

Original Article

Impact of tranexamic acid and autologous blood transfusion on postoperative complications after primary total knee arthroplasty: a retrospective comparative study

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Received August 13, 2015; Accepted November 10, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Blood loss during total knee replacement is a major concern for the operating surgeon as well as the patients. Various techniques have been adopted to reduce the blood loss and its consequent complications during the intra-operative and post-operative period. Of the various methods, tranexamic acid and autologous blood transfusions are widely used. There is however a paucity of data comparing the impact of these two techniques on post-operative complications and also the advantages of the combined use of two techniques. Methods: A retrospective study on postoperative blood management of TKA was done in 392 patients (279 female, 113 male). All the patients were divided into 4 groups. The first group comprised of patients who had received neither autologous transfusion nor tranexamic acid (Group A); the second group received autologous blood transfusion only (Group B); the third group received a combined management with tranexamic acid injection and autologous blood transfusion (Group C); the fourth group received tranexamic acid without any auto transfusion (Group D). Through routine blood tests, the blood loss was calculated by the Gross formula. Allogeneic blood transfusion amounts were also recorded. Knee swelling was evaluated by measuring the circumference of the knee. After surgery, suspicious deep vein thrombosis was excluded by B-ultrasound. During the first follow-up, we checked whether skin edge necrosis was present and examined range of motion. Results: After primary TKA surgery, intravenous injection of tranexamic acid could decrease the drainage amount (268.4 mL vs 318.7 mL, $P<0.01$), hidden blood loss (668.8 mL vs 762.1 mL, $P<0.01$), and allogenic blood transfusion rate (3.17% vs 5.74%). The use of VAC auto transfusion equipment on the patient led to an increase in the drainage amount (368.1 mL vs 318.7 mL, $P<0.01$), although it reduced skin edge necrosis (1.83% vs 4.59%, $P=0.409$). It could also reduce the swelling (1.17 mL vs 1.21 mL, $P=0.02$) and accelerate the recovery of ROM (2.48 vs 2.69, $P=0.023$). The combined use of tranexamic acid and the auto transfusion VAC system resulted in an increase in the drainage amount (268.4 mL vs 311.6 mL, $P<0.01$) and also could not reduce hidden blood loss (716.6 mL vs 668.8 mL, $P=0.023$) or the allogenic blood transfusion rate (3.75% vs 3.17%). However, the combined use did result in a significant reduction in knee swelling in the post-operative period (1.15 vs 1.18, $P=0.07$). Conclusions: The use of tranexamic acid reduces both apparent and hidden blood loss in the post-operative period in knee replacement patients. The use of the autologous transfusion system reduces the incidence of wound necrosis, decreases knee swelling, and improves rehabilitation. The combined use did not result in a significant reduction in blood loss but did decrease knee swelling on post-operative evaluation.

Keywords: Tranexamic acid, autologous blood transfusion equipment, blood management, total knee arthroplasty, postoperative complication

Introduction

Total knee arthroplasty is one of the most effective treatments to stage III and IV knee osteoarthritis and rheumatoid arthritis. Blood loss intra operatively and in the post-operative period are detrimental for medical reasons and may cause

local wound problems and hamper the optimal knee rehabilitation. There are racial variations and a host of patient factors that may impact the blood loss. It is generally considered that coagulation functions of Mongoloid people are relatively weaker than those of Caucasian and Negroid people [1, 2]. At the same time, elderly

Mongoloid females have a lower body mass index and surface area, and relatively small blood loss in actual volume may actually prove to be a great loss in terms of the overall percentage of the blood volume. Furthermore, after major orthopedic surgery, especially joint replacement, the probability of VTE (venous thrombus embolism) is also very high. Therefore, perioperative management of hemorrhage and coagulation is an important aspect in the post-operative management of total knee replacement patients. Proper monitoring and appropriate therapy establishment helps in reducing complications and improving outcomes.

One important aspect of management is an improved drainage method. Autologous transfusion drainage has been widely used in clinical practice and proved to have the advantages of higher post-operative hemoglobin levels and lesser total blood loss, even leading to better post-operative function and shorter hospital stays [3]. Some researchers advocate methods like delayed drain clamping, which may lead to some difficult complications, such as intra-articular hematoma and synarthrophysis [4, 5]. Many researchers have thus advocated for the use of simple drains for the wounds [6].

A concomitant line of therapy that is advocated is the use of hemostatic drugs. In TKA surgery, perioperative anticoagulation is widely recognized, and the guideline has changed several times. The newest guideline was laid down at ACCP-9 [7]. In 1995, Hiippala in his initial report about the use of hemostatic agent showed that giving 15 mg/kg of tranexamic acid (TXA) 2-5 minutes before releasing the tourniquet could reduce post-operative blood loss [8]. Following this, many researcher conducted similar clinical studies on the benefits and complications of TXA. A meta-analysis done by Alshryda et al. revealed that TXA could reduce blood loss and blood transfusion probability without increasing the VTE and PE (pulmonary embolism) occurrence [9]. Some Japanese researchers injected epinephrine solution into the articular cavity, which proved to be able to reduce bleeding. However, this has shown to cause skin edge necrosis and wound-related complications [5]. In order to evaluate these multiple modalities and their combined effects in TKA, we reviewed our patient data from the last 5

years. With changes in health care policy, our treatment also has changed several times. For reviewing these data, we set up a retrospective comparative trial using two common modalities-TXA injection and autologous blood transfusion either alone or in combination. While most studies so far were concerned with the dosage and mode of delivery of these modalities [10-12], our research is different and adds to the knowledge base as the outcomes of two modalities in isolation or in combination have not been frequently reported.

Materials and methods

General background

In total, 392 patients were enrolled in this retrospective comparative study (279 females, 113 males). These patients were divided into four groups. The first group comprised patients who had received neither autologous transfusion nor TXA (Group A); the second group received autologous blood transfusion only (Group B); the third group received a combined management with TXA injection and autologous blood transfusion (Group C); the fourth group received TXA without any auto transfusion (Group D). This was a retrospective comparative study. This was facilitated by the fact that the department recommended routine administration of TXA after July 2013. On the other hand, the practice of using autologous transfusion drainage was discontinued periodically from Jan 2012 to Mar 2012, Oct 2012 to Feb 2013, and Nov 2013 to Mar 2014. The patients who had severe vascular diseases, any signs of an ongoing infective process, and uncontrolled fasting blood glucose levels beyond 8 mmol/L were excluded from the trial. Patients who received intraoperative allogenic blood transfusion were also excluded from this study.

Operation procedure: Group A had 87 patients; Group B, 109; Group C, 133; and Group D, 63. All the knee replacement operations were performed by four senior surgeons in our medical center (XL Zhang, YS Chen, Y Jiang, and Q Wang). Two types of prostheses were used during the study: Genesis® (Smith & Nephew; n=209) and NexGen® (Zimmer; n=183). The medial para-patellar approach was used with midline incision. The patella was lifted off to the lateral side. A tourniquet was used during surgery, and TXA was administered in a dose of 10

Table 1. Basic population information of all groups

Variable	Group A	Group B	Group C	Group D
Mean age, years	64.9±9.56	65.3±8.89	64.9±11	64.6±10
Mean BMI	26.5±2.98	25.3±2.17	23.5±2.64	26.2±2.25
Sex (number, percent)	Female: 66, 75.8% Male: 21, 33.3%	Female: 82, 75.2% Male: 27, 24.8%	Female: 93, 69.9% Male: 40, 30.1%	Female: 38, 60.3% Male: 25, 39.7%
Primary disease (number, percent)	OA: 53, 60.1% RA: 34, 39.9%	OA: 62, 56.9% RA: 47, 43.1%	OA: 69, 51.9% RA: 64, 48.1%	OA: 39, 61.9% RA: 24, 38.1%
ASA Score (number, percent)	1: 16, 18.4% 2: 57, 65.5% 3: 14, 16.1%	1: 17, 15.6% 2: 76, 69.7% 3: 16, 14.7%	1: 30, 22.6% 2: 80, 60.1% 3: 23, 17.3%	1: 6, 9.5% 2: 48, 76.2% 3: 9, 14.3%

Table 2. Postoperative rehabilitation parameters of all groups

Variable	Group A	Group B	Group C	Group D
Apparent blood loss (mL) [☆]	318.7±38.0	368.1±60.3	311.5±46.2	268.4±30.9
Hidden blood loss (mL) ^Δ	762.1±160.9	762.3±187.8	716.6±170.2	668.8±162.1
Allogenic blood transfusion rate	5/87	4/109	5/128	2/61
DVT/PE	2/87	3/109	3/133	1/63
Skin edge necrosis	4/87	2/109	6/133	3/63
Ratio post/pre operation of circumference of knee [□]	1.21±0.11	1.18±0.09	1.15±0.12	1.18±0.093
ROM score [○]	2.48±0.71	2.70±0.55	2.61±0.67	2.60±0.68

Remarks: Statistically significant outcomes in **Table 2**. ☆: A, B, P<0.01, A-D, P<0.01, C, D, P<0.01. Δ: A-D, P<0.01, B, C, P=0.04. □: A, B, P=0.02. ○: A, B, P=0.02.

mg/kg once 3-5 minutes before releasing the tourniquet. The wound was wrapped with an elastic bandage, and the drainage was connected to the autologous transfusion drainage (ConstaVac™, stryker) or a negative pressure absorbing ball. Since most blood loss occurred in the first 12 hours after surgery, the auto-transfusion time was set at 12 hours after operation [10]. After 12 hours, if the drainage recycled more than 100 mL blood, then an auto-transfusion was done. Otherwise, the drainage was discarded. After 48 hours, the drain was removed, and patients were allowed to perform functional exercises under the supervision of the physiotherapy team. Oral anticoagulant drugs were given from the day after operation and continued for 3 weeks post-surgery.

As a retrospective study, our institutional review board granted ethical immunity to our follow-up.

Observed events

Calculating the apparent blood loss: With the intraoperative use of a tourniquet, we assume that, during surgery, blood loss was negligible.

Also, no allogeneic blood was admitted during surgery. The blood collected in the drainage system in first 48 hours minus the auto transfused amounts was considered the apparent blood loss. Through routine blood tests, pre/post-operative hemoglobin (Hb) and Hct were recorded for all cases. *Hidden blood loss calculation* was done using the Gross formula based on pre and post-operative Hb and Hct [11]. If the post-operative Hb was lower than 90 g/L and symptoms of low blood volume or any symptoms suggesting hypovolemia were recorded in the perioperative period, then the patient was transfused 2-6 U of allogeneic blood. In all these cases, hidden blood loss was calculated before transfusion regardless of time.

Clinical examination

Lower limb swelling: The circumference of the knee through the superior patellar pole was measured prior to the surgery and 2 days after the surgery.

DVT (deep vein thrombosis) occurrence: DVT was excluded by Doppler B-ultrasound 2 days after surgery or in the 2 weeks of follow-up for

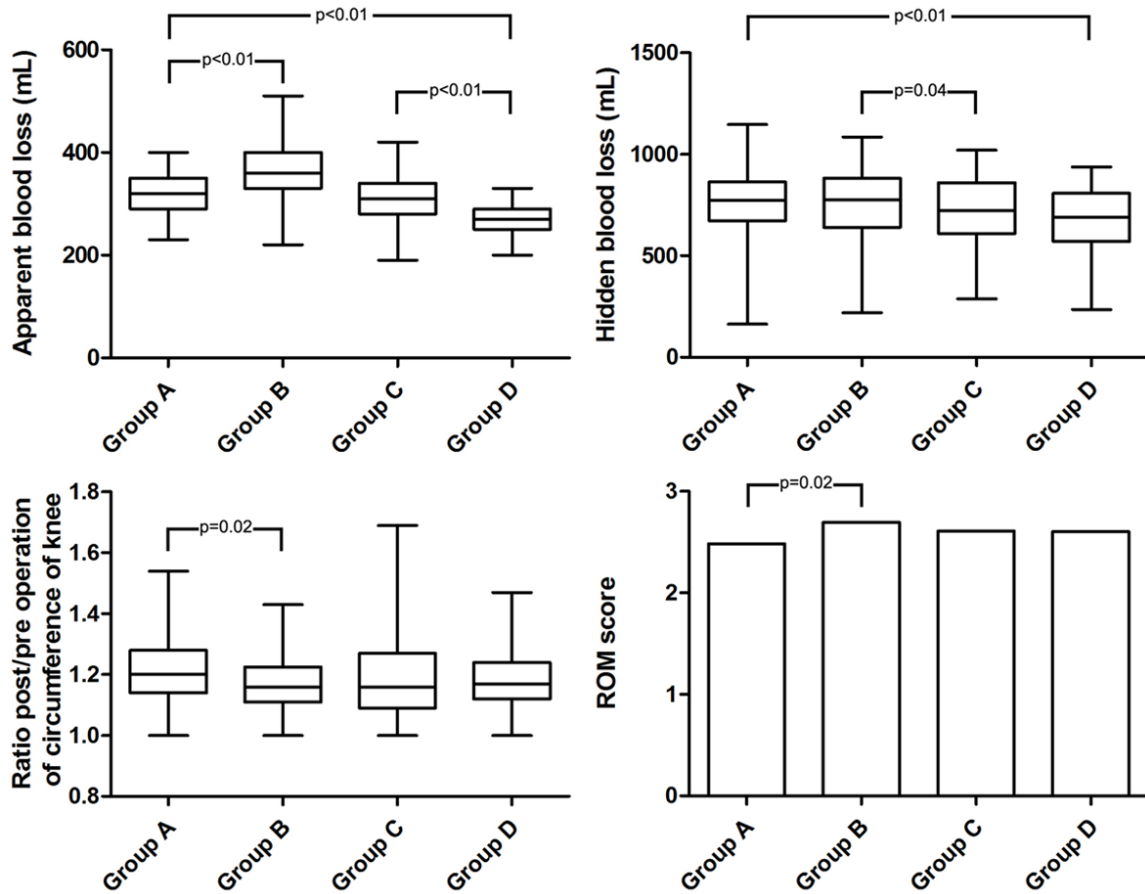


Figure 1. Postoperative rehabilitation parameters of all groups.

those patients with a swollen lower extremity. ROM (range of motion): ROM was examined at the 2-week follow-up. In order to standardize our comparisons, we defined that the full score of ROM was 3, and patients who could not make 0° extension or 90° flexion would be deducted 1 point each. A ROM less than 30° was given a score of 0.

Skin edge necrosis: Skin edge necrosis was examined when the stitches were removed at the 2-week follow-up.

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). The mean values between the four subgroups were compared using one-way analysis of variance (ANOVA) (for results described in subsections “Apparent blood loss”, “Hidden blood loss”, “Ratio post/pre operation of circumference of knee”, and “ROM score”). The ratios between all subgroups were compared using the chi-square test (for results described in subsec-

tions “Allogenic blood transfusion rate”, “DVT/PE”, and “Skin edge necrosis”).

Results

There were no significant differences in age, weight, height, sex, ASA, pre-operative Hb, physical status between the four groups (Table 1).

Comparison of blood loss

Apparent blood loss: The apparent blood losses of each group are shown in Table 2 and Figure 1. Compared to Group A, Group B had significantly greater blood loss ($P < 0.01$). The apparent blood loss in Group D was significantly less than that in Group A ($P < 0.01$) and Group C ($P < 0.01$). These data showed that autologous transfusion drainage increased the apparent blood loss irrespective of whether TXA was used, whereas TXA could reduce the apparent blood loss.

Hidden blood loss: The hidden blood losses of each group are shown in **Table 2** and **Figure 1**. The hidden blood loss in the Group A was significantly greater than that in Group D ($P<0.01$), and that in Group B was significantly higher than that in Group C ($P=0.04$). There were no significant differences in the hidden blood losses of Group A and Group B ($P=0.993$), Group C and Group D ($P=0.07$), and Group A and Group C ($P=0.056$). Use of TXA could reduce hidden blood loss significantly, whereas autologous transfusion drainage had no effect on hidden blood loss.

Comparison of complications

Allogenic blood transfusion rate: There was no significant difference between the four groups (Group A 5.75%, Group B 3.67%, Group C 3.76%, and Group D 3.17%) in the number of patients who required allogenic blood transfusion. In absolute terms, even though not statistically significant, the use of TXA and autologous transfusion drainage both reduced the allogenic blood transfusion rate. The combined usage had no statistically significant advantage though. On the other hand, considering the number of units that had to be transfused (allogenic blood transfusion) per patient, combined usage showed a statistically significant advantage, while a single use of both autologous transfusion drainage and TXA showed superiority to group A (Group A 3.2 unit/p, Group B 2.75 unit/p, Group C 1.8 unit/p, and Group D 2 unit/p). This sample was too small for statistical analysis.

DVT/PE: There was no significant difference between the four groups (Group A 2.30%, Group B 2.75%, Group C 2.56%, and Group D 1.59%). Use of TXA and autologous transfusion drainage did not increase the risk of DVT/PE after TKA surgery.

Skin edge necrosis: Statistically, there was no significant difference between the four groups (Group A 2.30%, Group B 1.83%, Group C 4.51%, and Group D 4.76%). Use of TXA and autologous transfusion drainage both made no difference in the skin edge necrosis occurrence. In the statistical analysis, autologous transfusion drainage could reduce the occurrence of skin edge necrosis. In contrast, TXA might increase the occurrence of skin edge necrosis.

Functional recovery

Swelling: The post/pre-operative knee circumference ratios in each group are shown in **Table 2** and **Figure 1**. There was a significant difference between the circumferences of knees of Groups A and B ($P=0.02$). However, there was no significant difference between the ratios in Groups A and D ($P=0.09$). Use of autologous transfusion drainage could help reduce swelling, whereas use of TXA did not have any effect.

ROM: The ROM of each group is shown in **Table 2** and **Figure 1**. There was a significant difference between Group A and Group B ($P=0.02$). However, there were no statistically significant differences between Groups A and D ($P=0.266$) and Groups C and D ($P=0.95$). When used alone, autologous transfusion drainage could enhance ROM after TKA surgery, whereas TXA alone did not have any effect.

Discussion

Blood loss-apparent and hidden-is considered a major problem during orthopedic surgeries, especially in major orthopedic operations like TKA. Owing to the usage of a tourniquet, the intraoperative blood loss in TKA is negligible. However, once the tourniquet is released, there is frequently a significant blood loss with some patients requiring allogenic transfusion [12] or developing a knee hematoma or persistent drainage that requires frequent dressing changes with consequent complications. Allogenic blood transfusions have their own set of risks including transfusion-associated infections, hemolytic transfusion reactions, and blood transmitted diseases [12]. Much research has been done to improve perioperative blood management and reduce the use of ABTs during TKA surgery. In view of these studies, many research and clinical studies are being done to find ways to reduce the blood loss post operation and improve the outcomes following knee replacement.

In our study, we evaluated two critical modifiers of blood loss-TXA and an autologous blood transfusion system individually as well as in combination. To the best of our knowledge, this was the first study that combined these two treatments together in TKA surgery. This study revealed that the use of the autologous-transfusion system could lead to an increase in the

apparent blood loss but had no influence on hidden blood loss or allogenic blood transfusion rates. Interestingly, this result is consistent with that of Cip and Martin who published similar findings about the use of autologous blood transfusion systems [13]. We also proved that in a clinical setting the use of TXA potentially decreases blood loss both apparent as well as the occult. Because of the usage of tourniquet and sample size, TXA might lower the ABT rate but this was only numerical and not statistically significant. Oddly, while using TXA, auto-transfusion might numerically increase the ABT rate, which we believed was influenced by vacuum activity, and auto-transfusion was done only when the actual drainage was over 100 mL.

When the various complications and their rates were evaluated, we found that the use of auto-transfusion could reduce skin edge necrosis and swelling and help in the functional recovery. However, the use of TXA had none of these advantages, though it also did not have any adverse effects. These advantages were also reported by Omonbude who suggested that a vacuum drain could reduce hematoma formation [4]. Also, the postoperative OKS in people in whom the closed suction drain was used was shown to be higher than in the no drain group [6]. Our results showed that neither TXA nor auto-transfusion would increase the infection rate unlike the results shown by some researcher who suggested that the autologous blood transfusion system may serve as a conduit for a retrograde infection traveling up the system, leading to prosthesis infection. On the contrary, ABT brought more infection risk than autologous blood transfusion [14, 15].

Much research has been done on the perioperative use of TXA. To our knowledge, all these studies support using TXA to reduce blood loss and the ABT rate in knee replacement surgery [9, 16-22]. Our study too reported similar findings with the use of TXA. While the optimal timing, dose, duration of treatment, and route of administration of TXA still remain controversial, our study does confirm its benefit. On the issue of TXA increasing the rates of the venous thrombo embolism, this is a highly controversial issue with two conflicting results being published in the same issue of a journal [23, 24]. Until now no research has provided concrete evidence that using TXA might increase the

exposure of DVT. In our four groups, the DVT rates were all below 3% and showed no significant differences, consistent with the universally agreed finding that the use of TXA does not increase VTE rates.

Unlike that of TXA, the therapeutic effect of autologous blood transfusion has always been debatable. There are various types and makes of autologous transfusion equipment, which can roughly be divided into two categories: washed shed blood (WSB) and unwashed shed blood (USB) transfusion equipment. USB was launched earlier but was shown to have significant problems and complication rates. Some anesthesiologists reported that the quality of USB was variable, but mostly bad and might lead to serious complications because of some soluble contaminants. The recommendations from studies were to abandon its use in both the intra and post-operative periods [25]. The autologous transfusion drainage (ConstaVac™, stryker) used in our study was USB, for which to date, no serious complications as mentioned by Hansen et al have been shown. The same results came from a meta-analysis by other group of orthopedic surgeons [26]. In our case, unlike with the use of intraoperative autologous transfusion, the wound was cleaned by a pulse irrigator before closure, which could get rid of impurities. This might explain why unwashed blood was of satisfactory quality and safe enough for reinfusion.

Many researchers agreed that auto-transfusion could reduce ABT exposure, skin edge necrosis, and infection [14, 15, 24, 27, 28], but recently, a report published on CORR concluded that the use of an auto transfusion system did not reduce the rate of postoperative ABTs [13]. They also reviewed some previous articles and found that most of them recorded no difference in administered ABT units per patient or even did not report these data [29-33]. These results have been shown to corroborate the findings of a meta-analysis as well [34]. Our study results concurred with these finding and demonstrated that use of auto-transfusion equipment would increase the apparent blood loss and not help in reducing total blood loss and ABT rate. Moreover, when used in combination with TXA, auto-transfusion equipment might paradoxically increase total blood loss by a small amount. This outcome might be caused by the vacuum

activity, which may be responsible for additional blood loss [35].

From a Pubmed search for auto transfusion and TXA usage, we found that various authors had customized their treatment protocol in order to minimize the intra and perioperative blood loss. A few studies also derived a formula and protocols for making the decision on the auto transfusion system usage. We believe that individual blood management, although effective, can result in lot of confusion. In a planned pre-operative autologous blood transfusion protocol, the blood needs to be collected 8 weeks before surgery and might lead to mistakes especially in centers where the patient load is high [13]. Using a formula to decide whether or not to use the collector system and for whom this is a feasible solution is a good way to formulate a transfusion strategy; however, it might lead to some unnecessary bandwagon effects in elderly Chinese patients [36]. Since TXA has been shown to potentially replace the function of auto-transfusion, we thought of combining TXA with simple closed vacuum drainage, which has all the positive effects of autologous blood transfusion except blood recycling. We deduced that accompanied with TXA, use of simple vacuum drainage instead of autologous blood transfusion might have a similar therapeutic effect while decreasing significant expenses (rough costs in our hospital: TXA \$20; autologous blood transfusion \$100; simple vacuum drainage \$5/day).

There were several limitations to our study. As a retrospective study, we could not enroll all the patients who underwent TKR, and this may have caused the study to become biased. Additionally, there could be a variety of confounding factors; one of the most important variates was indoor temperature, and a lower temperature that may lead to relatively lesser blood loss [37]. Another variate was that the prostheses used among groups were not exactly the same. Different groups underwent surgeries at different temperatures with different prostheses, and outcomes may have thus been influenced by various confounding factors. We thought this might have some impact on our results (all the wards were equipped with central air conditioning system, so there was no big change in indoor temperature). Another bias was caused by racial factors and sample size. In our study, all patients are Mongoloid, and

this population is known to have a lower incidence of post-operative DVT/PE [2]. In addition, the sample size was relatively small. Thus, the risk of DVT was not evaluated intensively. However, we do believe that the study has brought out some interesting observations that may impact clinical practice; also, it lays a foundation for future prospective and randomized controlled trials.

Conclusion

In our research, we proved that using TXA could reduce blood loss and the ABT rate, while using auto-transfusion could increase apparent blood loss without having an influence on the ABT rate. We also found out that autologous blood transfusion could increase functional recovery and reduce complications. Collating all our findings, we can conclude that using TXA and autologous transfusion may be an effective way to manage blood loss in the postoperative period in patients who undergo total knee replacement. Used in conjunction, the two methods decrease over all blood loss and complication rates and improve patient outcomes.

Disclosure of conflict of interest

None.

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