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Blood loss prevention in total knee arthroplasty (TKA): a systematic review

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ABSTRACT

Introduction: This exhaustive literature review aimed to find articles in relation to blood loss prevention in TKA via searching in databases such as PubMed and Google Scholar during 2005-2015.
Methods: In this study, we included all the articles focusing on the evaluation of blood loss during TKA using specific treatment methods to reduce blood loss. We explored the studies with control groups and placebo subjects, and other studies were excluded from this review. The obtained results of each surveyed articles were summarized and evaluated based on the objectives of this study.
Results: In total, 68 studies performed on 8,355 patients were included in this review, 18 of which were double-blinded, and 40 were open-label. A significant difference was observed in the transfusion thresholds of all the reviewed studies. According to our findings, frequency of prophylactic deep venous thrombosis (DVT) varied in the reviewed studies due to the use of different techniques to prevent blood loss after TKA; the incidence of DVT was reported in 15 articles.
Conclusion: Since ABT involves high risks and even morbidity, new techniques should be applied to prevent blood loss. Although several techniques are available to reduce blood loss in TKA, ABT is frequently practiced and might lead to anemia in TKA patients. On the other hand, the effectiveness of new methods used to prevent blood loss remains a matter of question since all these methods are associated with certain adverse side effects.

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Introduction

Total knee arthroplasty (TKA) is an orthopedic surgery performed to relieve the chronic, disabling pain caused by severe arthritis. In TKA, the diseased knee joint is replaced with artificial materials (1). The most significant challenge in this surgery is to reduce postoperative and intraoperative blood loss effectively.

The average estimated rate of blood loss following TKA surgery was 600-1500 ml; therefore,prevention of excessive blood loss after TKAis of paramount importance. In TKA, blood seeps through the cut in bone ends, or open intramedullary canal (2-4). Excessive blood loss most commonly occurs in simultaneous bilateral TKA, with the overall rate twice higher than unilateral joint arthroplasty. In addition, this type of blood loss may increase the number of allogenic blood units transfused to each patient (3-4 per person) (5,6). Allogenic blood transfusion (ABT) is associated with complications such as blood-borne infections, immunological reactions and high treatment costs (7-9).

According to the published literature, some of

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the complications associated with TKA blood loss are postoperative pain, hematoma and seroma formation, arthrofibrosis and persistent bleeding (10,11). As a method frequently used to control this blood loss, ABT is associated with high risks and even the chance of morbidity; consequently, the majority of surgeons tend to use other techniques to reduce blood loss after TKA. Such examples are autologous transfusion techniques, computer-assisted surgery (CAS), antifibrinolytic drugs, tourniquet, fibrin sealant and autologous platelet gel (APG) (12-16).

Proper investigation of different techniques used to control blood loss in TKA and the associated complications could lead us to the discovery of the most effective treatment procedures in this regard. This systematic review aimed to address the following questions:

- Is preoperative anemia or perioperative ABT responsible for the adverse side effects of this technique?
- What are the most effective methods used to reduce blood loss after TKA?
- What are the most common symptoms and complications associated with blood loss in TKA?

Methods

Literature Search Strategy

This exhaustive literature review aimed to find articles in relation to blood loss prevention in TKA via searching in databases such as PubMed and Google Scholar during 2005-2015.All the articles focusing on the evaluation of blood loss during TKA using specific treatment methods to reduce blood loss were included in this study.

Knee athroplasty is the main surgical intervention performed in TKA and is classified into two types of unilateral and bilateral arthroplasty. In this systematic review, the search for articles was conducted using only two key words (blood loss and total knee arthroplasty), and all the articles with related abstracts were identified and investigated. All the selected articles were published in English, and duplicate reports were excluded from the study. Additionally, if there were more articles in relation to one study, we would extract the data from all the published versions.

Article Selection

Open-label, single-blinded and double-blinded studies focusing on the evaluation of blood loss during TKA were selected for the present review. Moreover, we included the studies with control groups and placebo subjects, and other studies were excluded.

Additionally, all the studies using different techniques than ABT for blood loss prevention in patients undergoing TKA were included in our review. In this study, different variables including the rate of blood loss, hemoglobin (Hb) level and the rate of blood transfusions were evaluated in TKA patients.

Studies that used other orthopedic surgical procedures, such as total hip arthroplasty (THA), total joint replacement, spine surgery, ankle replacement and arthroscopic surgery, were excluded from this review.

Exclusion Criteria

Exclusion criteria of the present review were as follows: 1) studies performed on pediatric patients; 2) studies without control or placebo groups; 3) previous reviews, meta-analyses, expert opinions, consensus statements, case reports, editorials and letters; 4) qualitative studies and 5) articles published in languages other than English.

To conduct this systematic review, related data were extracted from the selected articles by one researcher independently. In total, 1,085 articles were identified, 311 of which were repeated in PubMed and Google Scholar databases, and 774 articles remained in the study for further analysis. Among these articles, 584 records were unbiased and inappropriate, which were excluded from the review. Moreover, 36 articles were without control or placebo groups, 31 articles used no specific techniques to reduce blood loss, 27 articles were meta-analyses and reviews, and 38 articles had missing data, all of which were excluded from this review. Also, 13 articles were not in full text, 4 studies were performed on pediatric patients, which were excluded from further analysis. As can be observedin Figure 1, 68 articles mainly focusing on the prevention of blood loss using standard techniques were investigated in this systematic review. After screening, the selected articles were reviewed in full text, and the references were carefully examined. The screening process used in this study is illustrated in Figure 1.

One of the researchers examined and verified the collected data, and different factors were assessed in this review. In addition, the obtained results of each of the surveyed articles were summarized and evaluated based on the objectives of the present review.

Results

Article Selection

In total, we selected 226 articles out of 1085 related studies after assessing their titles and abstracts. Studies without control or placebo groups (N=36) and studies without use of a standard treatment technique to reduce blood loss (N=31) were excluded from this review. Additionally,

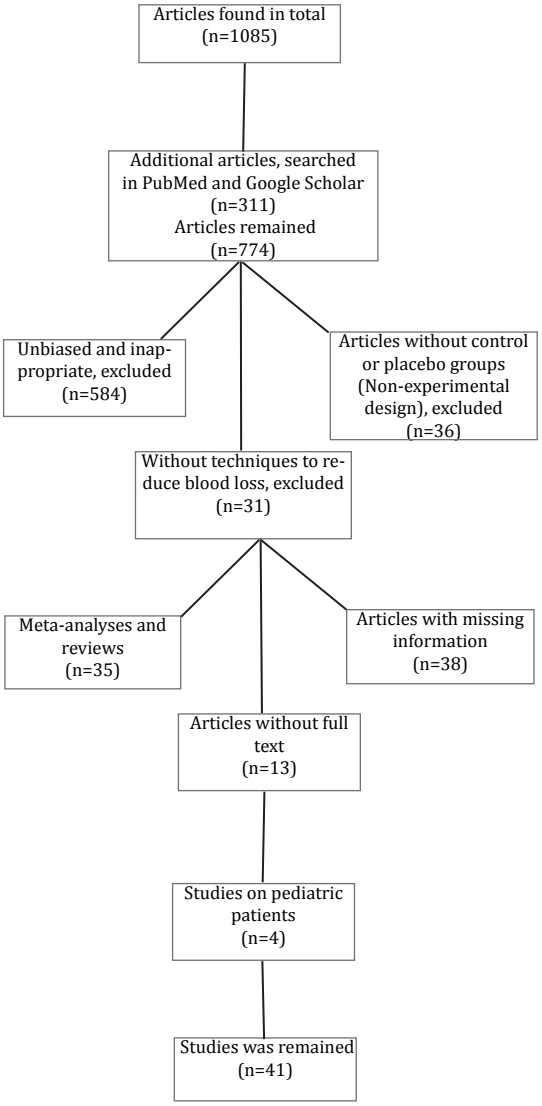

Figure 1. PRISMA flow diagram, screening process of articles in the current review.

meta-analyses and reviews were excluded from this study (N=27). Duplicated articles, studies performed on pediatric patients (N=4), studies with missing data (N=38), studies with unavailable data (N=14) and republished articles (N=8) were also excluded from further evaluation. Finally, 41 clinical trials were selected for the present analysis.

Study Design

Variables investigated in the present review including age, gender, rate of blood loss after TKA, preoperative and postoperative Hb level and the volume of transfused blood units are shown in Table 1. Other factors such as study design, standard treatment techniques, unilateral or bilateral TKA and complications and outcomes associated with TKA are presented in Table 2.

In total, 41 studies performed on 5,180 patients were included in this review, 8 of which were double-blinded, and 33 were open-label.

The majority of the selected studies were conducted on small sample sizes (less than 200 patients), and only 7 studies were performed on large sample sizes. In all the studies, the patients were undergoing TKA and received treatment by a single standard technique to reduce blood loss after the surgery. In addition, 8 studies involved primary knee arthroplasty, and 60 involved TKA.

Mean of the blood loss was variable, ranging from <200 to >2000 ml after the surgical operation. Furthermore, mean of postoperative Hb level was variable, ranging from <1 to >13 g/dL.

In some of the investigated articles, there were reports on the use of a specific transfusion protocol, which resulted in a significant difference between the control and experimental groups in all the studies. Moreover, a significant difference was observed in the transfusion thresholds of all the researches. In the present review, frequency of prophylactic deep venous thrombosis (DVT) varied between the studies due to the use of different techniques as to prevent blood loss after TKA; the incidence of DVT was reported in 15 articles.

Among 68 clinical trials selected for this review, 19 articles used tranexamic acid (TXA) to reduce blood loss after TKA, while three articles reported the use of other antifibrinolytics. In the majority of the selected studies, treatment with TXA was performed before TKA surgical operation. Mean dosage of the administered TXA was variable between the studies; with the exception of six articles, TXA was administered before tourniquet deflation. In 18 studies, DVT screening was performed as well.

On the other hand, 8 studies used only tourniquets, 7 studies used tourniquets during a long-term treatment, 4 articles used fibrin spray and 6 studies used autologous transfusion techniques. Additionally, a number of studies applied wound drains (N=4), unwashed shed blood (USB) (N=4), computer navigation (N=7) and combination therapy (N=6).

Discussion

Blood Loss, Hemoglobin Level and Blood Transfusion in TKA

Several studies have reported the range of blood loss between 1000-1790 ml after TKA surgery (53-58). According to the published literature, total blood loss could be visible or hidden. Approximately, 50% of total blood loss occurs during the postoperative period due to hidden blood loss, and this rate was estimated 38% in a study by Li et al. (21).

According to statistics, 30-50% of total knee replacement (TKR) patients receive ABT (58,59)and a review revealed the prevalence of preoperative

Table 1. Study Design: Evaluation of Number, Age, Gender, Postoperative Blood Loss, Preoperative and Postoperative Hemoglobin Level, Volume and Rate of Blood Transfusions.

Author Year Reference	Country	N	Type of TKA	Complications	Type of Study	Techniques for Blood Loss Reduction after TKA	Efficacy
Gardner 2007 [17]	New York, U S A	98	Unilateral	None	Retrospective Cohort, None-randomized	APG*	APG led to a smaller reduction in postoperative Hb compared to control group (statistically significant, P=0.026)
Wong et al. 2010 [18]	Canada	99	Unilateral	None	Prospective, Double-blinded, Placebo-controlled, Randomized Trial	1.5-3.0 g TXA (100 ml)	Postoperative blood loss reduced in experimental group compared to placebo group (P<0.017) Higher Hb levels in experimental group compared to placebo group (P<0.017)
Orpen et al. 2006 [19]	UK	29	Unilateral	No Evidence in Duplex Ultrasound Screening of Lower Limbs	Prospective, Randomized, Double-blinded, Controlled Trial	Injection of 15 mg/kg of TXA	Injection of 15 mg/kg of TXA significantly reduced blood loss in early postoperative period (P=0.006)
Kalairajah 2005 [20]	Southern Australia	60	Unilateral Primary TKA	Time-consuming Treatment Procedure	Prospective, Randomized	CAS**	Statistically significant difference in reduction of blood loss and Hb levels between CAS and conventional techniques.
Li et al. 2009 [21]	China	80	Bilateral	-	Prospective, Randomized	Tourniquet	Tourniquet caused postoperative blood loss and delayed postoperative rehabilitation.
Seo et al. 2013 [22]	South Korea	150	-	-	Prospective, Randomized, Placebo- controlled	TXA (1.5 g in 100 cc Saline) Administered Intravenously or Intra-articularly	Intra-articular administration of TXA was more effective than intravenous administration in blood loss reduction.
Molloy et al. 2007 [23]	Northern Ireland	150		One patient with DVT in topical fibrin spray group/ One patient with PE*** (no fatalities)	Prospective, Randomized, Controlled Trial	Topical Fibrin Spray (10 ml) or 500 mg Intravenous TXA	No significant difference in blood loss in topical fibrin spray group and TXA group (P=0.72).
Thorey et al. 2008 [24]	Netherlands	20	Bilateral Cemented TKA	No Postoperative Complications after a Six-month Follow-up	Prospective, Randomized	Pneumatic Tourniquet	No significant difference in preoperative blood loss; Tourniquet eliminated risk of extended anesthesia
Ishida et al. 2011 [25]	Japan	100	Unilateral	No Specific Complications (D-dimer Tests)	Prospective, Randomized	Drain Clamping Performed after TXA Injection (2,000 mg/20 ml)	Intra-articular TXA reduced knee joint swelling and blood loss after TKA
Tsumara 2006 [14]	Japan	212	Unilateral	None	Prospective, Randomized	Intra-articular Injection versus Postoperative Blood Salvage	Blood salvage and drain clamping with intra-articular injection were more effective than postoperative ABT
Alvarez et al. 2008 [26]	Spain	105	Unilateral	No Thromboembolic Complications	Double-blinded, Prospective	TXA (10 mg/kg) vs. Bolus followed by 1 mg/kg Perfusion per Hour	Rates of blood loss and transfusion decreased after TXA treatment, even in blood conservation program.
Tai et al. 2012 [27]	Taiwan	72			Prospective, Randomized, Controlled trial	Tourniquet	Tourniquet effectively reduced blood loss during TKA and inhibited postoperative inflammation and muscle damage.
Yavarikia et al. 2010 [28]	Iran	96	Unilateral	None Reported	Prospective, Randomized, Controlled Trial	Tourniquet	Tourniquet did not reduce blood loss but decreased surgery time.

Author Year Reference	Country	N	Type of TKA	Complications	Type of Study	Techniques for Blood Loss Reduction after TKA	Efficacy
Iwai 2009 [29]	Japan	78		None	Comparative, Controlled	Intraoperative TXA (1,000 mg) (Single-TXA 10 Minutes before Tourniquet Deflation, and (Twice-TXA 10 Minutes before Tourniquet Deflation and 3 Hours after Operation)	Blood loss after TKA reduced due to the use of twice-TXA
Sabatini 2012 [30]	Italy	70		None	Prospective, Randomized, Standard Treatment	Fibrin Sealant Tissue Adhesive	Fibrin tissue adhesive effectively reduced blood loss and need for blood transfusions/ Appropriate solution to enhance hemostasis in TKA.
Conteduca 2009 [31]	Italy	100	Unilateral	None Reported	Prospective, Comparative, Randomized	CAS	CAS effectively reduced blood loss after TKA
Konig 2013 [32]	Pennsylvania, USA	109		None	Prospective, Comparative	Topical TXA (3 g)	Postoperative blood loss and transfusion risks decreased using topical TXA.
Gasparini 2006 [33]	Italy	84		None	Prospective, Comparative	Norepinephrine Applied Locally before Tourniquet Release	Lower doses of norepinephrine effectively reduced blood loss and prevented blood transfusions in TKA patients
Lozano 2008 [34]	Spain	414		Thromboembolic Complications (Control: 2.8%, TXA Therapy: 1.5%, DVT: Experimental: 14.8%, Control: 30.1%)	Prospective, Comparative	TXA	TXA reduced RBC transfusions (67%) during TKA in patients without history of thromboembolic diseases/ TXA not associated with increased thromboembolic complications.
Camarasa et al. 2006 [35]	Spain	127		No Thromboembolic Complications Reported	Double-blinded, Randomized, Placebo-controlled, Clinical Trial	TXA 10 mg/kg (-1, Intravenous), Tourniquet	Blood loss reduced significantly in patients undergoing TKA after using antifibrinolytics, leading to reduced rate of blood transfusions.
Chareancholvanich 2012 [36]	Thailand	240	Unilateral Primary TKA	Postoperative Ecchymosis Around Knees	Prospective, Randomized, Double-blinded, Controlled Trial	Drain Clamping and TXA	Drain clamping combined with TXA administration led to postoperative blood loss and blood transfusion after TKA.
Mutsuzaki& Ikeda 2012 [37]	Japan	140	Unilateral Primary TKA	None	Non-randomized, Retrospective	Intra-articular TXA Injection (1000 mg) and Drain Clamping	Rates of blood loss and blood transfusion reduced by intra-articular retrograde TXA injection and one hour of drain clamping after TKA.
Stucinskas 2009 [15]	Sweden	60		None Reported	Prospective, Randomized Trial	Postoperative Conventional Suction Drainage vs. 4 Hours of Clamping Drainage	Postoperative clamping drainage in severe osteoarthritis, leading to reduced rates of blood loss and blood transfusions.
Ortega-Andreu 2011 [38]	Spain	132	Unilateral	Experimental: 4.9% Control: 9.8%	Cohort	Intravenous TXA Infusion (10-15 mg/kg) 15 Minutes before Tourniquet Release (3 Hours after Surgery)	Significant decrease in transfusion rate, blood loss and treatment costs after using TXA-based multimodal protocol.
Matziolis 2011 [39]	Deutschland	547		None	Retrospective Case Control	Tourniquet	Tourniquet reduced preoperative blood loss in TKA.

Author Year Reference	Country	N	Type of TKA	Complications	Type of Study	Techniques for Blood Loss Reduction after TKA	Efficacy
Everts et al. 2007 [40]	Netherlands	85	Unilateral	None Reported	Prospective, Comparative	APG and Fibrin Sealant	High Hb concentration reduced significantly compared to control group.
Munoz 2005 [41]	Spain	300	Unilateral	None		Unwashed Filtered Shed Blood	Postoperative requirement for ABT reduced, especially with preoperative Hb of >13 g/dL
Moonen et al. 2007 [42]	Netherlands	160		None Reported	Prospective, Comparative	Filtered Shed Blood	Postoperative retransfusion of filtered shed blood effectively reduced ABT rate after TKA.
Zhang et al. 2010 [43]	China	60		None (Color Doppler Imaging)	Randomized, Placebo- controlled	TXA and Intravenous Tourniquet	Significant difference between patients receiving TXA and control subjects (P<0.05).
McConnell et al. 2012 [44]	Scotland UK.	136		None	Retrospective, Preoperative	CAS vs. Standard Procedures	CAS significantly reduced rate of intraoperative blood loss in TKA.
Aguilera et al. 2013 [45]	Spain	68		DVT and PE (5% in Control Group	Single-centre, Retrospective Cohort	TXA (Two Intravenous Doses of 1 g)	TXA effectively and safely reduced rates of blood transfusion and blood loss in TKA.
Thiengwittayaporn et al. 2009 [16]	Thailand	80		None Reported	Prospective	CAS	Electromagnetic CAS did not reduce blood loss in minimally invasive surgery TKA (MIS-TKA).
Cheng et al. 2005 [46]	Hong Kong, China	60	Unilateral	None Reported	Randomized, Placebo- controlled	10 mg/kg TXA	Postoperative reinfusion of drained blood reduced the need for blood transfusion after total knee arthroplasty.
Dhillon 2011 [47]	India	108		None Reported		10 mg/kg TXA (Slower Intravenous Infusion)	TXA reduced total blood loss and ABT rate after TKA.
Charoencholvanich& Siriwattanasakul 2011 [48]	Thailand	100		None Reported	Prospective, Randomized, Double-blinded	Intravenous TXA (10 mg/kg) 10 Minutes before Tourniquet Inflation and 3 Hours after Surgery (250 mg/capsule; two capsules three times daily, orally) for 5 Days	TXA reduced postoperative blood loss and number of RBC transfusions after TKA/ No changes in symptomatic thromboembolic diseases.
Irisson 2012 [49]	France	197		None Reported	Retrospective	1 g TXA (15 mg/kg) at Incision and Wound Closure and at 6-Hour Intervals for 24 Hours	Rate of homologous blood transfusion reduced after TXA therapy/ No notable side effects/ TXA therapy led to rational use of blood salvage system .
Iwai 2009 [29]	Japan	78	Unilateral	None Reported	Comparative study	deflation of the tourniquet and Intravenous TXA	Administration of TXA twice reduced postoperative blood loss after TKA.
Alshryda 2013 [50]	United Kingdom	157		None Reported	Double-blinded, Randomized Controlled Trial	Topical Intra-articular TXA	Topical TXA reduced rate of blood transfusion.
Sa-ngasoongsong 2011 [51]	Thailand	48			Prospective, Triple-blinded, Randomized Controlled Trial	Intra-articular TXA Injection Combined with 2-Hour Clamp Drain	Low dosage of intra-articular TXA combined with 2-hour clamping drain effectively reduced postoperative blood loss and transfusion requirement in CAS-TKA without significant difference in postoperative complications or functional outcomes.

Author Year Reference	Country	N	Type of TKA	Complications	Type of Study	Techniques for Blood Loss Reduction after TKA	Efficacy
Ortega-Andreu 2011 [38]	Spain	71	Unilateral	None Reported	Prospective, Comparative	intravenous TXA infusion in 2 doses of 10-15 mg/kg	significant decrease in the transfusion rate, visible blood loss, and cost per patient.
Lin 2011 [52]	Taiwan	100		None Reported	Prospective, Comparative	Intravenous TXA before Tourniquet Deflation	Intraoperative injection of TXA decreased total blood loss and need for transfusion after MIS-TKA.

*Autologous platelet gel; **Computer-assisted surgery; ***Pulmonary embolism; ****Red blood cell

anemia to be 25% among these patients (60). In the articles reviewed in the current study, the rate of blood transfusion was higher among the patients in control groups. Preoperative anemia is considered as the most significant risk factor for the blood loss following orthopedic surgeries (59,61-63). According to the World Health Organization (WHO), anemia is detected when Hb concentrations are lower than 13 g/dL in men and lower than 12 g/dL in women (WHO) (64).

In the current review, postoperative Hb levels were considerably lower than the preoperative levels after TKA (3.0 g/dL). Furthermore, the prevalence of anemia increased after TKA surgery, and the postoperative anemia caused by surgical bleeding led to more significant iron deficiency (51%) (65). In the present study, the mean of Hb levels was variable in the reviewed articles, and there was a significant different between Hb concentrations before and after TKA surgery.

In one study, the level of Hb decreased by 82-83% immediately after TKA surgery, and 75-77% one week after the surgery (14). Moreover, a significant relationship was observed between preoperative Hb levels and the need for blood transfusions after TKA surgery. In other words, preoperative Hb levels could be a proper predictor for the rate of blood transfusion after TKA surgery (66).

In another study, preoperative Hb levels were shown to predict the markers of TKA outcomes (67). In addition, the results obtained by Salido et al. estimated the rate of ABT at 69% and 13% when preoperative Hb concentrations were lower than 13 g/dL and higher than 15 g/dL, respectively (68). This rate was reported to be 8% (69) and 13% (54) in two other studies. Increased levels of Hb could reduce the risk of blood loss in patients undergoing TKA; however, ABT might be required in some cases (70,71). According to a number of other studies, between 10-38% of TKA patients require ABT (20,72).

ABT is associated with certain risks and adverse clinical outcomes in TKA and is considered as an expensive procedure; therefore, patient blood management should be performed to minimize ABT requirement, and new techniques should be used for these patients (73,74).

In the current review, conflicting results were observed regarding the rate of transfusion thresholds in TKA patients. These rates ranged between >15% (39) and 60% in patients who received no treatments for blood loss reduction, as reported by Kalairajah et al. (20). On the other hand, ABTrates ranged between 10-89% in a review by Donat et al., and the mean of ABT rates and transfused blood volumes were estimated at 45% and 2.6 unites, respectively (60).

Postoperative mortality, ischemia and infections are among the most significant risk factors associated with preoperative anemia and ABT. In several randomized, controlled trials and cohort studies, interventions were performed before, during and after TKA surgery for the management ofpatient with blood loss. For the most part, these interventions were based on preoperative iron or drug therapy, as well as postoperative interventions, such as retransfusion of salvaged cells. Such efforts mainly aim to minimize or eliminate the rate of ABT, and according to the majority of reviewed articles, there was a statistically significant reduction in the rate of ABT in the patients of experimental groups compared to control subjects (75-78).

Interventions performed for the management of patient with bloodloss, which aim to increase preoperative and postoperative Hb levels, could also lead to the reduced rate of postoperative ABT. For instance, oral iron therapy is commonly used for the treatment of postoperative anemia. However, this method may not be effective in case of chronic anemia (79), and higher doses of erythropoietin might be required to trigger sustained erythropoiesis (80).

Applied Methods for Blood Loss Reduction

Investigation of different methods for reduction ofblood loss after TKA is of paramount importance. In recent studies, biological materials have been frequently used to assist hemostasis following TKA. According to the published literature, numerous strategies are applied to decrease postoperative

Table 2. Type of Study, Standard Treatment Techniques, Unilateral or Bilateral TKA and Associated Complications and Outcomes.

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Gardner 2007 [17]	New York, USA	Total: 98 Experimental (EX): 61 Control: 37	EX: 73.3 Control: 72.9	EX: 73%, Control: 77%,	EX: 27% Control: 23%	EX: 1351 ±715 ml	2.68	3.16		
Wong et al. 2010 [18]	Canada	3 g TXA: 33 1.5 g TXA: 31 Control: 35	3 g TXA: 63.9 ± 10.6 1.5 g TXA: 67 ± 11.9 Control: 68.4 ± 10.4	3 g TXA: 57% 1.5 g TXA: 81 % Control: 62%	3 g TXA: 43% 1.5 g TXA: 19% Control: 38%	3 g TXA: 1208§ (1078-1339) 1.5 g TXA: 1295§ (1167-1422) Control:1610 (1480-1738) (P=0.0001)	3 g TXA: 13.9±1.3 1.5 g TXA: 13.9±1.1 Control: 13.8±1.3 (P=0.873)	3 g TXA: 10.1§ (9.8-10.5) 1.5 g TXA: 10.0§ (9.5-10.4) Control: 8.6 (8.2-9.0) (P=0.008)	3 g TXA: 0 1.5 g TXA: 5 Units Control: 9 Units	3 g TXA: 0 1.5 g TXA: 12.9% Control: 14.3%
Orpen et al. 2006 [19]	UK	TXA: 15 Control: 14	TXA: 69 (63-74) Control: 73 (70-78)	TXA: 47% Control: 79%	TXA: 53% Control: 21%	TXA: 660 (496-824) Control: 726 (548-904)	TXA: 12.7 (12.6-14.1) Control: 13.24 (12.6-13.8)	(Day 1) TXA: 2.23 (0.1-4.5) Control: 2.97 (0-4.5) (Day 2) TXA: 2.49 (1.0-4.9) Control: 33.27 (1.3-5.7)		
Kalairajah 2005 [20]	Southern Australia	60 (EX: 30, Control: 30)	EX: 66 (11.8, 35-85) Control: 66 (10.9, 41-88)	EX: 63.3 Control: 60	EX: 37.7 Control: 40	EX: 1351 ml (715-2890, 95% CI, 1183-1518) Control: 1747 ml (1100-3030, 95% CI, 1581-1912) (P=0.001	EX: 128.7 (13.1, 109-161 g/dL) Control: 127.2 (12.2, 107-156 g/dL)	EX: 36.5 g/dl (95% CI,33.2-39.8) Control: 52.6 g/dl (95% CI, 46.4-58.7) (P<0.00001)	EX: 1.2 Units Control: 2.1 Units	EX: 20% Control: 60%
Li et al. 2009 [21]	China	80 (TXA: 40, Control: 40)	EX: 71±6 Control: 70 ± 7 (P=0.24)	TXA: 72% Control:67%	TXA: 28% Control: 33%	TXA: 1,298±285 ml Control:1,117±221 ml (P=0.04)	EX: 133±11.7 Control: 135±10.9 (P=0.53)	EX: 173.5±76.3 Control: 58.4±29.1 (P=0.00)		
Seo et al. 2013 [22]	South Korea	150 (Intravenous: 50, Intra-articular: 50, Control: 50)	Intravenous: 67.5±6.6 Intra-articular: 66.8±6.3 Control: 67.8±6.1	Intravenous: 90% Intra-articular: 88%, Control: 90%	Intravenous: 10% Intra-articular: 12%Control: 10%	Intravenous: 528±227 Intra-articular: 426±197 Control: 833±412 ml (P<0.001)	Intravenous: -1.6 ± 0.8, mg/dL Intra-articular: -1.8±0.8 mg/dL Control: 2.0±0.9 mg/dL (P<0.001)	Free Hemoglobin Concentration (Intravenous: 1.6±0.8 mg/dL, Intra-articular: 1.8 ± 0.8 mg/dL, Control: 2.0±0.9 mg/dL)	Intravenous: 273.6 ml Intra-articular: 129.6 mlControl: 920.8 ml	Intravenous: 66% Intra-articular: 80%Control: 6%

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Molloy et al. 2007 [23]	Northern Ireland	Topical Fibrin Spray: 50 TXA: 50 Control: 50				Topical Fibrin Spray: 1190±490 TXA: 1225±499 ml Control: 1415±416 ml	Topical Fibrin Spray: 11.96±0.91 TXA: 12.04±0.85 Control: 12.04±0.74	Topical Fibrin Spray: 2.68±1.02 TXA: 2.75±1.03 Control: 3.20±1.12	Topical Fibrin Spray: 2.68±1.02 TXA: 2.75±1.03 Control: 3.20±1.12	Topical Fibrin Spray: 14% TXA: 10% Control: 22%
Thorey et al. 2008 [24]	Netherlands	***ERT: LRT:		Both Groups: 65%	Both Groups: 35%	Preoperative ERT: 753±390 ml LR: 760±343 (P=0.930) (Day 1) ERT: 571±379 ml LR: 621±299 m (P=0.550)	Total: 13.9±1.19	Total: 10.8±1.14		
Ishida et al. 2011 [25]	Japan	TXA: 50 Control: 50	TXA: 73.3 (5.0) Control: 73.5 (6.1)	TXA: 88% Control: 88%	TXA: 12% Control: 12%		TXA: 12.5 (1.0 g/dL) Control: 12.6 (1.0 g/dL) (P=N.S)			Control: 2%
Tsumara 2006 [14]	Japan	*D: 106 B: 106	D: 72.8±6.4 B: 72.6±6.1	D: 87% B: 90%	D: 13% B: 10%	Drained Blood D: 352.1 ml B: 662.3 ml (P<0.0001)	D: 12.8±1.2 g/dL B: 12.7±1.3 g/dL (P=0.41)	(Day 1) D*: 2.4±0.8, B: 2.1±1.0 (P=0.03) (Week 1) D: 0.83+0.8, B: 0.83+0 (P=0. 78) (Month 1) D: -1.1+0.8 , B: -1.2+1.0 (P=0.58)		D: One Patient B: 0
Alvarez et al. 2008 [26]	Spain	EX: 46 Control: 49	EX: 71±9 Control: 72±7 (P=0.56)	EX: 85% Control: 80%	EX: 15% Control: 20%	EX: 1744 ±804 ml Control: 1301±621 ml (P=0.05)	EX: 41.3±3.9 Control: 41.5±3.8 (P=0.83)		Autologous Blood EX: 0 Control: 3 Units Allogenic Blood EX: 1Unit Control: 8 Units	EX: 4% Control: 73% (P=0.00001)
Tai et al. 2012 [27]	Taiwan	72				EX: 303± 19 ml Control: 423±197 ml		EX: 2.6±0.9 g/dL Control: 3.7±1.3 g/dL		

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Yavarikia 2010 [28]	Iran	***I: 29 II: 33 III: 22	I: 66 II: 64 III: 68 (P=0.87)	I: 77% II: 73% III: 73%	I: 23% II: 27% III: 27%	I: 810.0±244 II: 720.0±266 III: 705.0±295ml (P=0.062)	I: 12.23±1.21 II: 13.03±1.3 III: 13.49±1.22 (P=0.251)	(Day 1) I: 10.98±1.21 II: 11.02±0.93 III: 11.12±1.04 (P=0.132) (Day 2) I: 40.21±0.16 II: 41.56±5.67 III: 41.67±4.32 (P=0.454)	I: 248.00±201 II: 241.00±173 III: 239.00±144 ml (P=0.052)	
Iwai 2009 [29]	Japan	Control: 31 Single-TXA: 21 Twice-TXA: 26	Control: 73.7±7.3 Single-TXA: 74.7±5.3 Twice-TXA: 75.0±5.0			Apparent Blood Loss Control: 1000 ml Single-TXA: 500-1000 ml Twice-TXA: <500 ml	Control: 12.6±1.1 Single-TXA: 12.4±1.5 Twice-TXA: 12.8±1.6	(Day 1) Control: 10.6±1.2 Single-TXA : 10.2±1.1 Twice-TXA: 10.7±1.6 (Day 4) Control: 9.9±1.2 Single-TXA : 8.7±1.3 Twice-TXA:9.4±1.3 (Day 7) Control: 9.9±1.2 Single-TXA: 9.2±1.3 Twice-TXA: 9.6±1.4	Autotransfusion Control: 396.8±221 Single-TXA: 34.0±66.6 Twice-TX-A:0Allogeneic Control: 0 Single-TXA: 0 Twice-TXA: 0	
Sabatini 2012 [30]	Italy	EX: 35 Control: 35	EX: 70.4±6.7 Control: 70.7±6.4 (P=0.84)	EX: 71% Control: 82%	EX: 29% Control: 18%	EX: 910±292 ml Control: 1,250±546 ml18 (P=0.0000165)	EX: 13.5±1.5 g/dL Control: 13.2±1.2 g/dL (P=0.34)	EX: 2.72±1.28 g/dL Control: 2.54±1.15 g/dL (P=0.54)		EX: 34% Control: 5% (P=0.006)
Conteduca 2009 [31]	Italy	Conventional TKA: 50 CAS-TKA: 50	Conventional TKA: 73.6 CAS-TKA: 70.4	Both Groups: 68%	Both Groups: 32%	Conventional TKA: 1,974±817.6 (450–3,930) ml CAS-TKA: 1,677±463.8 (500-2,634) ml (P=0.0283)	Preoperative Conventional TKA: 12.8 (16.2-10.5) CAS-TKA: 12.5 (9.8-15.1)	Conventional TKA: 3.34±1.23 g/dL CAS-TKA: 3.08±1.03 g/dL (P=0.2667).	Conventional TKA: 543.3 ml CAS-TKA: 371.1 ml	
Konig 2013 [32]	Pennsylvania, USA	EX: 130 Control: 29	EX: 61±10 Control: 61±10 (P=0.75)	EX: 61% Control: 65%	EX: 39% Control: 35%	EX: 1166±390 ml Control: 1397±473 ml (P=0.01)		Discharge Hb level EX: 11.1±1.4 Control: 10.5±1.8 (P=0.05) Hb Drop (gm/dL) EX: 3.0±0.9 Control: 3.6±1.0 (P<0.01)		EX: 0 Control: 10% (P<0.01)
Gasparini 2006 [33]	Italy	EX: 29 Control: 55	EX: 70.3±6.1 Control: 71.5±6.2 (P=0.4)	EX: 83% Control: 78%	EX: 17% Control: 22%	EX: 821.9±270.8 Control: 1,270.8±394.5 (P<0.0001)	EX: 10.1±1.4 Control: 9.7±1.3 (P=0.2)	EX: 2.9±1 Control: 3.5±1 (P=0.01)		EX: 7% Control: 28% (P=0.03)

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Lozano 2008 [34]	Spain	EX: 199 Control: 215						EX: 10.1 g/dL Control: 9.3 g/dL	EX: 1.89 Units Control: 2.83 Units	RBC EX: 17.6% Control: 44%
Camarasa et al. 2006 [35]	Spain	127				EX: 1099±535 ml Control: 1784±660 ml (P<0.001)		Mean Reduction in Hb Level (Day 5) EX: 2.5±0.9 g/dL Control: 3.4±1.2 g/dL (P<0.001)	Packed RBC EX: 0.10 Units Control: 0.58 Units (P<0.001)	EX: 7.5% Control: 38.3% (P<0.001)
Chareanchol-vanich 2012 [36]	Thailand	**** Al: 60 B: 60 C: 60 C: 60	A: 69.8±6.3 B: 69.4±6.3 C: 68.9±7.5 D: 70.1±7.2 (P=0.418)	A: 87% B: 85% C: 83% D: 87%	A: 13% B: 15% C: 17% D: 13%	Volume of Drained Blood Al: 1182±411 B:724±246 C:821±337 D: 526±222 (P<0.001)	A: 12.5±1.1 B:12.4±1.1 C:12.4±1.1 D: 12.6±1.00 (P=0.515)	A: 3.3±0.9 B: 2.1±0.6 C: 2.8±0.8 D: 1.8±0.7 (P<0.05)	PRC Transfu-sion (Unit) A: 1.8±1.0 B: 0.7±0.7 C: 1.3±0.9 D: 0.4±0.5 (P<0.05)	A: 88.3% B: 56.7% C: 81.7% D: 38.3% (P< 0.05)
Mutsuzaki& Ikeda 2012 [37]	Japan	EX: 70 Control: 70	EX: 72.0±7.3 Control: 74.1±7.1	EX: 77% Control: 75%	EX: 23% Control: 25%	EX: 633.8±317.2 Control: 1276.0±327.1 (P<0.001)	EX: 12.6±1.4 Control: 12.7±1.4 (P=N.S)	Postoperative (Day 1) EX: 11.3±1.2 Control: 11.1±1.3 (P=N.S) Postoperative (Day 7) EX: 10.7±1.3 Control: 10.1±1.1 (P<0.001) Postoperative (Day 14) EX: 10.9±1.1 Control: 10.7±1.0 (P=N.S)	Autologous (ml) EX: 40.0±120.9 Control: 264.1±195.5 (P<0.001) Allogeneic (Units) EX: 0.2±0.7 Control: 1.1±1.7 (P<0.001)	Autologous EX: 10.0 Control: 65.7 (P< 0.001) Allo-geneic EX: 10.0 Control: 31.4 (P< 0.001)
Stucinskas 2009 [15]	Sweden	Clamped: 30 Non-clamped: 30	Clamped: 67±7 Non-clamped:70±7	Clamped: 77% Non-clamped: 90%	Clamped: 23% Non-clamped: 10%	(Day 1) Clamped: 1,470±555 Non-clamped: 1,627±752 ml (Day 3) Clamped: 2,014±790 Non-clamped: 2,160±532 ml	Clamped: 13.5±1.4 Non-clamped: 13.3±1.6 (P=0.6)	(Day 1) Clamped: 10.4±1.4 Non-clamped: 9.9±1.9 (P=0.25)	Clamped: 13 Non-clamped: 32 (P=0.07)	Clamped: 20% Non-clamped: 43% (P=0.09)
Ortega-An-dreu 2011 [38]	Spain	EX: 61 Control: 71	EX: 71 (53-85) Control: 69 (52-82) (P=0.144)	EX: 77% Control:70%	EX: 23% Control: 30%		EX: 14.3 (g/dL) Control: 14.4(g/dL) (P=0.642)	6, 24 and 48 Hours after Surgery: 12.2, 10.9 and 10.3 g/dL in Control Group 12.7, 12.1 and 11.3 in EX Group	EX: 0 Control: Total: 491 Units: 4 2 Units: 14 3 Units: 4 5 Units: One Pa-tient	EX: 0 Control: 37.7%

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Matziolis 2011 [39]	Deutsch-land	EX: 262 Control: 285				EX: 1.5±0.6 l (-0.2-4.3l) Control: 1.2±0.5l (-0.2-3.4 l) (P<0.001)				Erythrocyte Transfusion EX: 9.2% Control: 12.6%
Everts et al. 2006 [40]	Nether-lands	85						EX: 11.3 g/dL Control: 8.9 g/dL	Allogeneic EX: 0.17 Units Control: 0.52 Units (P<0.001).	
Munoz 2005 [41]	Spain	***** USB: 200 Control: 100	USB: 68.5 Control: 66.5	USB: 80% Control: 67%	USB: 20% Control: 33%	Preoperative USB: 118±101 Control: 123±165 Postoperative USB: 705±349 Control: 953±428	USB: 13.5±1.2 Control: 13.6±1.4	Postoperative 24-48 Hours USB: 10.4±1.3 Control: 10.4±1.4	Allogeneic USB: 0.29±0.87 Control: 1.31±1.27 (P<0.05) Autologous USB: 0.98±0.40 Control: 0 (P<0.05)	
Moonen Et al. 2007 [42]	Nether-lands	160					EX: 13.0 g/dL Control: 14.6 g/dL			EX: Control: 19%
Zhang et al. 2007 [43]	China	102	59%	41%	68 (59-77)	EX: 559±159 ml Control: 1208±243 (P<0.05) Postoperative Drainage Volume EX: 478±172 ml Control: 814±156		Hb Concentration EX: 1.0-1.1 g/dL Control: 0.6-0.8 g/dL	EX: 556±174 ml 1024±278	
McConnell et al. 2012 [44]	Scotland UK	****** Control: 68 Standard Treatments: 68				Control: 1137 ml Standard Treatments: 1362 ml (P=0.016)			Control: 3 Units	Control:1.5%
Aguilera et al. 2012 [45]	Spain	TXA: 19 NO-TXA: 21 Control: 28	TXA: 74 (5) NO-TXA: 74 (8) Control: 74 (5)	TXA: 68% NO-TXA: 62% Control: 89%	TXA: 32% NO-TXA: 48% Control: 11%	TXA: 1196± 2166 ml NO-TXA: 2454±2166 ml Control: 1693±689 ml				

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Thiengwittay-aporn et al. 2009 [16]	Thailand	******* MIS-CAS: 40 MIS: 40	MIS-CAS: 70.8 (7.84) MIS: 70.15 (7.76) (P=0.71)	MIS-CAS: 82.5% MIS: 85%	MIS-CAS: 11.5% MIS: 15%	MIS-CAS: 948.45 (431.63) MIS: 1,075.32 (419.02) ml	MIS-CAS: 37.91 (3.46) MIS: 37.67 (3.17) (P=0.672)		MIS-CAS: 142.50 (168.14) MIS: 176.75 (175.83) ml	
Cheng et al. 2005 [46]	Hong Kong, China	EX: 26 Control: 34	EX: 72 (57-84) Control: 69.4 (55-78) (P=0.83)	EX: 77% Control: 53%	EX: 33%) Control: 48%	EX: 273 (100-600) Control: 280 (100-800) (P=0.84)	EX: 124 (104-154) Control: 128 (96-147) (P=0.836)	(Day 1) EX: 101 (84-128) Control: 104 (87-137) (P=0.332) (Day 3) Postoperative EX: 98 (77-130) Control: 101 (77-130) (P=0.402)	ABT EX: 0.15 (0-1) Control: 0.46 (0-4) (P=0.033)	ABT EX: 15% Control: 38% (P=0.0050)
Dhillon 2011 [47]	India	EX: 65.75 (50-82) Control: 67.25 (51-82) (P=0.359)	EX: 65% Control: 64%	EX: 35% Control: 34%		EX: 12.78±1.85 Control: 13.04± 1.72 (P=0.459)		EX: 11.79±1.96 Control 10.25 ± 1.40 (P<0.0001)	EX: 0.80±0.90 Control: 3.17±0.81 (P<0.0001)	Control: 100% EX: 25% (P<0.0001)
Charoencholvanich& Siriwattanasakul 2011 [48]	Thailand	EX: 50 Control: 50	Control: 68.80±6.12 EX: 69.20±6.13 (P=0.44)	Control: 84% EX: 16%	Control: 86% EX: 14%		Control: 12.51±1.11 EX: 12.41±1.18 (P=0.53)	Control: 3.33±0.88 (1.40-5.40) EX: 2.12±0.64 (0.9-3.60) (P<0.0001)	PRC Units Control: 1.89±0.87 EX: 0.71±0.78 (0-2) (P<0.0001)	Control: 90% EX: 56% (P<0.0001)
Irisson 2012 [49]	France	Control: 108 EX: 89	Control: 72±7 EX: 72±8	Control: 62% EX: 55%	Control: 38% EX: 45%	Control: 1900±690 EX: 1260±620	(Day 1) Control: 14.0±1 EX: 14.2±1 (Day 8) Control: 10.7±1.2 EX: 11.8±1.2		Autologous Control: 350±190 EX: 110±125	
Iwai 2009 [29]		Control: 31 Single-TXA: 21 Twice-TXA: 26	Control: 73.7±7.3 Single-TXA: 74.7±5.3 Twice-TXA: 75.0±5.0			Apparent Blood Loss Control: 1000 ml Single-TXA: 500-1000 ml Twice-TXA: <500 ml	Control: 12.6±1.1 Single-TXA : 12.4±1.5 Twice-TXA: 12.8±1.6	(Day 1) Control: 10.6±1.2 Single-TXA : 10.2±1.1 Twice-TXA: 10.7±1.6 Postoperative (Day 7) Control: 9.9±1.2 Single-TXA: 9.2±1.3 Twice-TXA: 9.6±1.4	Autologous Donation Control: 371.6±100 Autotransfusion Control: 396.8±221 Single-TXA: 34.0±66.6 Twice-TXA: - Allogeneic: 0	

Author Year Reference	Country	N	Age (Mean)	Gender		Rate of Total Blood Loss after TKA	Hemoglobin Level (g/dL)		Mean of Blood Transfusions	
				Female	Male		Preoperative	Postoperative	Amount	Rate
Alshryda 2013 [50]	UK	Control: 78 EX: 79	Control: 67.1±10.2 EX: 65.5±9.6	Control: 44% EX: 62%	Control: 56% EX: 38%	Total: Control: 1725±823 EX: 919±487 (P<0.0001)	Preoperative Control: 13.6±1.3 EX: 13.2±1.3	Postoperative Control: 10.69±1.35 EX: 11.52±1.33 (P<0.0001)		Control: 16.7% EX: 1.3% (P=0.001)
Sa-ngasoong-song 2011 [51]	Thailand	TXA: 24 Control: 24	TXA: 69.0 (8.2) Control: 69.2 (7.6) (P= 0.942)	TXA: 92% Control: 75%	TXA: 8% Control: 25%	EX: 206.3±115.4 Control: 385.1±145.2 (P<0.0001)	Preoperative EX:12.5±1.3 Control: 12.2±1.1	Postoperative EX:2.1±0.9 Control: 3±0.7 (P=0.0005)		EX:42% Control: 33% (P=0.023)
Ortega-Andreu 2011 [38]	Spain	EX: 61 Control: 71	EX: 71 (53-85) Control: 69 (52-82) (P=0.144)	EX: 77% Control:70%	EX: 23% Control: 30%.		Preoperative EX: 14.3 (g/dL) Control: 14.4(g/dL) (P=0.642) 6, 24 and 48 Hours	after Operation: Control: 12.2, 10.9, 10.3 g/dL EX: 12.7 , 12.1, 11.3		
Lin 2011 [52]	Taiwan	Control: 50 EX: 50	Control: 68.3 EX: 69.2 (P=0.508)	Control: 82% EX: 88%	Control: 18% EX: 12%	Control: 1453 (383, 733-2537) ml EX: 833 (144; 374-1014) ml (P<0.001) (P<0.001)	Control: 13.5 EX: 13.5 (P=0.075)	(Day 1, 2, 4) Control: 10.9, 29.3, 48.7 EX:11.5, 10.5, 10.0 (P=0.050) (P<0.001) (P<0.001)	Control: 0.48 (1.0) EX: 0.08 (0.39) (P=0.013)	Control: 20% EX: 4% (P=0.014)

* Drain Clamping, *Blood Salvage, **I: Without Tourniquet, II: With Tourniquet, III: Tourniquet after Wound Closure and Application of Compressive Dressing, *** ERT: Early Release Technique, LRT: Late Release Technique, **** Group A: Non-clamping Drainage and Placebo Administration, Group B: Non-clamping Drainage and Tranexamic Acid Administration, Group C: Clamping Drainage and Placebo Administration, Group D: Clamping Drainage and Tranexamic Acid Administration. ***** Unwashed Filtered Shed Blood, ******Computer-navigated, *******Minimally Invasive Surgery

blood loss in major orthopedic procedures, such as TKA and THA (17). In this regard, the most common methods used for prevention ofblood loss include ABT (81), use of antifibrinolytics (82), hypotensive anesthesia (83), drain-clamping (84), use of fibrin sealant tissue adhesive (85) or compression bandage, and cryotherapy (25,86).

Autologous Transfusion Techniques

The main methods used for blood reinfusion are preoperative autologous blood donation (PAD), acute normovolemichemodilution (ANH) and intraoperative cell salvage (ICS) (87). Patients who receive autologous blood transfusions before surgery may not require postoperative transfusions (68,88-91).

According to several studies, PAD reduces the overall rate of ABT by 84% in patients undergoing orthopedic surgeries (87). In addition, ICS is another method with emphasis on blood conservation and a major form of auto-transfusion used to avoid the possible side effects of blood transfusion. ICS is also used to minimize ABT rates in surgical interventions involving major blood loss (92). As estimated by previous findings, ICS could reduce the overall rate of ABT by 65% in patients undergoing orthopedic surgeries (87).

In one study, after the administration of intravenous iron sucrose and preoperative erythropoietin via blood salvage following unilateral TKA, only 4% of the patients required ABT (93). In another study by the same researchers, transfusion of iron ferrous sulfate, vitamin C and folic acid was reported to be effective in avoiding ABT in non-anemic TKA patients (70).

In the study conducted by Tsumara et al., the rate of ABT was estimated at 2.8% among the TKA patients using blood salvage and 0.9% in those receiving drain clamping (14), which were significantly lower than the overall ABT rates reported by other studies (54,69,94).

In another systematic review in this regard, three autologous transfusion techniques were compared, and the results indicated that these methods could consistently reduce the frequency of allogeneic transfusions by 63%, 42% and 31% in PAD, ICS and ANH, respectively (87).

Antifibrinolytic Drugs

According to several studies, blood loss could be reduced and prevented using anticoagulants after orthopedic surgeries. In this regard, hemostatic techniques could be applied to diminish the prevalence of serious thromboembolic events associated with such procedures (95). Using biological hemostatic methods during TKA could be remarkably effective in the prevention of total blood loss (17,71,96-98).

Tissue fibrinolysis could be inhibited by TXA for up to 17 hours, and the possibility of clots entering the extravascular space could be controlled; therefore, antifibrinolytic drugs are considered as safe measures for the reduction of total blood loss (37). Other medicines such as erythropoietin, TXA and aprotinin could be effective in the prevention of blood loss as well (2). Antifibrinolytics cause a significant decrease in blood loss in patients undergoing TKA, which is normally reflected in the decreased number of required blood transfusions (10,11,35).

Tranexamic Acid (TXA)

Surgical procedures and the use of pneumatic tourniquets may lead to the increased activity of the fibrinolytic system, resulting in more severe blood loss (19). TXA is a synthetic amino acid, which inhibits the activation of fibrinolysis via binding to one of the enzymes at the start of the coagulation cascade (37). TXAis the most popular drug used for the treatment and prevention of blood loss in TKA patients. In one study, blood loss and Hb drop were reported to be higher by 25% and 27%, respectively when TXA was administered during TKA (32).

According to the findings of Good et al., TXA decreased total blood loss by nearly 30%, which resulted in the reduced rate of blood transfusions (72). The results of another study reported the rate of homologous blood transfusion to reduce from 4% to 0% due to a 34% decrease in the total blood loss after TXA administration. Moreover, the rate and volume of ABT plunged by 38% and 68%, respectively (49). Several studies have confirmed the efficacy of TXA in the reduction of blood loss (12,18,19,26,52,99-110).

TXA could be administered intravenously or via topical application, and the effectiveness of different doses of this drug has been investigated inprevious studies (37,111). When intravenously administered, TXA reaches the target location and inhibits tissue fibrinolysis (25). According to one study, the mean of blood loss decreased after administration of 15 ml and 10 ml TXA, while the rate of combined autologous and ABT volumes was significantly lower in the experimental group compared to control subjects ($P<0.01$) (112). Efficacy of intravenous TXA in the reduction of total blood loss has been confirmed by many studies (48,113-116).

On the other hand, Seo et al. stated that the intra-articular administration of TXA was more effective than the intravenous administration in reducing total blood loss. In their study, about 66%, 80% and 6% of the patients in the intravenous

administration, intra-articular administration and control groups, respectively did not require blood transfusions. Since TXA helps maintain hemodynamic stability, it plays a pivotal role in improving the general condition of patients (22). This finding is consistent with the results obtained by other studies (25,37,110).

It is also noteworthy that TXA affects blood loss differently depending on the dosage of intravenous administration; therefore, the ideal method of TXA administration remains controversial among medical researchers (111).

Intravenous injection of antifibrinolytics could reduce the rate of blood transfusions in orthopedic surgeries by 50% (117-119). However, thromboembolic complications have been reported in patients who are at the higher risk of DVT and pulmonary embolism (PE). Therefore, there are concerns about the use of antifibrinolytics among researchers (120,121). In this regard, it has been suggested that the risk of thromboembolic complications may diminish through the topical application of antifibrinolytics due to the lower systemic absorption of these drugs. This finding has been confirmed in a number of other studies (18,32,57). The topical application of TXA was first reported in an orthopedic surgery performed by Akizuki (122).

According to the study conducted by Wong et al., the rate of postoperative blood loss reduced by 20- 25% after the topical application of TXA. Furthermore, Hb levels increased by 16-17% in patients administered with TXA compared to the placebo subjects (18). Another study in this regard indicated that the rate of postoperative transfusions was significantly lower in patients using topical TXA compared to the control group (0% vs. 10%) (51,82,123).

TXA could be administered before and after TKA surgery. In one study, it was claimed that TXA administration after the surgical operation could reduce total blood loss by 40%, while the hemostatic effect of this drug was most remarkable when administered before the surgery (124).

One of the major concerns among medical professionals is the increased rate of venous thromboembolism caused by fibrinolytic activity after different surgeries (125-127). Although TXA therapy could not influence the fibrinolytic activity of vein walls (128), increased venous thrombosis in patients undergoing TKA has not been reported in any of the previous studies (100, 129).

Fibrin Spray

Recently, fibrin sealants have been increasingly used as the hemostatic and tissue sealing agents during TKA, and some studies have indicated that fibrin sealants could effectively improve hemostasis. In one study, total efficacy of topical fibrin was estimated at 55% (23), which was consistent with the findings of several other studies (45,55,95,97).

According to the results obtained by Molloy et al., there was a significant reduction in the total blood loss between the control group, topical fibrin spray group (P=0.016) and TXA group (P=0.041). However, no significant difference was observed in the reduction of blood loss between the patients using topical fibrin and TXA (P=0.72). Moreover, despite the higher mean of blood loss in the TXA group, the rate of ABT was significantly lower among these subjects compared to those in the topical fibrin group. This could be due to the breach of the relevant transfusion thresholds since some of the patients required blood transfusions due to hypotension or tachycardia (23).

In another study, Sabatini et al. evaluated the hemostatic efficacy and safety of fibrin tissue adhesive (Quixil) in patients undergoing TKA. According to their findings, there was a significant reduction in the total blood loss of the patients who used fibrin tissue adhesive, and the rate of blood transfusion was also lower in these patients compared to the control group (30).

Tourniquets

A tourniquet is normally used to minimize the blood loss caused by orthopedic surgeries, such as TKA. Using tourniquets could lead to the activation of fibrinolysis transiently through enhancing the release of the tissue plasminogen activator (99). Moreover, tourniquets could reduce the risk of venous thromboembolism and increase the rate of post-surgical hemorrhage (128,130,131).

According to the literature, use of tourniquets could reduce intraoperative blood loss (132,133]; however, medical opinions are variable regarding the exact effects of tourniquets on the total blood loss (40,53,134). While some studies have associated the use of tourniquets with reduced total blood loss (21,53), others have dissented from this viewpoint (135-137).

On the other hand, a number of prospective (96) and retrospective studies (133,138) have confirmed the efficacy of tourniquets in the prevention of blood loss after surgeries. With respect to TKA, intraoperative tourniquet is the most effective measure in reducing total blood loss after this surgical operation (27,43,139-141). According to other studies in this regard, tourniquets have more significant effects on blood loss reduction compared to other common methods, such as compressive bandaging (133,138), use of low-dosage vasopressors and

saline infusion (17,142).

Computer-assisted Surgery (CAS)

Accurate intraoperative positioning of components without breaches in the intramedullary cavities is recognizable via advanced computer navigation. According to previous studies, computer navigation could contribute to blood loss reduction. However, this method has certain shortcomings; for instance, it involves a time-consuming process, which might negate the potential benefits (20). Computer-assisted surgery (CAS) in TKA was first used by Stulberg et al. (143, 144) and it was observed to be effective in the reduction of the blood loss caused by accurate placement and limb arrangement, without any breaches in the intramedullary cavities (145-147). In another study, Conteduca et al. reported CAS to be an effectual measure to prevent bleeding after surgical operations (31), and this finding was confirmed by several other studies (20,148-152).

Autologous Platelet Gel (APG)

According to the published literature, APG could contribute to the completion of hemostasis. This substance is derived from platelet-rich plasma, which is extracted from the blood of the patient. APG could be applied to exposed surfaces of thetissues and reduce the pain caused by TKA surgery. In addition, use of APG could result in reduced preoperative blood loss. In a study by Grander et al., total blood loss was minimized in the patients receiving treatment with APG. Moreover, these patients did not require narcotic and oral medications, had better pain management and shorter hospital stay (17). Although fibrin sealant has been shown to have numerous benefits, it is normally made from human plasma, and the use of this substance may involve the risk of viral infection transmissions (153-156). In this regard, the risk of viral transmissions, such as parvovirus B19, has been estimated to be as high as 20% (17,155).

In another study, Everts et al. compared the efficacy of APG and fibrin sealant in patients undergoing unilateral TKA. According to their results, postoperative Hb levels were higher, and ABT rates were lower among the experimental subjects compared to the control group. Additionally, wound leakage and disturbance of wound healing were lower in the experimental group compared to the control group (40).

Other Common Techniques used for Blood Loss Reduction

Several studies have evaluated other techniques used to reduce blood loss in THA, and some studies have reported drain clamping to be effective in the reduction of blood loss after TKA (13,14,157).

Furthermore, drainage clamping combined with epinephrine infusion has been proposed as a new approach to decrease postoperative blood loss (158,159). Despite the efficiency of this method in reducing postoperative bleeding, it has been associated with complications such as delayed wound healing with skin-edge necrosis, hematoma, severe hemorrhage and DVT (13).

According to the findings of Tsumara et al., the efficacy of drain clamping after intra-articular injection of saline is mostly associated with postoperative blood salvage in the prevention of blood loss (14). On the other hand, unwashed red blood cell (RBC) salvage after TKA was reported to be an effectual technique to reduce total blood loss (160,161).

In another study performed by Peter et al., only 30 patients who had received retransfusions from wound drains required additional homologous transfusion, which was indicative of the reduced need for autologous blood donation (132). This finding has been confirmed by another similar study (162).

On the other hand, a number of studies have indicated that the re-infusion of unwashed shed blood (USB) could be effective in eliminating the need for ABT (41,163,164). In the study by Munoz et al., USB return decreased the rate of ABT by 77% (41). In another study by Moonen et al., the rate of ABT was 6% and 19% among the patients receiving postoperative retransfusion of filtered shed blood (308 ml) and control subjects, respectively (42); this difference was considered to be significant. In addition, no significant correlations were observed between the retransfusion of filtered shed blood and postoperative fever among the patients (42,165).

Complications caused by Blood Loss in TKA

The major complications caused by TKA are blood loss, postoperative pain, leg swelling and need for blood transfusions [166]. Postoperative pain could be alleviated using narcotic medications; however, sedation, respiratory depression and constipation are among the possible side effects of these drugs. TKA complications may be exacerbated in elderly patients, and total blood loss is considered as the major risk factor for TKA. Preoperative blood loss after TKA surgery often brings up the need for blood transfusions; therefore, hemostasis should be taken into account in patients undergoing TKA (85,167,168).

According to the published literature, life-threatening diseases such as HIV, hepatitis and cytomegalovirus infectionsmay be transmitted

through homologous transfusions (169).

Furthermore, blood transfusions may be followed by certain reactions; problems such as administrative errors or bacterial overgrowth are more commonly observed in pre-donated autologous transfusions compared to homologous transfusions. Also, these procedures are known to impose heavy treatment costs (170). Therefore, several studies have attempted to develop new strategies to eliminate the need for ABT due to the numerous consequences. For instance, complications such as DVT and hematoma have been known to occur in patients undergoing TKA (133). In a study conducted by Tanaka, the postoperative incidence of thromboembolism was observed during 7-14 days after TKA surgery (124).

Despite the advantages of antifibrinolyticsas safe and effective agents used for the prevention of blood loss in TKA surgery, these drugs may give rise to adverse side effects, such as subclinical DVT (37). Antifibrinolytic drugs were used in the majority of the reviewed articles to diminish the rate of ABT among the patients undergoing TKA (2,34,95).

Moreover, the possibility of thromboembolism was evaluated in many of the studies using antifibrinolytics to reduce blood loss in TKA. For instance, Orpen et al. attempted to assess the impact of TXA therapy on clinical and sub-clinical DVT and observed no significant relationship between the treatment with 15 mg/kg TXA and incidence of DVT (19).

In the study by Wong et al., no significant difference was observed in the rates of DVT or PE between the patients administered with TXA and the control group (18). The majority of the reviewed articles in the current study were indicative of no significant difference in the incidence of thrombosis or PE between the patients receiving TXA and control subjects.

Conclusion

Despite the availability of different methods for blood loss reduction in TKA, the rate of ABT is still relatively high, and the subsequent anemia is a frequent complication among the patients undergoing TKA. Of course, the effectiveness of different techniques used for blood loss prevention is not yet clear, and many of them are associated with adverse side effects. According to the results of the present review, intraoperative/ postoperative blood salvage and autologous transfusion techniques are among the relatively safe options for blood preservation, avoidance of ABT and prevention of transfusion reactions in patients undergoing TKA. Moreover, TXA therapy was found to be the most common technique used to decrease postoperative blood loss and the rate of blood transfusions.

One of the limitations of the current review was the presence of conflicting data in large scales, which would not allow the researchers to concur with a generalized hypothesis. In this regard, a standardized framework including a single definition of anemia and transfusion triggers, preoperative patient blood management, comprehensive recognition of all the techniques used for blood loss reduction in orthopedic surgeries and the associated complications of each technique is required to discover more efficient methods to prevent postoperative blood loss in different patients.

Conflict of Interest

The authors declare no conflict of interest.

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