous blood donation	Antifibrinolytic agents	
	Topical fibrin sealants	
	Intra-operative cell salvage	
	Peri/intra-articular (bupivacaine and epinephrine) injections	
	Bipolar *vs* monopolar sealant	
	Platelet-rich plasma	
	Bone wax	
	Sealing femoral tunnel	

MIS: Minimally invasive; TKA: Total knee arthroplasty.

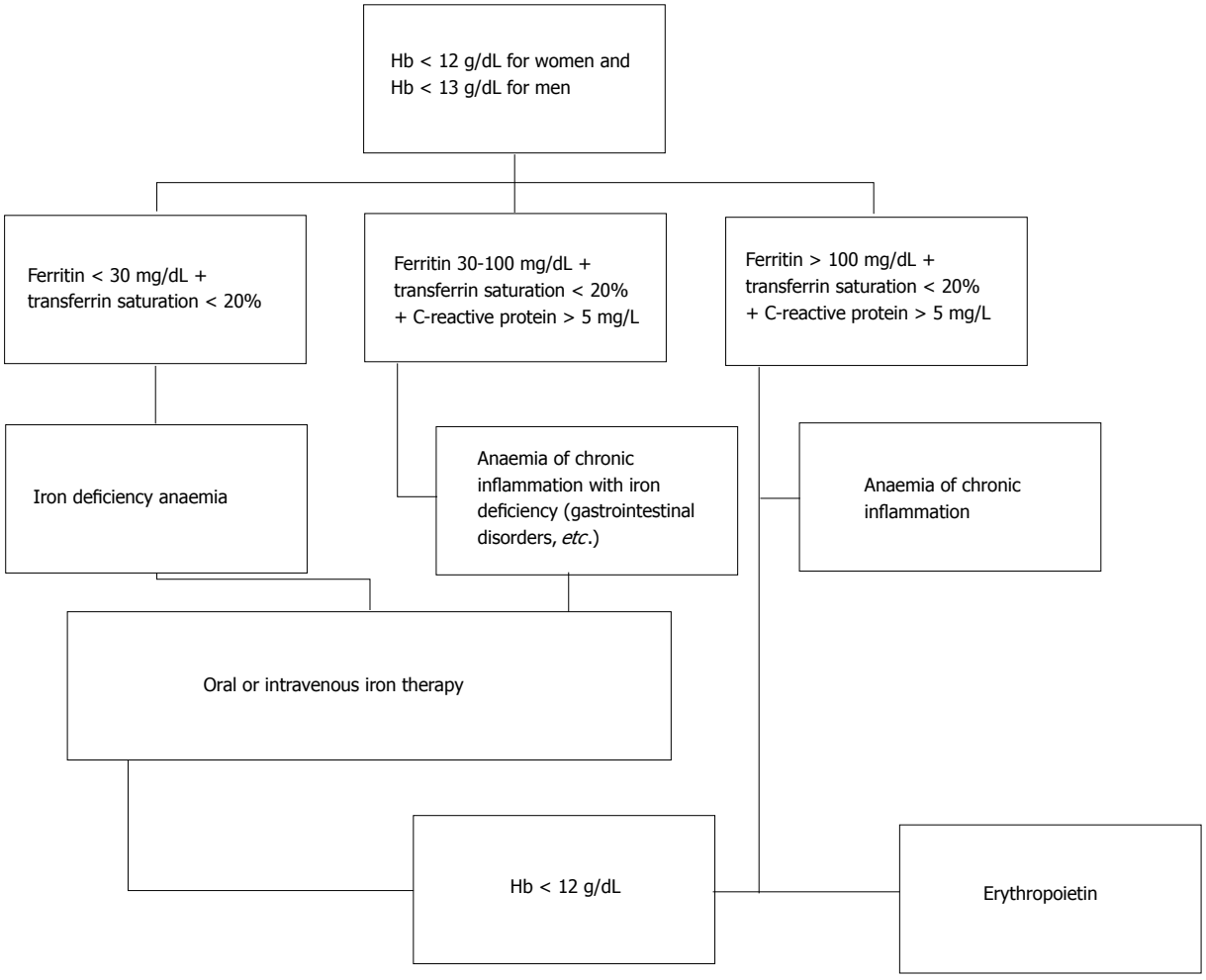

Figure 1 Algorithm proposed for low hemoglobin investigation. Hb: Hemoglobin.

pulmonary embolism (PE), fever, hypokalemia, urinary tract infection, nausea, hypoxia, and vomiting[39-41]. Briefly, EPO can reduce the need for ABTs in high-risk patients undergoing TKA; however, it was not found to be cost-effective compared to other blood conservation methods[42].

Perioperative management of antiplatelet agents

Cardiovascular disease is common in patients planning to undergo to TKA. Antiplatelet agents, used as monotherapy or in combination, have a key role in preventing cardiac and vascular events[43]. Many of these patients have already undergone previous percutaneous coronary intervention (PCI) with stent implantation. American Heart Association's/American College of Cardiology Foundation's guidelines suggest dual antiplatelet therapy with

aspirin and an adenosine diphosphate (ADP) inhibitor (*e.g.*, clopidogrel) for at least 1 mo after bare-metal stent implantation and for 1 year after drug-eluting stent implantation in order to avoid late thrombosis[44]. There is a distinct proof that elective surgeries like TKA should be avoided (if it's possible) within the first year of stent implantation, as it's been reported a 5- to 10-fold increase in acute stent thrombosis[45]. Of course, after the first year most of these patients continue with single antiplatelet therapy[46].

Our main concern about antiplatelet agents is the perioperative bleeding that can occur during the procedure. Recent review reports bleeding increase up to 50% in patients with dual antiplatelet therapy. Regarding the monotherapy, the same review found that blood loss increased 2.5%-20%[47]. From an anaesthesiologist's perspective, the incidence of spinal haematomas associated with epidural or spinal anaesthesia is the main reason for antiplatelet's discontinuation. Regarding the literature, 61 cases of spinal haematomas associated with epidural or spinal anaesthesia are reported between 1906 and 1994[48].

The two most prescribed antiplatelet drugs (with different mechanism of action) are aspirin and clopidogrel. Regarding the aspirin, guidelines suggest its discontinuation 7-10 d before surgery without major consequences. Post-operatively, aspirin should be resumed preferably within 24 h (when bleeding risk is low). Conversely, patients who are in high cardiovascular risk should not stop aspirin therapy in the perioperative period[49]. Clopidogrel acts by inhibiting the ADP receptor on platelet cell membranes. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) suggest discontinuation of clopidogrel 5 d prior to surgery and if additional DVT prophylaxis is needed a low molecular weight heparin (LMWH) should be used.

The key point is that both the continuation and the discontinuation of antiplatelet therapy can be associated with major risks. Therefore, (especially in dual antiplatelet therapy) the management of these medications in the perioperative setting should be discussed between the cardiologist, orthopaedic surgeon, and anaesthesiologist. This "team" should weigh the patient's risk of thrombosis with the risk of surgical bleeding to determine the right choice for him and if/when dual antiplatelet therapy can safely be discontinued.

Transfusion protocol agreement

ABTs are responsible for many complications like human immunodeficiency virus (HIV)'s, hepatitis'B and C transmission (despite donor screening), whereas allergic reactions may cause minor reactions (*e.g.*, fever) to fatal ABO blood group incompatibility[50,51]. Therefore, it's really crucial to analyse and update the transfusion protocols that are being used in hospitals and especially in orthopaedic departments. We'd like to notice that although transfusion is a post-operative process, we include it in pre-operative measures as an agreement/protocol about the "transfusion trigger" should be achieved before the surgery.

The main factor that should be investigated is the so called "transfusion trigger". It's the Hb threshold at which the physician decides to transfuse the patient. Many protocols/rules like 10/30 have been used in the past; but it's not the case any longer[52]. Low transfusion trigger point seems to be effective in reducing ABTs[53,54]. Reviews suggest transfusion triggers (Hb levels) between 8 g/dL and 9 g/dL (excluding severe cardiovascular disease, renal failure, and hematologic disorders)[55,56]. Unquestionably, symptomatic anaemia resulting in tachycardia, change in mental status, cardiac ischemia or shortness of breath should always been treated followed by ABT. Based on literature, in our department we use a mini transfusion algorithm/protocol (Figure 2). This protocol has already documented significant reductions in the rates of red cell transfusion and worthwhile blood conservation. Noticeably, this strategy seems to be really cost-effective.

Briefly, a blood management protocol with restrictive typing and screening, cross-matching, and transfusion should be adopted by national health systems in order to reduce the wastage of unused blood units and the rate of ABTs without increasing patients' morbidity or mortality.

Pre-operative autologous donation

In 1980, the recognition that ABTs were associated with potential risks like viral transmission (*e.g.*, HIV) and bacterial infection prompted the development of PAD programs[57,58]. In 1992, PAD accounted for nearly 8.5% of all blood collected in United States. Nevertheless, pre-donation decreased to 3.5% of the blood units collected by 1997[59].

PAD's main target is providing a resource of safe blood for patients that are candidates for scheduled surgery (like TKA). Meanwhile, this process increases the patient's total red blood cell (RBC) mass due to the PAD-induced stimulation of erythropoiesis before elective surgery.

Many studies and meta-analyses concluded that PAD strategy managed to reduce the use of ABTs by 40%-52%, increase the overall transfusions (allogeneic and autologous) by 30%. On the contrary, it's really important to mention that patients' Hb concentration decreased by more than 1 g/dL from before starting PAD to immediately prior to surgery[60-62]. PAD's poorly cost-effectiveness (about 300$ per unit), combined with new blood saving strategies and new drugs has led to a decline in its use[63,64]. In our days, the use of PAD has therefore lost its acceptance and is no longer being used in TKA patients.

INTRA-OPERATIVE

Plentiful methods, strategies, technologies and drugs have contributed in blood loss minimization and ABTs' reduction. Some of them have gained ground during the last decades and others didn't manage to prove their effectiveness. Intra-operative blood saving seems to play the most important role between the strategies and techniques indicated in the three pillars of patient

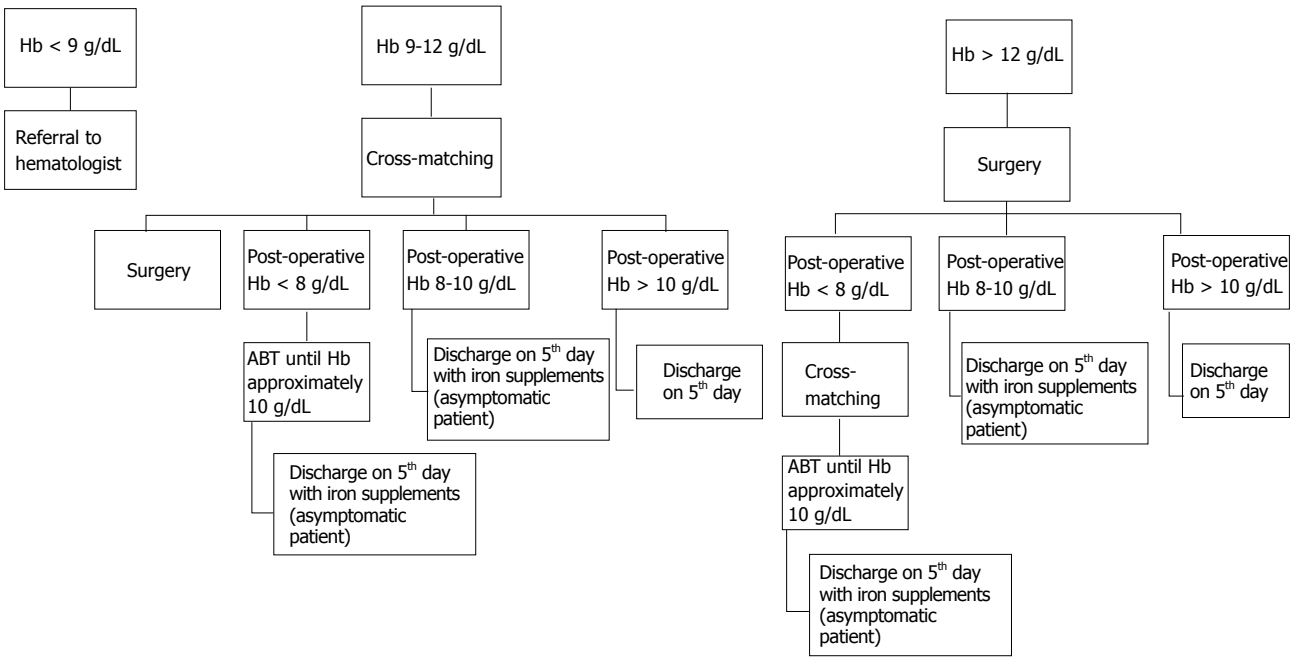

Figure 2 Algorithm used in our department regarding the allogeneic blood transfusion strategy. Hb: Hemoglobin.

blood management.

Minimal invasive and/or navigated minimal invasive TKA

Many of the patients that have decided to have a TKA might consider a minimally invasive procedure with or without navigation. This type of surgery uses smaller incisions and less cutting of the tissue surrounding the knee. The advantage of such a surgery except for the smaller incision is the promising recovery, a shorter hospital stay and less blood loss.

A meta-analysis revealed the superiority of minimal invasive (MIS) to the standard parapatellar approach in visual analog score (VAS) and range of motion (ROM) in the short term (postoperative 2 wk)[65]. No differences were noticed in straight leg raise, hospital stay, post-operative complications and blood loss. Comparable results pointed out between MIS TKA and MIS navigated TKA[66]. In conclusion, MIS TKA has proved the ability to couple the benefits of less invasive surgical approach without compromising the long-term established success of conventional TKA, especially in blood loss.

Tourniquet

A tourniquet is a compressing device, used to control venous and arterial circulation to an extremity (lower extremity in TKA) for a period of time. Although the majority of orthopaedic surgeons still use it widely, its role is controversial. Tourniquet's use was believed to be effective in decreasing intraoperative blood loss. However, reactive blood flow after tourniquet's release seems to balance out the total blood loss compared to the non-tourniquet TKA method[67]. A meta-analysis of thirteen randomized controlled trials (RCTs) demonstrated that non tourniquet use in TKA has better clinical outcomes, less complications and better ROM in early postoperative period. The most important finding of this meta-analysis is that the true blood loss in TKA was not reduced using a tourniquet[68]. Therefore, it can be explicitly deduced that TKA with a tourniquet reduces the intra-operative blood loss but postoperatively increases the hidden blood loss[68]. To sum up, tourniquet's effectiveness and safety in TKA should be carefully considered when surgeon decides to use it.

Hypotensive epidural anesthesia

In April of 1989 Sharrock *et al*[69] published the first description of hypotensive epidural anesthesia. To date, HEA is not a popular method in elective orthopaedic surgery like TKA. HEA was developed to combine the advantages of epidural anesthesia (airway problem, reduced rate of DVT) with the benefits of induced hypotension.

Its mechanism of action is well-described. A sympathetic blockade (including cardiac sympathetic fibers), using local anesthetic at an upper lumber interspace (T12-L1/L1-L2), causes a reduction in arterial pressure. Mean arterial pressure (MAP) is maintained at 50-55 mmHg with end result the reduction of blood loss. It's really important to mention that concurrently, a low dose of epinephrine is being infused (till MAP reaches 75-80 mmHg) achieving circulation's stabilisation[70,71].

Although HEA's use seems to be really advantageous, without complications, it's not a "first line" method regarding blood loss in TKA. A few studies have proved its safety and efficacy in total hip arthroplasty (THA), but further studies are needed to assess its use in TKA[70,72,73].

Acute normovolemic haemodilution

Acute normovolemic haemodilution (ANH) is a technique in which whole blood is removed from a patient, while

circulating volume is maintained with crystalloid fluid. It is performed shortly before or shortly after induction of anaesthesia. A close monitoring of the patient is necessary and when Hb level drops down to 8-9 g/dL ANH is being halted[74]. Postoperatively, sufficient blood is administered to maintain patient's Hb over 8-9 g/dL.

Many studies suggest ANH's use in elective orthopaedic surgeries as it contributes in ABT's reduction[75-77]. In contrast, there are studies that noted no significant difference between control and ANH group[78-81]. Undoubtedly, more studies would be needed to prove/rebut its efficacy in blood loss management.

Antifibrinolytic agents

The most famous blood saving management of the last decade is the use of antifibrinolytic agents. TXA, ε-aminocaproic acid (EACA) and aprotinin are the most commonly used antifibrinolytic agents[82-84].

TXA and EACA are lysine analog antifibrinolytics that reversibly bind both plasmin and plasminogen. TXA is a current trend in TKA and THA. Many studies have proved its efficacy without an increased risk of complications (DVT, PE, and wound infection). Latest studies and meta-analyses focused on the best route of administration combined with multiple dose regimens[85-88]. Regarding the route of administration and plasma concentration, maximum plasma concentration of TXA is reached within 5-15 min after intravenous (IV) injection, 30 min after intramuscular (IM) injection and 2 h after oral tablets[89]. IV TXA seems to be more effective compared to topical administration. However, the topical administration seems to outcompete IV in patients with high risk of thromboembolic events[90]. On the contrary, a recent meta-analysis showed no statistically significant difference in total blood loss, drain output, transfusion requirements and thromboembolic complications between topical TXA and IV-TXA in TKA[91].

The most efficacious regimen is still under debate, but multiple IV boluses regimens (pre/intra/post-operatively) prove to have a better result compared to a single IV dose[92]. Nevertheless, two RCTs concluded that intra-articular regimen of TXA is as effective as three doses IV regimen in preventing blood loss without any difference in thromboembolic complications[93,94]. In addition to all these studies some authors have noticed that the combination of IV and intra-articular TXA is more effective than either regimen used alone[95,96]. All these conflicting results suggest that more well-conducted randomised controlled trials are needed to produce strong evidences about it. In our orthopaedic department two RCTs have already been completed, showing the high effectiveness of TXA's both in TKA with tourniquet and TKA without tourniquet and one more is currently running[87,88]. The aim of the current study is to determine whether or not repeated dosing of IV TXA reduces (additionally) the post-operative reduction in hemoglobin, hematocrit, number of transfusions, and post-operative blood loss following primary TKA.

Studies comparing EACA to TXA on the reduction of perioperative bleeding and on the number of transfusions needed showed no significant differences between the two antifibrinolytic agents. The only advantage of TXA compared to EACA is its lower price[97].

Aprotinin, a nonlysine antifibrinolytic agent, was more effective at decreasing blood loss but was associated with increased cardiovascular complications (increased risk for myocardial infarction) and was therefore removed from the market in 2008[98-100].

Topical fibrin sealants

Fibrin sealant is comprised mostly of fibrinogen and human thrombin which form a stable fibrin clot and can mimic the last phase of physiological blood coagulation cascade. Many studies have proved their efficacy without increasing the risk of DVT, PE, hematoma, wound infection or other complications for patients undergoing TKA[101,102]. However, their main disadvantage is the high cost compared to other blood management methods (like TXA)[103,104]. Moreover, newer studies appear to confute the initial hypothesis of fibrin sealants' haemostatic role. All these studies report no effect of fibrin sealant in terms of blood or transfusion savings after TKA[105-107].

Intra-operative cell salvage

Intraoperative blood salvage, also known as cell salvage, is a medical procedure involving recovering blood lost during surgery and re-infusing it into the patient[108]. Many devices and processes have been developed to assist in salvaging the patient's own whole blood since the 1970s, when it was popularized in major thoracic or abdominal procedures[109]. Unwashed blood revealed poor results as it may contain hemolyzed RBC, clotting factors and cytokines[110,111]. Therefore, cell separation and washing showed better results with an autologous red cell concentrate with normal function and no complications[112].

Literature's evidence strength is really limited regarding the safety and effectiveness of this method. Current studies have low level of evidence which means that they are incompetent to compare the post-operative infection rates with and without cell salvage use. A general outcome of these studies is that intra-operative cell salvage reduce ABTs but more studies needed to clarify the importance and the risk of this method[113-115].

Peri/intra-articular (bupivacaine and epinephrine) injections

Epinephrine is the agent of choice for topical haemostatic vasoconstriction[116]. Anderson *et al*[117] injected bupivacaine and epinephrine just before wound closure (one-third pericapsular, two-thirds peri-incisional). They managed to prove a 32% less drain output in study group. However, no statistically significant differences were noticed in the transfusion rate between the two groups. Moreover, a new study by Yang *et al*[118] reports controversial results, as the initial hypothesis regarding the haemostatic role of intra-articular epinephrine after

TKA is not being supported by the various bleeding parameters.

Bipolar vs monopolar sealant

Monopolar electrocautery is a device that delivers electrical current to patient's tissue through a pen-like stylus. Intra-operative temperatures can be higher than 300 ℃, resulting in smoke and eschar formation[119]. Opposed to monopolar electrocautery, bipolar sealing delivers radiofrequency energy combined with continuous-flow saline in order to prevent temperatures higher than 100 ℃. Although bipolar sealant is being used for decades in oncology, thoracic, spine and brain surgery it seems to be a novel approach in TKA[120-123]. However, latest studies (including RCTs) and the results of the comparison between bipolar and monopolar sealers used in TKA report no significant difference in postoperative drain output, postoperative Hb level and transfusion requirement[119,124,125].

Platelet-rich plasma

Platelet-rich plasma (PRP) has been used in surgeries to promote cell regeneration since 1987[126]. Today, PRP injections is being safely used in many fields like cosmetics, sports medicine, orthopaedics, and fasciomaxillary[127,128].

PRP is defined as plasma with a platelet level above peripheral blood concentration. There are two methods to obtain it: (1) ready PRP kits (higher cost); and (2) a wide variation of reported protocols for standardization and preparation of PRP (most of them use two-step centrifugation protocol)[129,130]. The final volume contains platelets and factors (*e.g.*, platelet-derived growth factor and transforming growth factor-β) whose haemostatic and wound-healing effects have been well-described[131-134]. Gardner *et al*[135] in their retrospective study report less blood loss during the post-operative period. Despite that a consensus about the high concentration of growth factors and its efficacy in wound healing has been reached, its haemostatic role is still debatable[136,137].

As a final point, we'd like to note that understanding of basic principles of centrifugation is of vital importance in preparation of PRP. Many protocols have been described with different consistency of PRP yield. Thus, it is advisable to standardize individual, cost-effective preparation protocols, which are easy to adapt in clinical practice[130].

Bone wax

Bone wax is a waxy substance used to help mechanically control bleeding from bone surfaces during surgical procedures. It consists of a mixture of beeswax, paraffin and isopropyl palmitate[138]. Although its use in elective orthopaedic surgery hasn't been well-demonstrated, Moo *et al*[139] suggest bone wax's application in TKA for reducing total blood loss and maintaining higher hemoglobin levels.

It's remarkable to mention that complications like allergic reaction, inflammation and foreign bodies formation need extra attention by the physicians[140]. Undoubtedly, further studies are needed to confirm its safety and efficacy in TKA.

Sealing femoral tunnel

In recent decades most of the orthopaedic surgeons use an intramedullary alignment system regarding the placement of the femoral component in TKA[141]. The intramedullary (IM) femoral rod that is being used damages the cancellous bone and its vascularization resulting in high blood loss. Nowadays, many surgeons seal this tunnel with autologous bone in order to minimize the bleeding. Although autologous bone grafting is a safe and non-time consuming process, its efficacy regarding the reduction in blood loss is still debateable[142,143]. Additionally, studies report that the use of an extramedullary (EM) femoral alignment guide system resulted in reduction of the drained blood and consequently in lower transfusion rates[144,145]. Our only concern is the influence of IM and EM femoral cutting guides on survivorship of the TKA, as IM seems to demonstrate superiority over the EM[146].

POST-OPERATIVE

Last but not least, post-operatively blood saving methods are integrated in order to reduce blood loss and blood transfusion, and promote the rehabilitation of patients. Post-operative strategies include compression, cryotherapy, use (or not) of drainage systems, cell saving systems and post-operative leg position.

Compression and cryotherapy

Knee swelling after TKA is common and most of the time impairs early rehabilitation. Use of an inelastic compression bandage after TKA seems not to reduce total blood loss. However, it offers a slight but non-significant improvement regarding the postoperative pain and early functional outcomes[147,148]. On the other hand many studies report no difference in compression method[149-151].

Recently Desteli *et al*[152] and Kullenberg *et al*[153] reported that cryotherapy was beneficial in minimizing blood loss after TKA. Many cryotherapy devices have been used in the past (gel packs, circulating ice water) in order to help patients' rehabilitation[154,155]. However, Adie *et al*[156] in their systematic review and meta-analysis does not support the routine use of cryotherapy after TKA.

Limb position

Another option in order to reduce blood loss after TKA is the limb position. Different knee flexion positions (*e.g.*, hip elevation by 60° combined with 60° knee flexion) have been reported to have promising results with respect to reducing perioperative blood loss[157-159]. Based on these studies, we conclude that post-operative knee flexion is an easy, inexpensive and effective method in blood loss reduction.

Post-operative cell saving

It's been calculated that 50% of the total blood loss in a TKA occurs post-operatively[6]. Therefore, post-operative

cell saving and return of unwashed, filtered blood from drains represents an alternative to ABTs method[160]. This system consists of a collection bag and an autologous transfusion bag (filtered blood collected). Re-transfusion can take place in the first 6 h after the end of surgery in order to avoid bacterial infection[161-163]. After this period it can be used as a vacuum drain. Its cost-effectiveness and efficacy seems to be maximized in patients with pre-operative Hb between 12 g/dL and 15 g/dL, whereas in patients with Hb < 12 g/dL post-operative cell saving system should be combined with other blood-saving techniques in order to increase its efficacy[164].

Drainage clamping

Although it is commonly believed that a suction drain, placed intra-articularly reduces the formation of a haemarthrosis and enhances rehabilitation, many studies have yielded controversial results regarding its use[165-169]. Senthil Kumar *et al*[170] in report that most of the post-operative blood loss occurs in the first few hours and especially in the first four hours. As a result, drainage's clamping should help in minimizing blood loss acting like a tamponade. Although drainage's use is still debatable, many different drainage's clamp intervals have been described[168,171-173]. In a prospective study, Yamada *et al*[174] noted that extended drainage's clamping increased complications significantly. There is no consensus about the best protocol but it's noticeable that drainage's clamping combined with TXA can reduce blood loss after TKA[175]. Surprisingly and in contrast with the above literature, 2010 Tai *et al*[176] found no advantage of using the "clamping" method compared with non-drainage at all.

CONCLUSION

It's more than clear that TKA is a surgery with a blood loss reaching up to 1500 mL. Undoubtedly, the consequent ABTs and/or anaemia occurring post-operatively are causes of increased morbidity, cardiovascular risks, length of stay, decreased vigor and slow rehabilitation. Over recent decades, many blood saving strategies and methods have been described. Nevertheless, there are no concise guidelines, as few/limited studies have compared the relative efficacy of these techniques.

The common target of all blood saving methods is the cost-effective decrease of ABTs. The aim of this review was to evaluate current evidence regarding the efficacy, the safety and the cost-effectiveness on the various pre/intra/post-operative management strategies for patients undergoing TKA. As we described above there is a plethora of methods that can be used in the different periods of the surgery. Many studies have successfully/unsuccessfully described the advantages/disadvantages of each method with/without their limitations. We faced many controversial results in the majority of these strategies. For that reason larger prospective randomized studies comparing not only the individual strategies, but also their combination, are needed.

Scrutinizing the recent literature, we conclude that there is no "consensus success story" about a common efficient/safe blood management strategy in TKA. And if we hazard a guess, we'd say that this consensus cannot be achieved. The current trend is the patient-specific strategy (PSS). This idea is based on the notion that each patient has a different impact on the risk of requiring a transfusion. For example the PSS in a healthy man with Hb > 13 g/dL who undergoes TKA could be a "do nothing" (except Hb reaches transfusion trigger). Conversely, a Jehovah's Witness patient and/or a patient with significant cardiopulmonary compromise should be monitored carefully and more blood management strategies should be considered in order to avoid ABTs. In other words, the above methods that have been analyzed, the advantages and the disadvantages of each method, are just the different parameters that every surgeon should take on board in order to achieve the best result in a specific patient.

The take home message after our in-depth search is that the first important step in blood management is the thorough pre-operative evaluation of each patient. Consideration should be given to the existing physiologic/pathologic variables of the patient and the concomitant actions that should be taken in order to allow prompt optimization of the patient's physiologic status. The 2nd principal arm of effective blood management is the restriction of ABTs' to patients meeting well-established transfusion criteria. Nowadays, this trigger has been decreased to 8 g/dL. The old common belief that all patients with Hb below 10 g/dL should be transfused, has been surpassed. However, when clearly the blood is indicated (clinical signs and symptoms of anemia), administration should not be delayed. Additionally, the use of TXA perioperatively (with different routes of administration) is a widely accepted, effective and safe method in reducing perioperative blood transfusion. These three steps are the "baseline" in our daily practice regarding the perioperative care of the surgical patient.

In our daily practice, it's been proven to be really challenging and unfeasible to apply the same practices in all patients. In simple terms, no single method achieved to provide significantly superior results over another in ABTs' reduction. Primarily, every orthopaedic surgeon should be able to plow through and understand each method separately. Consequently, he must tailor these methods to result in an individualistic blood saving model.

In conclusion, an appropriate combination of the above blood management strategies could further result in ABT's reduction. Additionally, we should highlight the importance of a team approach (*e.g.*, orthopaedic surgeon, anesthesiologist, hematologist) in order to optimize the patients perioperatively and succeeding in the best result.

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