

Comparison of Efficacy & Safety Between Intravenous and Intraarticular Tranexamic Acid in Reducing Blood Loss after Total Knee Arthroplasty

Arojuraye Soliudeen Adebayo¹, Salihu Mohammed Nuhu¹, Alabi Ibrahim Abolaji¹, Isa Nurudeen¹

¹ Department of Clinical Services, National Orthopaedic Hospital, Dala, Kano, Nigeria

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Arojuraye Soliudeen Adebayo, Department of Clinical Services, National Orthopaedic Hospital, Dala, Kano, Nigeria

Email: doctoraroju@yahoo.com
Telephone: +2348032929051

Received: January 22, 2019

Revised: March 3, 2019

Accepted: March 7 2019

Published online: June 28, 2019

ABSTRACT

Total knee arthroplasty (TKA) is associated with significant postoperative blood loss necessitating blood transfusion. Tranexamic acid is an antifibrinolytic drug that has shown good efficacy in reducing this postoperative morbidity. Although, the most commonly used route of administration is intravenous; the optimal route of administration has not been agreed upon.

AIM: The aim of this study was to evaluate and compare the efficacy and safety of intravenous and intra-articular administration of tranexamic acid in reducing blood loss following TKA.

METHOD: The study was a prospective, interventional; randomized controlled study involving 63 patients who underwent unilateral uncomplicated TKA for severe osteoarthritis of the knee at the

National Orthopaedic Hospital, Dala – Kano, Nigeria. The patients were randomized into 3 groups using online random team generator; (1) Intravenous group, (2) Intraarticular group and (3) Control group.

RESULTS: The postoperative blood loss was significantly greater in the control group than in intravenous and intraarticular groups ($p = 0.02$). Also, the postoperative fall in Hb level and the need for blood transfusion were significantly higher in the control group than in intravenous and intraarticular groups (0.00). However, Intravenous and Intraarticular groups did not differ significantly in terms of the measured variables. There was no significant difference between the preoperative and postoperative platelet counts ($p = 0.81$), INR ($p = 0.21$) and serum creatinine ($p = 0.39$) in all the three study groups.

CONCLUSION: Intravenous and intraarticular tranexamic acid were equally effective and safe for reducing blood loss after TKA.

Key words: Intravenous; Intraarticular; Tranexamic acid; Total knee arthroplasty; Blood loss

© 2019 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Arojuraye SA, Salihu MN, Alabi IA, Isa N. Comparison of Efficacy & Safety Between Intravenous and Intraarticular Tranexamic Acid in Reducing Blood Loss after Total Knee Arthroplasty. *International Journal of Orthopaedics* 2019; 6(3): 1085-1089 Available from: URL: <http://www.ghrnet.org/index.php/ijo/article/view/2507>

INTRODUCTION

Perioperative blood loss has been a problem in contemporary arthroplasty because up to 1000 mL to 1500 mL of blood is commonly lost and the consequences of such blood loss impact negatively on both the individual patient and the healthcare system in general, as it may be associated with symptomatic anaemia requiring blood transfusion^[1,2]. Blood transfusion is a life-saving procedure in acute hemorrhage. However, it is expensive and associated with many hazards including risk of infections, immune suppression, anaphylaxis, volume overload, and transfusion - related lung injury, to mention just a few^[3].

Various methods have been tried to reduce perioperative blood loss; including tourniquet use, hypotensive anesthesia, intraoperative blood

salvage, and the use of diathermy^[4]. Total knee arthroplasty (TKA), is often carried out using a tourniquet to minimize intraoperative blood loss. However, its application transiently activates fibrinolysis by enhancing the release of tissue plasminogen activator (t-PA) which is responsible for significant postoperative blood loss following total knee arthroplasty. The use of antifibrinolytic drugs such as tranexamic acid has been established to reduce this complication^[5].

There are many peer-reviewed studies published to evaluate the effectiveness of tranexamic acid in total hip and knee arthroplasties. Meta-analyses of these literatures have convincingly demonstrated that the use of tranexamic acid (intravenous and intraarticular) reduces blood transfusion rate, does not increase the prevalence of thromboembolic events and does not affect the clotting profile^[6, 7].

Plasma levels after topical application of tranexamic acid are approximately 70% less than intravenous administration of equivalent dose. Therefore, because tranexamic acid acts locally in the wound, its topical application may be superior to intravenous administration especially in patients with renal insufficiency and other systemic morbidities^[6].

PATIENTS AND METHODS

The study was a prospective, interventional, randomized, controlled study involving 63 patients who underwent unilateral uncomplicated TKA for severe osteoarthritis of the knee at the National Orthopaedic Hospital, Dala - Kano, Nigeria between September 2016 and December 2018 and who consented to be part of the study. The patients were randomized into 3 study groups: (1) control, (2) intraarticular and (3) intravenous groups using online random team generator.

The following category of patients were excluded: (1) History of allergy to tranexamic acid; (2) Preoperative anaemia of haemoglobin less than 10g/dL; (3) Bilateral TKA at the same sitting; (4) Preoperative use of anticoagulant; (5) Thrombocytopenia < 100,000/mL³; (6) Deranged clotting profile with INR > 1.4; (7) History of thromboembolic disease; (8) Renal insufficiency. The study was carried out after approval by the Hospital Research Ethic Committee. Data analysis was performed using Statistical package for social sciences (SPSS) version 20 for Windows (Microsoft Corporation, Redmond WA). Chi-square test was used to compare all categorical variables. Two-sided independent t-test and one-way ANOVA were used to compare all normally distributed continuous variables. Statistical significance was defined as $p < 0.05$.

RESULTS

During the study period, a total of 74 total knee arthroplasties were performed on 64 patients. Ten patients had simultaneous bilateral TKA and were excluded from the study. Another one patient was also excluded because of renal impairment with serum creatinine of 129µmol/L. Each of the remaining 63 patients recruited into the study were followed up for at least 1 year and the findings were as documented below.

Table 2 Patients' Baseline Laboratory Parameters.

| Laboratory Parameters | Control (n = 22) (Mean ± SD) | IA Group (n = 21) (Mean ± SD) | IV Group (n = 20) (Mean ± SD) | P value |
|---|------------------------------|-------------------------------|-------------------------------|---------|
| Preoperative Hb (g/dl) | 12.2 ± 1.0 | 12.5 ± 1.1 | 12.4 ± 1.0 | > 0.05 |
| Preoperative INR | 0.99 ± 0.09 | 0.97 ± 0.05 | 0.96 ± 0.06 | > 0.05 |
| Preoperative Plat (x10 ⁹ /l) | 226.59 ± 49.14 | 232.33 ± 51.24 | 217.45 ± 35.40 | > 0.05 |
| Preoperative Cr (µmol/L) | 88.91 ± 9.64 | 89.38 ± 7.89 | 89.85 ± 5.05 | > 0.05 |

IA: Intraarticular, IV: Intravenous, Hb: Haemoglobin, INR: International Normalized Ratio, Plat: Platelet, Cr: Creatinine.

The table 1 below shows the demographic characteristics of all the three study groups. There were no significant differences in the mean age and sex distribution of the three study groups.

Table 2 below shows the patients' preoperative baseline investigation results. The preoperative hemoglobin concentration, platelet count, serum creatinine and INR were not significantly different in the three study groups.

In this study, as shown in the table 3 below, there was significant difference in postoperative blood loss between the control group and tranexamic acid groups ($p < 0.05$). However, there was no significant difference in blood loss between the intravenous and intraarticular tranexamic acid groups ($p > 0.05$). Similarly, the postoperative drop in Hb level was significantly higher in the control group, but there was no significant difference between the two tranexamic acid groups.

The need for blood transfusion was significantly higher in the control group where 16 (72.7%) patients were transfused with a total of 34 units of blood. However, there was no significant difference in the need for blood transfusion in both tranexamic acid groups where 3 patients (14.3%) were transfused with a total of 4 units in intraarticular group and 4 patients (20%) were transfused with 5 units in intravenous group (Figure 1).

Table 4 below shows that there was no significant difference between the preoperative and postoperative platelet counts, INR and serum creatinine in all the three study groups ($p > 0.05$).

Figure 2 below illustrates the postoperative complications in the 3 study groups. Two (9.1%) patients in the control group, 2 (9.1%) patients in intravenous group and one patient (4.5%) in the intraarticular group developed asymptomatic DVT detected from routine postoperative doppler ultrasonography. One (4.5%) patient in the control group had superficial surgical site infection which was managed by local wound care and a course of oral antibiotics based on sensitivity pattern. Another patient (4.5%) in the control group developed prosthetic joint infection which was managed successfully with exploration, joint irrigation and parenteral antibiotics therapy. One (4.5%) patient in IA group developed haematoma noticed 6 days postoperatively and was treated successfully by wound exploration and haematoma evacuation.

DISCUSSION

The incidence of transfusion requirement following unilateral TKA has been reported to range from 11% to 67%^[4]. There have been numerous studies and meta-analyses to evaluate tranexamic acid as

Table 1 Patients' Demographic Characteristics.

| | Control (n = 22) | IA Group (n = 21) | IV Group (n = 20) | P value |
|-----------------------|------------------|-------------------|-------------------|---------|
| Mean Age ± SD (Years) | 65.7 ± 5.1 | 66.3 ± 6.6 | 68.3 ± 8.7 | 0.48 |
| Sex | | | | |
| M | 9 | 8 | 8 | 0.25 |
| F | 13 | 13 | 12 | |

n: Group size, IA: Intra-articular, IV: Intravenous

a means of reducing operative blood loss^[8,9,10]. The current study was also able to demonstrate that tranexamic acid significantly reduces postoperative blood loss, hemoglobin drop, and the need for blood transfusion in patients who underwent primary uncomplicated unilateral TKA ($p < 0.05$). However, the study did not find any significant difference between intravenous and intraarticular tranexamic acid groups ($p > 0.05$). This is in conformity with what has been found by the previous researchers^[2,11].

It has been sufficiently shown that tranexamic acid administration is a useful tool to decrease postoperative blood loss in major orthopedic surgeries^[12,13]. However, in spite of several studies performed, the most appropriate route of tranexamic acid administration remains controversial. In topical administration, the drug is directly applied to the bleeding vessels thereby induces microvascular hemostasis by preventing dissolution of the fibrin clot^[14,15].

Sohrab *et al*^[11] reported a randomized controlled trial of 120 patients who underwent unilateral total knee replacement and found

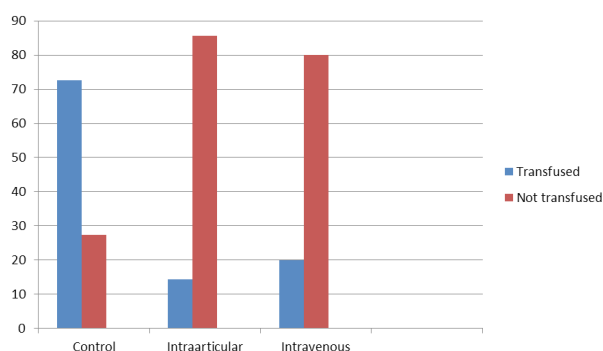


Figure 1 Frequency of blood transfusion in the three study groups.

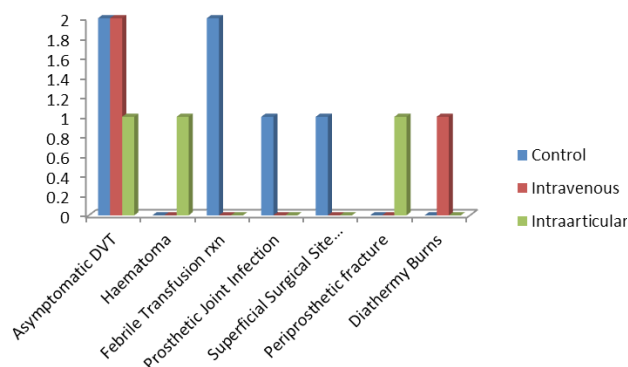


Figure 2 Postoperative Complications.

Table 3 Comparing the blood loss, postoperative drop in Haemoglobin.

| | Control (n = 22) Mean ± SD | IA (n = 21) Mean ± SD | IV (n = 20) Mean ± SD | P value |
|-------------------|-------------------------------|--------------------------|--------------------------|---------|
| Blood loss (mL) | 733.41 ± 134.51 | 442.14 ± 93.87 | 477.50 ± 147.86 | 0.02 |
| Fall in Hb (g/dL) | 3.93 ± 0.92 | 2.47 ± 0.78 | 2.51 ± 0.73 | 0 |

Table 4 Comparing Preoperative & Postoperative Laboratory Parameters.

| | Control (n= 22) Mean ± SD | IA Group (n = 21) Mean ± SD | IV Group (n= 20) Mean ± SD |
|--|---------------------------|-----------------------------|----------------------------|
| Preoperative Pl ($\times 10^9/l$) | 226.59 ± 49.14 | 232.33 ± 51.24 | 217.45 ± 35.40 |
| Postoperative Pl ($\times 10^9/l$) | 230.23 ± 43.72 | 215.43 ± 33.53 | 214.65 ± 28.52 |
| Preoperative Cr ($\mu\text{mol/L}$) | 88.91 ± 9.64 | 89.38 ± 7.89 | 89.85 ± 5.05 |
| Postoperative Cr ($\mu\text{mol/L}$) | 89.50 ± 8.57 | 89.57 ± 8.93 | 88.85 ± 9.01 |
| Preoperative INR | 0.99 ± 0.09 | 0.97 ± 0.05 | 0.96 ± 0.06 |
| Postoperative INR | 0.97 ± 0.04 | 0.96 ± 0.03 | 0.99 ± 0.08 |

similar results with the present study. Their methodology was similar to the present study except in the following respects: (1) only one surgeon performed all their surgeries as against 2 surgeons in the present study; (2) all their surgeries were performed routinely under general anaesthesia as against spinal anaesthesia in the present study; (3) Five hundred milligrams of tranexamic acid was used for intravenous group and 3g for intraarticular group as against 1g to both intraarticular and intravenous groups in the present study.

Patel *et al*^[2], in a randomized controlled study of 100 patients who were given tranexamic acid to reduce blood loss after total knee arthroplasty demonstrated that topical (intraarticular) tranexamic acid has a similar efficacy to intravenous tranexamic acid in reducing perioperative blood loss following primary TKA. Their primary outcome measure, the drop in hemoglobin level was not statistically different between the two groups, resulting in a non-inferior therapeutic result for the use of topical tranexamic acid, compared to intravenous administration. Fall in haemoglobin was probably used as primary outcome measure in their study as against drain output in the present study because tourniquet was released before wound closure. This might have led to varying degree of intraoperative blood loss which their study did not account for. Similarly, Wang *et al*^[16] in a meta-analysis showed that topical tranexamic acid is similar to intravenous tranexamic acid administration in reducing blood loss and rate of transfusion without compromising patient safety. The primary outcome measure of the present study was total drain output which is a better outcome measure than postoperative haemoglobin concentration in detecting postoperative blood loss.

On the contrary; Pispati *et al*^[6] in India found that the average decrease in hemoglobin was significantly more for the intravenous group (average 1.6 g/dL, range 0.8-2.8 g/dL) than the topical group (0.9 g/dL, range 0.4-2.0 g/dL) ($p < 0.05$) but no significant difference in drain output, the need for blood transfusion and the number of blood units transfused in both study groups. The significant difference between intravenous & intraarticular groups noted by Pispati *et al* might be as a result of difference in methodology. They practiced deflation of tourniquet at the end of cementation, careful hemostasis, and wound closure followed by drug delivery by injection. They believe this leads to better hemostasis and importantly identification of any inadvertent large vessel leak. In this study however, the drug was given just before the tourniquet was released which was done after wound is closed and dressed.

Other researchers who found better outcome for intraarticular than intravenous administration include Hamlin *et al*^[17] and Seo *et al*^[18]. Hamlin *et al.* showed that topical (intraarticular) tranexamic acid diminished the rate of transfusion compared to intravenous tranexamic acid in patients who underwent primary TKA (0% versus 2.4%). In that study, 1g of tranexamic acid was used for intravenous group while 3g of tranexamic acid was used for intraarticular group. This significant dosage disparity might be responsible for the favor of intraarticular over intravenous administration.

Seo *et al*^[18] also found that topical tranexamic acid was more effective in terms of reducing blood loss and the frequency of blood

transfusion in patients with TKA. Their study was done using extramedullary minimally invasive techniques; so it may be difficult to compare their results to the current study, which utilized more conventional TKA techniques with intramedullary instrumentation.

In a systematic review and meta-analysis which included 14 randomized controlled trials (11 in knee replacement, two in hip replacement and one in both) which investigated the effect of topical tranexamic acid on blood loss and rates of transfusion; Alshryda *et al*^[12] showed that the indirect comparison of topical and intravenous tranexamic acid indicated that topical administration is a more appropriate route. However, no study was found to demonstrate superiority of intravenous over intraarticular tranexamic acid administration for reducing blood loss.

Tranexamic acid was associated with lower allogenic blood transfusion rates and blood loss in hip and knee arthroplasty patients. Avoidance of allogenic blood transfusions has economic benefits and minimizes the risk of related infections and other adverse reactions and is associated with reduced morbidity and shorter hospital stays^[19,20].

In this present study, there were no significant differences between preoperative and postoperative renal function (serum creatinine) and blood coagulation (INR) in all the 3 study groups. Most studies used clinical suspicion as a trigger point for further investigation of possible thromboembolic events. Therefore, the incidence of deep venous thrombosis observed in such studies may be lower than the true occurrence.^[2] In this present study however, routine preoperative and postoperative doppler ultrasonography of the lower limb was done for all patients. This was to be able to detect even the asymptomatic cases of DVT but this study did not show any particular risk of deep venous thrombosis (DVT) following the use of tranexamic acid.

Two (9.1%) patients in the control group, 2(9.1%) patients in intravenous group and one patient (4.5%) in the intraarticular group developed asymptomatic DVT detected from routine postoperative doppler ultrasonography. They were treated with Subcutaneous Clexane 1 mg/kg/day for 2 weeks followed by oral Pradaxa (Dabigatran) 220 mg daily for 1 month. None of the patients developed any symptom of venous thromboembolism.

One (4.5%) patient in the control group had superficial surgical site infection which was managed by local wound care and a course of oral antibiotics based on sensitivity pattern. In a study of 86 patients by Pispati *et al*⁶ in which 40 of them received IV administration while 46 received topical administration of tranexamic acid and all patients were given equal dose of 1 g of tranexamic acid; there was evidence of postoperative infection in two cases each of the intravenous group (0.5%) and topical (intra-articular) group (0.43%). Also, two cases each of DVT for topical (0.43%) and IV group (0.5%) were recorded and no cases of symptomatic pulmonary thromboembolism in either of the groups.

Complications rate are similar for all the three groups in our study. This is also comparable to all other previous studies of tranexamic acid. Special emphasis was given to any increased risk of thromboembolic event since this is the greatest theoretical risk of this drug. But like most other studies, the present study also confirmed that tranexamic acid, even topically has no increased risks of venous thromboembolism when used within therapeutic dose.

The infection rate is kept low by observing strict aseptic techniques, judicious use of prophylactic antibiotics, keeping operating room clean and keeping patients in the wards away from those for infected patients^[21].

One (4.5%) patient in IA group developed haematoma in the present study. The haematoma was noticed 6 days postoperatively

and was treated successfully by wound exploration and haematoma evacuation. The cause of the haematoma was however not known as the protocol was not different from all other patients and the patient did not have clothing derangement. The Robert Jones dressing has enjoyed widespread popularity as a postoperative or post-traumatic bandage to prevent wound haematoma. It refers to a “pressure crepe bandage over copious wool dressing” which is applied to the knee of patient after trauma or surgery^[22]. By supporting the soft tissues, the Robert Jones dressing relieves pain and may facilitate healing and when used properly, it diminishes oedema of the extremity and limit effusions and haematoma formation^[22].

The strengths of this study include: (1) the study is a prospective randomized controlled study, (2) routine preoperative and postoperative creatinine levels; clotting profile and doppler USS were done to objectively look for the risks of renal impairment, coagulopathy and deep venous thrombosis respectively; (3) Only two surgeons performed all the surgeries using the same protocol. The weakness of the study however is that the study is a hospital based.

It is concluded that tranexamic acid use is effective and safe in reducing blood loss after total knee arthroplasty (TKA). However, there is no difference in the efficacy and safety of intra-articular versus intravenous administration of tranexamic acid in reducing blood loss after TKA.

Ethical approval

The study was carried out after approval from the hospital research ethics committee (HREC).

Informed consent

Informed consent was obtained from the patients using a standard informed consent format.

REFERENCES

1. Watts CD, Pagnano MW. Minimising blood loss and transfusion in contemporary hip and knee arthroplasty. *J Bone Joint Surg Br*; 2012; 94-B, **Supple A**: 8-10. [PMID: 23118371]; [DOI: 10.1302/0301-620X.94B11].
2. Patel JN, Spanyer JM, Smith LS, Huang J, Yakkanti MR, Malkani AL. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: A prospective randomized study. *J Arthroplasty* 2014; **29**: 1528-1531. [PMID: 24768543]; [DOI:10.1016/j.arth.2014.03.011]
3. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. *J Anesthesiology*; 2010; **113(2)**: 482-495. [PMID: 20613475]; [DOI:10.1097/ALN.0b013e3181e08e97].
4. Jagadish S, Harsharaj K, Rajesh S, Edward N. The effect of tranexamic acid on blood loss during total knee arthroplasty. *J Dent Med Sci*.2014; **13(5)**: 85-88.
5. Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: How should we use it? *J Trauma Acute Care Surg*. 2013; **74(6)**: 1574-1586. [PMID: 23694890]; [DOI: 10.1097/TA.0b013e318292cc54].
6. Ameet P, Parag G, Nikhil P, Abhijeet S, Nitin J, Animesh K. Is intraarticular administration of tranexamic acid better than its intravenous administration in reducing blood loss after total knee arthroplasty? *J Orthop Allied Sci*. 2013; **1(2)**:28-32. [DOI: 10.4103/2319-2585.125039].
7. Dang PP, Schwarzkopf R. Tranexamic acid and total knee arthroplasty. *Ann Orthop Rheumatol*. 2013; **1(1)**: 1001-1006.
8. Zhang Y, Fu X, Liu WX, Li YM, Ma XL, Li ZJ. Safety and efficacy of intra-articular injection of tranexamic acid in total knee arthroplasty. *J Halit Orthop*. 2014; **37(9)**: e775-e782. [PMID:

- 25350619]; [DOI: 10.3928/01477447-20140825-53].
9. Fu DJ, Chen C, Guo L, Yang L. Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Chin J Traumatol.* 2013; **16** (2): 67-76. [PMID: 23540893].
 10. Jashvant P, Rehana R, Suzuko S, Thomas D, Madhu M, Friedrich B, Memtsoudis G. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014; **349**: g4829. [PMID: 25116268]; [DOI: 10.1136/bmj.g4829].
 11. Sohrab K, Ali AE, Mohammad RA, Farshad S. Which route of tranexamic acid administration is more effective to reduce blood loss following total knee arthroplasty? *Arch Bone Jt Surg.* 2016; **4**(1): 65-69. [PMID: 26894222].
 12. Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg Br.* 2011; **93** (1): 39-46. [PMID: 21196541]; [DOI: 10.1302/0301-620X.93B1.24984].
 13. Daniel V, Remi AZ, Bruno CW, Bruno BL, Natália Z, Gisele PL. Use of tranexamic acid in primary total knee replacement: effects on perioperative blood loss. *Rev Bras Anesthesiol.* 2016; **66** (3): 254-258. [DOI: 10.1016/j.bjane.2014.11.004].
 14. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick DJ, Gandhi R, Syed KA, Muhammad OS, De Silva Y, Chung F. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am.* 2010; **92**(15): 2503-2513. [PMID: 21048170]; [DOI: 10.2106/JBJS.I.01518].
 15. Jang B, Kao M, Bohm MT, Harris IA, Chen DB, MacDessi SJ. Intra-articular injection of tranexamic acid to reduce blood loss after total knee arthroplasty. *J Orthop Surg.* 2014; **22** (2): 146-149. [PMID: 25163943]; [DOI: 10.1177/230949901402200205].
 16. Wang H, Shen B, Zeng Y. Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled and prospective cohort trials. *Knee.* 2014; **21**(6):987-93. [PMID: 25450009]; [DOI: 10.1016/j.knee.2014.09.010].
 17. Hamlin BR, DiGioia AM, Plakseychuk AY, Levison TJ. Topical versus intravenous tranexamic acid in total knee arthroplasty. *J Arthroplasty* 2015; **30**(3): 384-386. [PMID: 25458092]; [DOI: 10.1016/j.arth.2014.10.007].
 18. Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and intravenous tranexamic acid for reducing blood loss during total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc.* 2013; **21**(8): 1869-74. [PMID: 22729012]; [DOI: 10.1007/s00167-012-2079-2].
 19. Charoencholvanich K, Siriwattanasakul P. Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. *Clin Orthop Relat Res.* 2011; **469**: 2874-2880. [PMID: 21512813]; [DOI: 10.1007/s11999-011-1874-2].
 20. Jessica M, Kathy A, Shawn C, Ian H. Tranexamic acid in anesthetic management of surgical procedures. *AANA J* 2016; **84**(3): 201-209. [PMID: 27501656]
 21. Anderson DJ, Podgorny K, Berrios-Torres S, Bratzler DW, Dellinger EP, Greene L *et al.* Strategies to prevent surgical site infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2014; **35**(6): 605-627. [PMID: 24799638]; [DOI: 10.1086/676022].
 22. Brodell JD, Axon DL, Evarts CM. The Robert Jones Bandage. *J Bone Joint Surg.* 1986; **68**(5): 776-779. [PMID: 3782244].