Acta Orthop. Belg., 2021, **87**, 697-703

ORIGINAL STUDY

Should tranexamic acid be used for 3 days after total knee replacement? A randomized study in 250 patients

Nilen Shah, Vatsal Khetan, Hari Sivanadan

From the Smt S R Mehta and Sir K P Cardiac Institute, Mumbai, India

The aim is to study whether a 3 day course of Tranexamic acid (TXA) is more effective in reducing blood loss following a TKR than a 1 day course. 250 patients were prospectively randomised into Group A (n=138; Perioperative and additional oral TXA for two days) and Group B (n=112; only perioperative TXA). Total Blood loss was calculated by the Haemoglobin (Hb) loss method at 4 days and compared in both groups using Mann Whitney test. The mean peri-operative blood loss in group A was 631.69 ± 264.99 ml as compared to 685.55 ± 239.033 ml in group B (p=0.0434). Use of TXA for 3 days following a TKR can be more effective in reducing blood loss.

Keywords: Tranexamic acid; total knee replacement; routes; duration.

INTRODUCTION

True blood loss following a TKR is the sum of the visible and hidden blood loss. The visible blood loss consists of the loss measured intra-operatively and the post-operative drainage. The hidden blood loss consists of bleeding into the joint and other tissues and RBC loss due to haemolysis *(1-3)*. Chen et al showed that the maximum blood loss can be estimated postoperatively on day 4 *(4)* and Newman et al showed that the hidden blood loss can exceed the visible blood loss *(5)*.Various published articles have looked at perioperative blood loss following a TKR in different ways. These articles have been included in a recent major meta-analysis *(6)*.

Various studies have shown *(7)* that the increased fibrinolysis after TKR lasts for 1 day and peaks within a few hours after TKR especially when a tourniquet is used. As TXA is an antifibrinolytic agent, it is traditionally used for 1 day to counter the hyperfibrinolysis induced by surgery and tourniquet.

The half-life of TXA is approximately 2 hours *(8)*. In surgical specialities, where there is a risk of continued bleeding, TXA has been used for multiple days to reduce bleeding e.g. for 4 to 5 days in reducing menorrhagia *(9)* in prostate surgery for up to 7 days or till macroscopic haematuria is resolved *(10)* and in cases of hepatic resection for up to 3 days *(11)*.

The use of TXA to reduce blood loss in joint replacement surgeries was first demonstrated in 1995-96 *(12-14)*. Currently, TXA is used commonly for 1 day either as a single dose or in divided doses *(6)*. As the total blood loss following a TKR does not manifest till 4 days and the half-life of TXA is a few hours, the question arises as to whether a

Level of Evidence- III

The Authors declare no conflicts of interest.
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

■ Nilen Shah
■ Vatsal Khetan
■ Hari Sivanadan
Smt S R Mehta and Sir K P Cardiac Institute, Mumbai, India.
Correspondence : Dr Vatsal Khetan, 9 Oakwood Hall Drive, Moorgate, Rotherham, South Yorkshire S603AQ.
Email : drvatsalortho2015@gmail.com

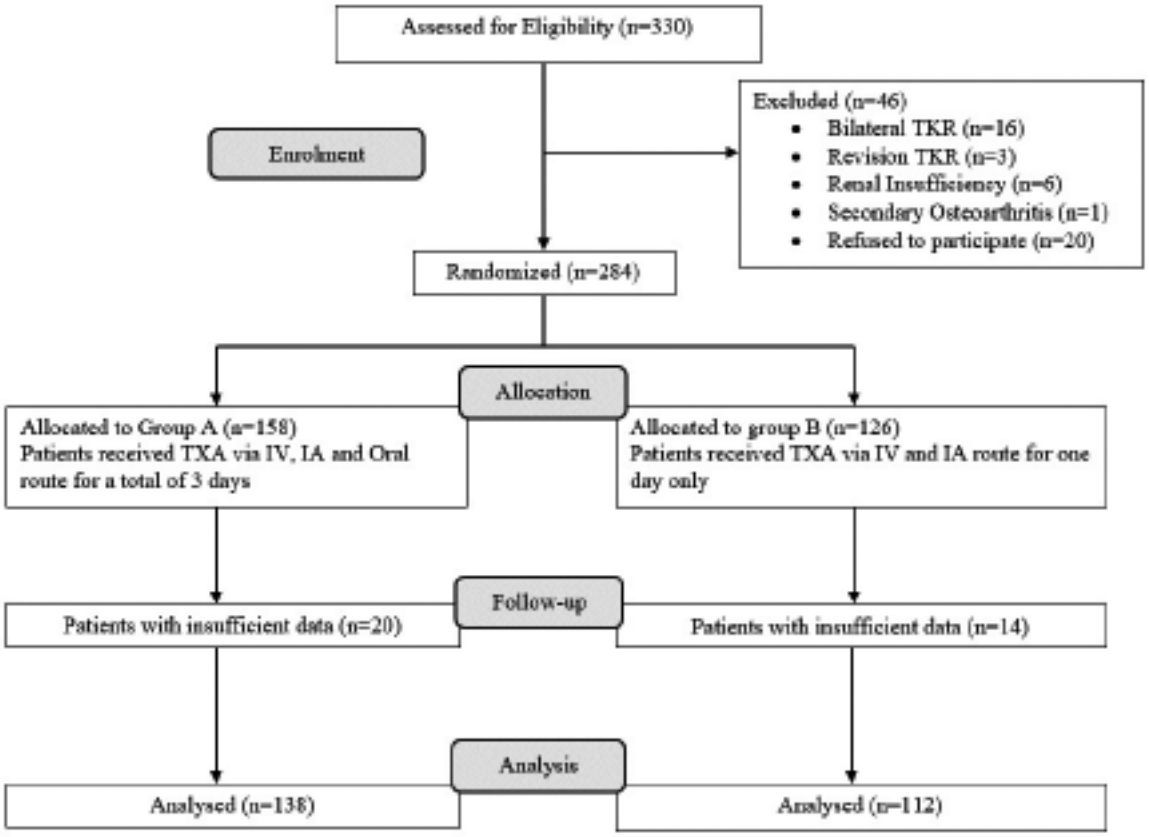


Figure 1. — Flowchart depicting study design

multiple-days therapy of TXA can be more effective than a single-day treatment and yet be safe.

The purpose of this study was to compare, in a randomised trial, the blood loss following TKR in two groups of patients: those that received TXA only on the operative day and those that received TXA for three days after TKR. We hypothesized that the blood loss in both the regimes would be the same.

MATERIALS AND METHOD

A total of 330 patients were operated between September and December 2018 out of which consecutive 284 patients planned for unilateral TKR were selected for the study (Figure 1). The patients were randomised by place as we operated in different hospitals. All patients in 1 Hospital (A) received oral Tranexamic acid for 3 days and the patients in other Hospital (B) did not.

We recorded the demographic and medical details of all the patients. We excluded patients with Bilateral TKR (n=16), Revision TKR (n=3) and previously operated patients with secondary osteoarthritis (n=1) to avoid confounding factors.

Patients with renal compromise (n=6) were also excluded. The patients who refused to participate in the study (n=20) were also excluded. This left 284 patients who were enrolled in the study.

Of these, 34 patients had incomplete data which left a total of 250 patients who were included in the study.

An a-priori power analysis (G*Power 3.1; two-tailed, α = 0.5) with an expected high correlation from a previous study *(15,16)* determined a sample size of 226 with power of 0.80.

Technique and use of tranexamic acid

All surgeries were performed by the senior author using a standard mini-subvastus approach

(17) under spinal anaesthesia (heavy sensorcaine without additives - 2.6 ml to 3.2 ml). Adductor Canal Block (ACB) was utilized for post-operative pain relief. 30 mL of saline with adrenaline (1: 300,000) was infiltrated into the skin, subcutaneous tissues, and joint capsule before making the surgical in-cision. Standard surgical techniques were used for intraoperative haemostasis. Tourniquet was not applied. No surgical drains were used. Post-operatively, we used local infiltrative analgesia (LIA) which was a mixture of Ropivacaine 0.2 % (20 ml), Fentanyl (2ml; 100 mcg), Cefuroxime 500 mg and Kenacort 40 mg (steroid).

3 doses of IV Tranexamic acid were administered to all - 15 mg/kg TXA preoperatively 30 minutes before incision and 10 mg/kg TXA at 3 and 6 hrs postoperatively. After final implantation of the components and prior to wound closure, a sponge soaked in TXA and isotonic saline solution (1g TXA in 100ml NS) was applied for five minutes *(18)* (intra-articular TXA) in all patients. The study group A was administered 1 g oral TXA (500 mg bd) for the next two days.

The knee was kept in 40 degrees flexion post-operatively for the first four hours after surgery *(19)*.

Below-knee TED stockings and chemoprophylaxis for DVT was used for all. Chemoprophylaxis consisted of a subcutaneous (SC) weight adjusted dose of low molecular weight heparin (LMWH) (inj. Enoxaparin) 12 hours postoperatively followed by oral tablets for 6 weeks (a Factor Xa inhibitor (Rivaroxaban 10 mg) for two weeks followed by tablet Aspirin 75 mg for four weeks.)

If the patients were on anti-platelet therapy preoperatively instead of Rivaroxaban their usual antiplatelet therapy was restarted post-operatively.

Postoperatively, mobilization was early and aggressive. Static quadriceps exercises, straight leg raising exercises and range of movement (ROM) exercises were started from day zero. Patients were encouraged to get out of bed and walk as tolerated after the first 6 hours.

Patients were examined daily for any clinical symptoms and signs of DVT whilst in Hospital. All surgical and medical adverse events and thromboembolic events occurring (if any) during the first six weeks after surgery were recorded at the time of the follow-up.

Blood was transfused if Hb dropped below 7.5 gm/dl and if there were systemic signs of anemia *(20)*.

The patient's blood volume (PBV) was calculated using the formula of Nadler and colleagues *(21)*.

$PBV = k_1 \times height^3\ (m^3) + k_2 \times weight\ (kg) + k_3$ where $k_1 = 0.3669$, $k_2 = 0.03219$, $k_3 = 0.6041$ for men and $k_1 = 0.3561$, $k_2 = 0.03308$, $k_3 = 0.1833$ for women.

Multiplying the PBV by the haematocrit will give the total red cell volume. Any change in red cell volume can therefore be calculated from the change in haematocrit *(22)*.

Total red blood cell (RBC) volume loss = PBV x (Hctpreop - Hctpostop)

Using this formula, all patients' blood volume and peri-operative blood loss was calculated by the haemoglobin balance method indirectly *(23)*.

The Statistical analysis was performed using SPSS software (v24.0). The continuous data with normal distribution were expressed as means ± standard deviation and non-normal distribution as media (range). A chi-square test was used for the comparison of nominal data and an unpaired Student's t-test was used for comparisons of continuous data, when the data appeared to be normally distributed. The Mann-Whitney U test was used for data, where the assumption of normality did not hold. Testing of normality was done using Shapiro-Wilk Test. Differences at a level of $P<0.05$ were considered statistically significant.

RESULTS

The demographic parameters in both groups viz: age, height, weight, male: female ratio and BMI are presented in Table I and are similar in both the groups.

The comorbidities of the patients are presented in Table II.

The mean perioperative blood loss in Group A was 631.69 ± 264.99 ml as compared to 685.55 ± 239.033 ml in Group B($p<0.05$). This data is tabulated in Table III and graphically presented in Graph 1. The mean reduction in haemoglobin level

Table I. — Patient demographic characteristics of both study groups (the data is presented in Mean ± SD or Number)

Parameters	Group A (N=138)	Group B (112)	Statistical Test	p-Value
Sex (F/M)	103/35	94/18	χ^2	0.074
Age (Years)	67.39 ± 8.39	68.18 ± 7.47	t-test	0.434
Weight (kg)	72.86 ± 11.95	72.28 ± 12.31	t-test	0.706
Height (cm)	153.44 ± 9.43	156.10 ± 7.73	t-test	0.020
BMI (kg/m^2)	31.32 ± 7.37	29.74 ± 4.8	t-test	0.052

was 1.9 ± 0.8 gm/dl in group A compared to 2.1 ± 0.7 gm/dl in group B.($p<0.05$). Thus, there is a significant difference in blood loss between the two groups in favour of Group A thus disproving the Null Hypothesis.

Nine patients in group A and six patients in group B had a history of a previous thrombotic event and were on antiplatelet therapy (aspirin and/or clopidogrel). 75 mg of Aspirin was continued perioperatively but the clopidogrel was stopped a week prior to surgery and restarted on the first postoperative day. The mean blood loss in patients on antiplatelet therapy was 573.58 ± 212.78 ml in Group A against 948.13 ± 397.94 ml in Group B, which was found to be statistically significant ($p<0.05$).

None of the patients developed DVT or any other thromboembolic complication.

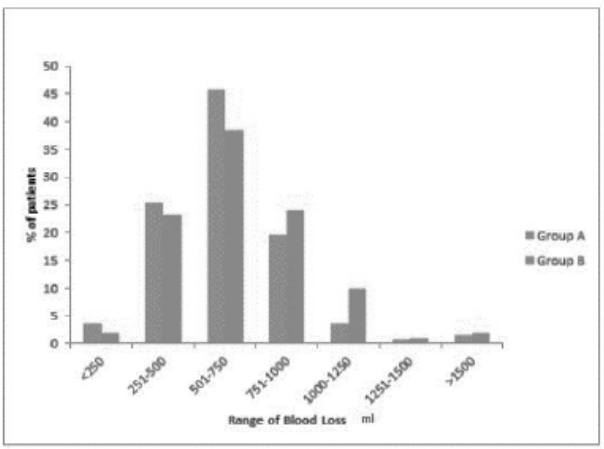
One patient in group A and two in group B were transfused with one unit of packed red cells.

DISCUSSION

Our results show that the use of tranexamic acid for three days following a TKR can be more effective in reducing the perioperative blood loss as compared to using it only for 1 day. Despite the fact that the maximum blood loss after TKR is evident on the 4th day postoperatively *(4)* and that the half-

Table II. — Comorbidities in patients of both groups

Comorbidity	Number of patients in Group A	Number of patients in Group B
Diabetes mellitus (DM)	27	22
Hypertension (HTN)	41	28
Dyslipidemia	4	4
Hypothyroidism	10	5
Parkinson's disease	0	1



Graph 1. — Comparison of blood loss in both groups

Table III. — Analysis of blood loss data (the above data is presented in Mean ± SD or Number)

Parameters	Group A(n=138)	Group B(n=112)	Statistical Test	p-Value
Total blood loss (mL)	631.69 ± 264.99	685.55 ± 239.033	Mann-Whitney U Test	0.043
Haemoglobin (Hb) difference (gm/dl)	1.93 ± 0.84	2.10 ± 0.69	Mann-Whitney U Test	0.016

life of TXA is only a few hours *(8)*,surprisingly, only a few studies in the current literature *(24)* have used TXA beyond the first day.

TXA(1-(aminomethyl)-cyclohexane-4-carboxylic acid or AMCHA) was first described in 1962 *(25)* in Japanese literature as a more powerful alternative to Epsilon Amino Caproic Acid (EACA). Its use in elective joint replacement surgeries was described in 1995. The reason for this delay could be the mistaken belief that TXA is a pro-thrombotic agent, and its use would lead to a further increase to the already higher risk of postoperative thromboembolism. Recent studies have unequivocally confirmed that the use of TXA does not increase thromboembolism *(26)*.

Currently, there is a consensus that TXA should be used in TKR, but the timing, dosage, duration, route and combinations, if any, of administration of TXA differ in various published studies. We believe that we need to find the most effective, safest and the most user friendly regime of tranexamic acid for perioperative use in TKR. Recent recommendations suggest that a single, adequate IV, oral or an intra-articular dose of TXA is sufficient to reduce the perioperative blood loss and thereby, the transfusion requirements post TKR *(6)*.However, it is acknowledged that there are different conclusions of various studies and different articles suggest a higher dose *(27)* or multiple doses *(28)* of TXA post TKR and that good quality, high-powered research studies may still be lacking.

The reasons for differing opinions in literature are manifold because the end point of different studies *(6)* have been different; viz visible blood loss, drain output, total blood loss on different postoperative days, Hb drop on different postoperative days or transfusion requirements post TKR. The transfusion guidelines in different articles are also varied, with the more recent studies suggesting that a postoperative Hb of 7 gm% *(29)*, or even as low as 6 gm% *(30)*, may be tolerated; in healthy individuals. Obviously if the transfusion trigger in different studies is different, there may be differing recommendations regarding tranexamic acid use in articles that focus on transfusion requirements post TKR.

Surgery activates fibrinolysis and it peaks in the first 6 hours *(31,32)* after surgery and lasts for up to 24 hours. The use of an intraoperative tourniquet will also increase the fibrinolysis which typically lasts for the first 6 hours after surgery. The fact that hidden blood loss continues to accumulate until 4 days after surgery would imply that some degree of fibrinolysis must be occurring even after the first day and would justify a longer duration of TXA treatment. Hence, some authors *(24)* have used IV TXA for 3 days after TKR. However, in that study, Janssen et al compared only the visible blood loss in patients who received TXA for 3 days to a control group of patients who did not receive TXA perioperatively and concluded that TXA is useful to reduce perioperative blood loss.

Oral TXA tablets ingested 2 hours prior to surgery have worked in several studies *(33,34)* but will surely depend on the effective absorption from the GI tract to reach an effective intra-vascular dose to inhibit fibrinolysis. It has been shown that for TXA to be maximally effective, an adequate circulating blood level of tranexamic acid needs to be achieved prior to the occurrence of fibrinolysis. This can be achieved most reliably by an intravenous injection. A single, pre-incision intravenous high dose TXA (30 mg/kg) has been recommended by Hourlier et al. *(27)*This can be effective, but the higher single dose has not been used in other recent studies probably due to the fear of toxicity. A recent study *(35)* suggests that dividing the pre-op dose of 30 mg/kg to two doses of 15 mg/kg separated by 3 hours is more effective than a single dose. Maniar et al have suggested that a 3 dose regime is the most effective *(28)*. The addition of intra-articular TXA to the regime of IV TXA seems to be an elegant method for reducing the local activation of fibrinolysis and increasing the local thrombus production without increasing any systemic side effects. This is the reason why several articles that use local TXA have stated that they have found reduced postoperative swelling in cases where local TXA has been used *(36)*. We also added local tranexamic acid to the IV regime and have shared our results *(15)* which showed that addition of intra articular TXA to the IV route can reduce the blood loss more than using it only systemically. Others *(37)* have also found a synergistic effect but

some authors *(38)* have not found a synergistic effect in navigated TKR.

It has been shown in a study by Sabbag et al. *(26)* that it is safe to give TXA to patients who are on antiplatelet medicines. Similar to their study, we also found that not only is it safe to administer TXA in patients who are receiving antiplatelet medication, but TXA helps in reducing blood loss in such patients. We also found that the blood conserving effect of a 3 day course of TXA, is even more marked in these cases. However, this result needs to be reproduced and confirmed in a study involving a larger number of patients.

The trend of fast track Knee Replacements and Day care surgery implies that IV medications beyond the first few hours after surgery may not be practical. Hence, our regime of 3 doses of IV TXA on the day of the surgery (plus IA), combined with two additional days of oral TXA, fits in nicely with fast track or day care surgery. Performing Hb estimations on the fourth day of surgery may be impractical in some centres as most patients are at home by this time or much before this. However, it is of critical value to determine the total blood loss after the surgery and this may help surgeons to diagnose and treat postoperative anaemia.

The limitations of our study are: 1) all surgeries were performed by a single high volume surgeon using the mini-subvastus approach, 2) all surgeries were performed without using a tourniquet, 3) no biochemical assays were utilised to detect the degree of fibrinolysis and 4) we did not perform routine USG or venography to screen for DVT.

The strengths of our study are that it is a large study that looks at the total blood loss on the 4th day post TKR and that all the patients have been operated and managed by an identical technique. The study shows that there is a synergistic effect of TXA by combining the different routes without increasing the complications. However, further research needs to be done at other centres to confirm these results.

CONCLUSION

The use of tranexamic acid for 3 days post TKR is more effective than a single day use, in reducing the blood loss after TKR, without increasing the complications.

REFERENCES

1. **Sehat KR, Evans R, Newman JH.** How much blood is really lost in total knee arthroplasty? *The Knee*. 2000; 7(3): 151-5.
2. **Pattison E, Protheroe K, Pringle RM, Kennedy AC, Dick WC.** Reduction in haemoglobin after knee joint surgery. *Ann Rheum Dis*. 1973; 32(6): 582-4.
3. **Li B, Wen Y, Wu H, Qian Q, Lin X, Zhao H.** The effect of tourniquet use on hidden blood loss in total knee arthroplasty. *Int Orthop*. 2009; 33(5): 1263-8.
4. **Chen Z-Y, Wu H-Z, Zhu P, Feng X-B.** Postoperative Changes in Hemoglobin and Hematocrit in Patients Undergoing Primary Total Hip and Knee Arthroplasty. *Chin Med J* (Engl). 2015; 128(14): 1977-9.
5. **Newman JH, Bowers M, Murphy J.** The clinical advantages of autologous transfusion. A randomized, controlled study after knee replacement. *J Bone Joint Surg Br.* 1997; 79(4): 630-2.
6. **Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, *et al.*** The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. *J Arthroplasty.* 2018; 33(10): 3090-3098.e1.
7. **Blanié A, Bellamy L, Rhayem Y, Flaujac C, Samama CM, Fontenay M, *et al.*** Duration of Postoperative Fibrinolysis after Total Hip or Knee Replacement: A Laboratory Follow-up Study. Thromb Res. 2013; 131(1): e6-11.
8. **Pilbrant A, Schannong M, Vessman J.** Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol.* 1981; 20(1): 65-72.
9. **Hurskainen R, Leminen.** Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety. *Int J Womens Health*. 2012; 413.
10. **Pabinger I, Fries D, Schöchl H, Streif W, Toller W.** Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr.* 2017 1; 129(9): 303-16.
11. **Wu C-C, Ho W-M, Cheng S-B, Yeh D-C, Wen M-C, Liu T-J, *et al.*** Perioperative Parenteral Tranexamic Acid in Liver Tumor Resection. *Ann Surg*. 2006; 243(2): 173-80.
12. **Hiippala S, Strid L, Wennerstrand M, Arvela V, Mäntylä S, Ylinen J, *et al.*** Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *Br J Anaesth.* 1995; 74(5): 534-7.
13. **Benoni G, Carlsson A, Petersson C, Fredin H.** Does tranexamic acid reduce blood loss in knee arthroplasty? *Am J Knee Surg*. 1995; 8(3): 88-92.
14. **Oremus K.** Tranexamic acid for the reduction of blood loss in total knee arthroplasty. *Ann Transl Med* [Internet]. 2015 May [cited 2020 Aug 16]; 3(Suppl 1). Available from: https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC4437933/

15. **Jain NP, Nisthane PP, Shah NA.** Combined Administration of Systemic and Topical Tranexamic Acid for Total Knee Arthroplasty: Can It Be a Better Regimen and Yet Safe? A Randomized Controlled Trial. *J Arthroplasty.* 2016; 31(2): 542-7.
16. **Kerakkanavar S, Venkatesh R, Gopinath KM, M P.** Effect of intravenous tranexamic acid on blood loss and blood transfusion in total knee replacement: a prospective, randomized study in Indian population. *Int J Res Orthop.* 2017; 3(5): 916-21.
17. **Shah N, Nilesh G, Patel N.** Mini-subvastus approach for total knee arthroplasty in obese patients. *Indian J Orthop.* 2010; 44(3): 292.
18. **Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, *et al.*** Topical Application of Tranexamic Acid Reduces Postoperative Blood Loss in Total Knee Arthroplasty: A Randomized, Controlled Trial. *J Bone Jt Surg-Am.* 2010; 92(15): 2503-13.
19. **Fitzgerald MC, Mason L, Fairclough S, Rice R.** Does knee flexion reduce blood loss post total knee replacement? *J Adv Perioper Care*. 2010; 4: 73-7.
20. **Mutschler M, Paffrath T, Wölfl C, Probst C, Nienaber U, Schipper IB, *et al.*** The ATLS® classification of hypovolaemic shock: A well established teaching tool on the edge? *Injury*. 2014; 45: S35-8.
21. **Sharma R, Sharma S.** Physiology, Blood Volume. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 May 1]. Available from: http: //www.ncbi.nlm.nih.gov/books/NBK526077/
22. **Nilen Shah M, Anand Gupta DO, Dipak Patel M** (USA). Strategies to Decrease Blood Loss in Patients Who Undergo Total Knee Replacement: A Prospective Study of One Hundred and Fifty Cases. *Reconstr Rev* [Internet]. 2013 Dec 30 [cited 2019 Apr 19]; 3(3). Available from: https: // reconstructivereview.org/ojs/index.php/rr/article/view/43
23. **Gao F-Q, Li Z-J, Zhang K, Sun W, Zhang H.** Four Methods for Calculating Blood-loss after Total Knee Arthroplasty. *Chin Med J* (Engl). 2015; 128(21): 2856-60.
24. **Jansen AJ, Andreica S, Claeys M, D'Haese J, Camu F, Jochmans K**. Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. *Br J Anaesth.* 1999; 83(4): 596-601.
25. **Okamoto S, Okamoto U.** Amino-Methyl-Cyclohexane-Carboxylic Acid: AMCHA. *Keio J Med.* 1962; 11(3): 105-15.
26. **Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW.** Tranexamic Acid Was Safe in Arthroplasty Patients With a History of Venous Thromboembolism: A Matched Outcome Study. *J Arthroplasty.* 2017; 32(9): S246-50.
27. **Hourlier H, Reina N, Fennema P.** Single dose intravenous tranexamic acid as effective as continuous infusion in primary total knee arthroplasty: a randomised clinical trial. *Arch Orthop Trauma Surg.* 2015; 135(4): 465-71.
28. **Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar PR.** Most Effective Regimen of Tranexamic Acid in Knee Arthroplasty: A Prospective Randomized Controlled Study in 240 Patients. *Clin Orthop.* 2012; 470(9): 2605-12.
29. **Liu D, Fracs, Dan M, Martos SM, Beller E.** Blood Management Strategies in Total Knee Arthroplasty. *Knee Surg Relat Res*. 2016; 28(3): 179-87.
30. Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006; 105(1): 198-208.
31. **Benoni G, Fredin H.** Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br.* 1996; 78(3): 434-40.
32. **Álvarez JC, Santiveri FX, Ramos I, Vela E, Puig L, Escolano F.** Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. *Transfusion* (Paris). 2008; 48(3): 519-25.
33. **Fillingham YA, Kayupov E, Plummer DR, Moric M, Gerlinger TL, Della Valle CJ. The James A.** Rand Young Investigator's Award: A Randomized Controlled Trial of Oral and Intravenous Tranexamic Acid in Total Knee Arthroplasty: The Same Efficacy at Lower Cost? *J Arthroplasty*. 2016; 31(9): 26-30.
34. **Lee QJ, Chang WYE, Wong YC.** Blood-Sparing Efficacy of Oral Tranexamic Acid in Primary Total Hip Arthroplasty. *J Arthroplasty.* 2017; 32(1): 139-42.
35. **Sun Q, Yu X, Wu J, Ge W, Cai M, Li S.** Efficacy of a Single Dose and an Additional Dose of Tranexamic Acid in Reduction of Blood Loss in Total Knee Arthroplasty. *J Arthroplasty*. 2017; 32(7): 2108-12.
36. **Ishida K, Tsumura N, Kitagawa A, Hamamura S, Fukuda K, Dogaki Y, *et al.*** Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. *Int Orthop*. 2011; 35(11): 1639-45.
37. **Lin S-Y, Chen C-H, Fu Y-C, Huang P-J, Chang J-K, Huang H-T.** The Efficacy of Combined Use of Intraarticular and Intravenous Tranexamic Acid on Reducing Blood Loss and Transfusion Rate in Total Knee Arthroplasty. *J Arthroplasty*. 2015; 30(5): 776-80.
38. **Song E-K, Seon J-K, Prakash J, Seol Y-J, Park YJ, Jin C.** Combined Administration of IV and Topical Tranexamic Acid is Not Superior to Either Individually in Primary Navigated TKA. *J Arthroplasty.* 2017; 32(1): 37-42.