RESEARCH ARTICLE

Comparison of Intraarticular Versus Combined Intravenous and Intraarticular Tranexamic Acid Administration in Patients Undergoing Primary Unilateral Total Knee Arthroplasty: A Randomized Controlled Trial in the Middle Eastern Patient Population

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Abstract

Background: This study aimed to determine whether combined intravenous (IV) and intraarticular (IA) tranexamic acid (TXA) reduces blood loss and the requirement of blood transfusion compared to IA use alone in the middle eastern patients undergoing primary cemented unilateral total knee arthroplasty (TKA).

Methods: The present study is a double-blind randomized controlled trial (RTC) comparing the efficacy of IA alone to combined IA and IV routes of TXA administration in patients undergoing primary cemented TKA using a tourniquet performed by two senior surgeons. There were 21 patients in the IA alone and 29 in the combined group. The primary outcome measure was blood transfusion requirement, hemoglobin drop, and the total estimated blood loss on day three of postoperative period. The secondary outcomes were complications including thromboembolic events, wound complications, periprosthetic infection, patient-reported outcomes (PROs) of pain visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and EuroQol 5-dimension (EQ-5D) as well as the range of motion (ROM) at one-year follow-up.

Results: None of the patients in either of the comparison group required blood transfusion in the perioperative period. The drop in hemoglobin levels (2.1±1.0 vs. 2.2±1.1, P=0.84) and the total estimated blood loss (884±489 vs. 877±324, P=0.96) on the third postoperative day in the IA alone group showed no statistically significant difference compared to that in the combined group. Moreover, there were no complications noted in patients of either group. At one-year follow-up, there was no significant difference between the two comparison groups regarding the mean PROs of pain VAS, WOMAC, and EQ-5D, as well as ROM.

Conclusion: According to the obtained results, this RCT in the middle eastern patient population found no additional benefit of TXA administration through combined IV and IA route over the IA alone in reducing the requirement of blood transfusion and the total blood loss. Further similar studies with larger sample sizes are needed to ascertain the ideal route of TXA administration in patients undergoing primary TKA.

Level of evidence: I

Keywords: Arthritis, Blood loss, Blood transfusion, Total knee arthroplasty, Total knee replacement, Tranexamic acid

Introduction

Total knee arthroplasty (TKA) is a reliable procedure for treating patients with end-stage knee degenerative diseases.[1,2] Although considered safe, TKA can result in a significant blood loss of up to 1500 mL in the perioperative period.[3] Substantial blood loss after TKA may result in a blood transfusion requirement, which is associated with the risk of periprosthetic infection and adverse hypersensitivity

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reaction.[3,4] Furthermore, excessive blood loss in TKA patients increases the economic burden on healthcare systems and patients due to the requirement of blood transfusion, in addition to lengthier hospital stay.[5]

Tranexamic acid (TXA), an antifibrinolytic agent, is widely considered safe and effective in reducing blood loss during TKA.[6,7] While the current guidelines recommend the routine use of TXA during TKA, the preference for the ideal dosage and route of administration remains controversial.[8]

The literature is inconsistent on whether the intravenous (IV) alone, intraarticular (IA) alone, or combined IV and IA is the ideal route for administering TXA for TKA.[9-11] Further well-designed randomized controlled clinical trials (RCTs) are needed to evaluate the ideal route of TXA administration in TKA while avoiding blood transfusion and adverse thromboembolic events. Furthermore, to the best of our knowledge, there are no studies regarding the efficacy of TXA in TKA in patients from the United Arab Emirates (UAE).

This RCT aimed to determine whether combined IV and IA TXA reduces blood loss and blood transfusion requirement compared to IA alone in local UAE patients. A secondary goal was to compare the postoperative patient-reported outcomes (PROs) of pain and functional outcomes between patients with IA alone and combined TXA administration undergoing primary unilateral TKA.

Materials and Methods

This study is a prospective RCT conducted on patients undergoing unilateral TKA at a single tertiary care center Mediclinic City Hospital, Dubai, UAE. The Ethics Committee approved the protocol of this study of Dubai Healthcare City Authority with IRB number 03/240413/ITRAX. Furthermore, the trial was prospectively registered on the PROSPERO database (2016 CRD42016037938).

Patient Inclusion

Between January 2016 to January 2018, patients undergoing unilateral cemented TKA were screened for this trial. The inclusion criteria were diagnosis with primary osteoarthritis scheduled for unilateral primary cemented TKA without patella resurfacing. On the other hand, the exclusion criteria were a diagnosis other than primary osteoarthritis, simultaneous bilateral TKA, severe ischemic heart disease, coagulation disorders, preexisting hepatic or renal dysfunction, a history of thromboembolic disease, and use of anticoagulation therapy to reduce potential confounders of the outcomes.[11] Patients who did not complete a one-year follow-up after TKA were also excluded from the final analysis. Out of 133 patients who underwent primary TKA during the study period, 50 were eligible for this study [Figure 1]. Eligible patients were randomized into two groups: combined IV and IA or IA alone. None of

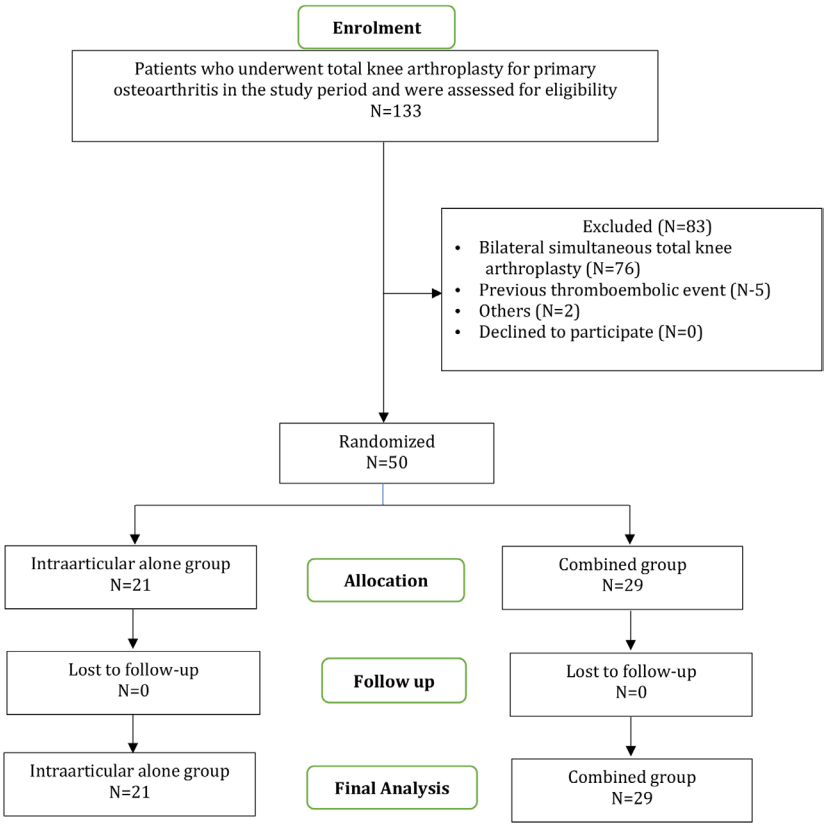

Figure 1. Flow diagram shows the number of patients assessed and included at each stage of the randomized control trial.

the patients were lost to follow-up [Figure 1]. The flow diagram shows the number of patients assessed and included at each stage of the RCT.

Randomization and Blinding

Randomization of the 50 included patients was conducted using computer software which generated random numbers for each patient, allotting them into two groups. Black envelopes with these numbers were placed within the patient's medical notes and presented to the anesthetist in the operation theatre. Of the 50 included patients, 21 were allocated to the IA alone TXA group (IA alone group), and 29 were placed in the combined IA and IV TXA groups (combined group) [Figure 1]. All investigators were blinded to patient groups before, during, and after the trial, as well as the follow-up. Blinding was only compromised once all data had been collected for data analysis. The investigator involved in allocation and data analysis was not involved in administering medication, surgery, or follow-up assessments.

Surgical Technique

All patients underwent a unilateral cemented TKA utilizing the medial midvastus approach. They were operated on by one of the two senior surgeons (AA or SA) in the same institution with the standardized surgical technique of a combination of measured resection and soft tissue balancing. All patients were given spinal anesthesia. A pneumatic tourniquet with a pressure of approximately 200 mmHg above the systolic blood pressure was used in all patients, which was inflated immediately before the skin incision and deflated following the closure of the joint capsule. The medullary canal of the femur was plugged with a bone block after all bone cuts were made and before the prosthesis was fixed with cement. Patients received the same implant (Genesis II, Smith & Nephew PLC, Watford, UK), and no drain was used in any of the patients. Postoperative anticoagulation was standardized in all patients and consisted of rivaroxaban commenced 12 h after the operation and continued for 14 days. In the postoperative period, a blood transfusion was given to patients with a hemoglobin level of less than 7 g/dL, as well as those with a hemoglobin level of between 7 g/dL and 8 g/dL and persistent anemic symptoms, such as dyspnea or tachycardia despite volume replacement.[11] The physician who decided on the blood transfusion requirement was blinded to the study groups.

Administration of Tranexamic Acid

The patients in the IA group received a single dose of IA alone TXA (15 mg/kg). The TXA dose of 15 mg/kg is a standardized protocol based on the recommended dose by the manufacturer, which is 1 gm IV for a 70 kg adult with no renal impairment. The combined group of patients received an additional 15 mg/kg IV dose, apart from the IA 15mg/kg dose. This total TXA dose of 30 mg/kg in the combined group accommodates the maximum recommended dose of 30 mg/kg by the manufacturer to avoid the theoretical risk of thromboembolic adverse events.

For IV TXA administration, 10 mins before the tourniquet inflation, the anesthetist prepared and delivered the IV dose of either 15mg/kg of TXA for the combined group patients or normal saline for the IA alone group. At the end of the surgery, an IA dose of 15mg/kg of TXA was administered after capsule closure to all patients.

Data Collection

Data were prospectively collected and anonymized. This included demographic data such as age, gender, body mass index (BMI), comorbidities, blood hemoglobin level, PROs, and range of movement (ROM). The intraoperative variables included the duration of surgery from skin incision to skin closure and the sizes of femoral, tibial, and polyethylene insert components.

The primary outcome measure consisted of the requirement of blood transfusion in the preoperative period, the drop in the blood hemoglobin level on postoperative days one and three, and the total estimated blood loss, which was calculated based on the maximum drop in hemoglobin postoperatively on day three using the method described by Meunier et al.[12] The hemoglobin blood test was performed pre-operatively and postoperatively on days one and three.

The secondary outcome measures collected preoperatively and at a minimum of one year postoperatively consisted of PROs of pain visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and EuroQol 5-dimension (EQ-5D), as well as ROM. [13,14] Pain VAS was measured on a 10-point scale with 0 being the minimum and 10 being the maximum pain. The EQ-5D score is a PRO measure used to assess global health status based on five key domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[14] The complications noted in the postoperative period were the occurrence of symptomatic deep vein thrombosis and pulmonary embolism, wound complications, and periprosthetic joint infection.

Statistical Analysis

The sample size was determined based on the expected postoperative third-day blood hemoglobin level drop. With IV TXA, the hemoglobin level dropped by a mean of 2.8 g/dL±1.0 g/dL (*P<0.05*) on the third postoperative day. For a combined IV and IA TXA regimen, the reported hemoglobin loss was 2.24 g/dL±1.0 g/dL at the end of the third day.[15] The confidence level (α) was set at 0.05, the Beta error level (β) at 5%, with a power of 80%, and the ratio of sample size in each group at 1:1. Therefore, the sample size of each group was 35 in each treatment arm.[16] Despite aiming to recruit 35 patients in each arm, only 21 patients could be recruited in the IA alone group and 29 in the combined group. This was due to the early termination of the study resulting from the deviation of surgical technique by the senior surgeons. They switched to robotic-assisted TKA in January 2018 before 35 patients could be recruited in each group. Nonetheless, all included patients were followed up until one year postoperatively, and there was no loss to the follow-up.

The patient data were entered into the computer using the IBM-SPSS software for windows (version 23, SPSS Inc., Chicago, USA). Categorical variables were described by proportion and continuous ones by the measure of tendency and dispersion. Categorical variables were cross-tabulated to examine the independence between variables. For such variables, the Chi-squared test or Fisher's exact test, as appropriate, was used. Kolmogorov-Smirnov was used to test the normality of continuous variables and the Mann-Whitney U test was used to compare the means of the two groups. When comparing the means between more than two groups, the Kruskal-Wallis test was utilized. A *P-value* of <0.05 was considered significant in all statistical analyses.

Baseline Variables

The included patients had a mean age of 64.4 years (45 to 77 years). There was no significant difference in demographic characteristics of gender, age, and BMI between the two groups [Table 1]. In addition, the proportion of patients with diabetes mellitus, cardiovascular disease, and peripheral vascular was not significantly different between the two groups. The blood levels of hemoglobin, pain VAS, WOMAC, and EQ-5D, as well as ROM, were also not significantly different between the two groups at the preoperative stage. The intraoperative variables of the duration of surgery and the sizes of femoral, tibial, and polyethylene insert components were also comparable between the two groups.

Results

Blood Transfusion Requirement and Blood Loss

None of the patients in IA alone and combined groups required blood transfusion in the preoperative period [Table 2]. The drop in postoperative hemoglobin levels on days one and three showed no statistically significant difference between the two comparison groups. Similarly, the total estimated blood loss based on hemoglobin drop on day three was not statistically different between the IA alone and combined groups.

Patient-Reported Outcomes

At the final follow-up of one year, the PROs of pain VAS,

Table 1. Comparison of baseline variables, including demographics and preoperative patient-reported outcomes and range of motion between intraarticular alone and combined intraarticular and intravenous groups

	Intraarticular alone (N=21)	Combined (N=29)	*P-value*
Baseline variables			
Age (years)	65.4±11.7	63.3±7.1	0.51
Female, N (%)	17 (81)	21 (72)	0.49
Weight (kg)	82.4±22.5	83.4±11.9	0.17
BMI (kg/m^2)	32.2±7.3	31.9±5.1	0.91
Diabetes mellitus, N (%)	4 (19)	10 (35)	0.23
Cardiovascular disease, N (%)	2 (10)	3 (10)	0.92
Peripheral vascular disease, N (%)	1 (5)	0	0.24
Preoperative hemoglobin (g/dL)	12.4±1.2	12.7±1.7	0.56
Patient-reported outcomes and range of motion			
Pain VAS	8.1±2.1	8.5±2.6	0.38
WOMAC	73.9±20.6	77.4±25.3	0.78
EQ-5D	83.2±16.2	81.8±18.9	0.68
Flexion, degrees	136.4±14.6	131.2±13.1	0.28
Extension, degrees	1.5±8.0	5.9±4.6	0.48
Intraoperative variables			
Duration of surgery, mins	82.5±8.3	78±13	0.32
Femoral component size	4.0±1.4	4.1±1.2	0.84
Tibial component size	2.8±1.2	3.0±1.2	0.92
Tibial insert thickness	10.4±1.7	10.5±1.3	0.55

All values are expressed in mean±SD, unless specified
BMI: body mass index
VAS: visual analog scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
EQ-5D: EuroQol 5 dimension

Table 2. Primary outcome measures assessing post-operative blood loss between intraarticular alone and combined intraarticular and intravenous groups

	Intraarticular alone (N=21)	Combined (N=29)	*P-value*
The number of patients who required blood transfusion.	0	0	-
Hemoglobin drop (g/dL)			
Day 1	1.6±0.81	1.3±1.0	0.231
Day 3	2.1±1.0	2.2±1.1	0.838
Total estimated blood loss (mL)	884±489	877±324	0.958

All values are expressed in mean±SD unless specified.
"- "indicates that statistical analysis was not required.
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
EQ-5D: EuroQol-5 dimension

WOMAC, and EQ-5D did not show a statistically significant difference between IA and combined groups [Table 3]. Similarly, the final postoperative ROM was not statistically significantly different between the two groups.

There were no patients with postoperative complications in the form of symptomatic deep vein thrombosis, pulmonary embolism, wound complications, and periprosthetic joint infection.

Table 3. Comparison of postoperative patients reported outcomes and range of motion at the one-year follow-up between intraarticular alone and combined intraarticular and intravenous groups

	Intra-articular alone (N=21)	Combined (N=29)	*P-value*
Pain VAS	2.6±2.1	2.4±1.3	0.77
WOMAC	91.3±3.8	87.2±7.9	0.14
EQ-5D	83.2±16.2	81.8±18.9	0.68
Flexion, degrees	140.0±11.3	135.4±15.6	0.81
Extension, degrees	0.62±1.8	0±0.3	0.28

All values are expressed in mean±SD unless specified.
VAS: visual analoge scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
EQ-5D: EuroQol 5 dimension

Discussion

The key finding of this RCT in our matched cohort from the UAE undergoing primary cemented TKA was that there was no additional benefit of the combined route of TXA administration over IA alone for the requirement of blood transfusion and total blood loss. The route of TXA administration also did not influence the rate of thromboembolic and wound complications, PROS for pain and function, and ROM at one-year follow-up.

The primary finding was that the combined IA and IV TXA (30 mg/kg, approximately 2 gm total dose) route does not offer additional benefit over the IA alone (15 mg/kg or 1 gram dose) route, providing corroborative evidence to previous RCTs on the topic in unilateral and bilateral cemented primary TKA.[11, 17] Lee et al. randomized 376 patients undergoing primary TKA to four groups based on TXA administration: IV alone (1gm), IA alone (1gm), low-dose combined IV and IA (1 gm each), and high-dose combined (2 gm each). None of the study patients needed blood transfusion.[17] The IA alone TXA group had a similar reduction in blood loss to the low-dose and high-dose combined groups. The decline in blood loss was lower in the IV alone group than in the other three groups. On the other hand, Zhang et al., in an RCT, found that combined TXA administration had a greater effect on reducing blood loss than the IA alone route.[20] The contrary results to the current study could be explained by fundamental differences in the methodology by Zhang et al., such as using a higher dose of TXA (3 gm) and drain, which influence the estimation of blood loss and study results. Therefore, the most currently available high-level literature, including the current study, points toward the similar efficacy of IA alone TXA compared to a combined IA and IV regimen.

Another significant finding of this study was that none of the patients had any adverse thromboembolic events, wound complications, or periprosthetic complications. This further supports the favorable safety profile of TXA in patients undergoing primary TKA, as reported by previous studies.[11] Notably, Fillingham et al., in their meta-analysis of the safety profile of TXA in patients undergoing total joint arthroplasty noted that most studies, similar to the present one, excluded patients with a history of previous thromboembolic events.[21] Future studies of the safety profile of TXA in patients with previous thromboembolic events undergoing TKA are needed to fill this lack of knowledge in the literature.

This study also found that the route of TXA administration did not influence pain and functional

outcomes, as well as ROM, at one year, either through IA alone or combined. This is supported by previous studies which reported a similar function at early postoperative and short-term follow-ups after TKA in which TXA was administered by either of these two routes.[17]

The principal limitation of this study is that the sample size in both treatment arms was less than the estimated sample size needed to reach 80% power, which was due to the early termination of patient recruitment in the study to accommodate the change in the surgical technique of using robotic assistance for TKA by senior surgeons. Another limitation of this study is that the surgeries were performed by two surgeons, bringing heterogeneity in surgical technique and postoperative management. However, this heterogeneity is perhaps minimal as both surgeons followed the same principle of surgical method of TKA, used the same implant design, and routinely employed the same hospital staff for preoperative management of TKA patients. Despite the limitations, the prospective study design, use of validated outcome tools for assessment and blinding of the investigators add value to the quality of this study. To the best of our knowledge, this is the first RCT on UAE patients to evaluate the efficacy of TXA in TKA.

Based on the findings, this RCT in the middle eastern patient population found no additional benefit of TXA administration through the combined IV plus IA route or the IA alone route in reducing the requirement of blood transfusion and total blood loss. Further similar studies with larger sample sizes are needed to ascertain the ideal route of TXA administration in patients undergoing primary TKA.

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Declaration of ethical approval for study: The protocol of this study was approved by the ethics committee of Dubai Healthcare City Authority with IRB number 03/240413/ITRAX on 17th April, 2019 and valid for Mediclinic City Hospital, Dubai Healthcare City, Dubai. The trial was prospectively registered on the PROSPERO database (2016 CRD42016037938).

Declaration of informed consent: There is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patients.

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References

1. Jauregui JJ, Cherian JJ, Pierce TP, Beaver WB, Issa K, Mont MA. Long-Term Survivorship and Clinical Outcomes Following Total Knee Arthroplasty. J Arthroplasty. 2015;30(12):2164-6. doi: 10.1016/j.arth.2015.05.052.
2. Tiwari V, Meshram P, Park CK, Bansal V, Kim TK. New mobile-bearing TKA with unique ball and socket post-cam mechanism offers similar function and stability with better prosthesis fit and gap balancing compared to an established fixed-bearing prosthesis. Knee Surg Sports Traumatol Arthrosc. 2019;27(7):2145-2154. DOI: 10.1007/s00167-019-05430-5
3. Chen X, Ji ZL, Chen YZ. TTD: Therapeutic Target Database. Nucleic Acids Res. 2002;30(1):412-5. doi: 10.1093/nar/30.1.412.
4. Wang H, Shen B, Zeng Y. Comparison of topical versus intravenous tranexamic acid in Primary total knee arthroplasty: a metaanalysis of randomized controlled and prospective cohort trials. Knee. 2014;21(6):987–993. doi: 10.1016/j.knee.2014.09.010.
5. Alvarez 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. 2008;48(3):519-25. doi: 10.1111/j.1537-2995.2007.01564.x.
6. Drain NP, Gobao VC, Bertolini DM et al. Administration of Tranexamic Acid Improves Long-Term Outcomes in Total Knee Arthroplasty. J Arthroplasty. 2020;35(6S):S201-S206. doi: 10.1016/j.arth.2020.02.047.
7. Kim TK, Chang CB, Koh IJ. Practical issues for the use of tranexamic acid in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2014;22(8):1849-58. doi: 10.1007/s00167-013-2487-y.
8. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic acid in total joint arthroplasty: the endorsed clinical practice guides of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. Reg Anesth Pain Med. 2019;44(1):7-11. doi: 10.1136/rapm-2018-000024.
9. Li J, Liu R, Rai S, Ze R, Tang X, Hong P. Intra-articular vs. intravenous administration: a meta-analysis of tranexamic acid in primary total knee arthroplasty. J Orthop Surg Res. 2020;15(1):581. doi: 10.1186/s13018-020-02119-1.
10. Sun Q, Li J, Chen J, Zheng C, Liu C, Jia Y. Comparison of intravenous, topical or combined routes of tranexamic

acid administration in patients undergoing total knee and hip arthroplasty: a meta-analysis of randomised controlled trials. BMJ Open. 2019;28;9(1):e024350. doi: 10.1136/bmjopen-2018-024350.

11. Meshram P, Palanisamy JV, Seo JY, Lee JG, Kim TK. Combined Intravenous and Intraarticular Tranexamic Acid Does Not Offer Additional Benefit Compared with Intraarticular Use Alone in Bilateral TKA: A Randomized Controlled Trial. Clin Orthop Relat Res. 2020;478(1):45-54. doi: 10.1097/CORR.0000000000000942
12. Meunier A, Petersson A, Good L, Berlin G. Validation of a haemoglobin dilution method for estimation of blood loss. Vox Sang. 2008;95:120–124. doi: 10.1111/j.1423-0410.2008.01071.x.
13. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes. 2003;1:17. doi: 10.1186/1477-7525-1-17.
14. EQ-5D instruments. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ Assessed on Apr 7, 2022
15. 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 Relat Res. 2012;470(9):2605-2612. doi: 10.1007/s11999-012-2310-y.
16. Sample Size Calculator, DSS research 2014. Available at https://www.dssresearch.com/KnowledgeCenter/toolkitcalculatorsstatisticalpowercalculators.aspx. Assessed 2 Jan, 2022
17. Lee SY, Chong S, Balasubramanian D, Na YG, Kim TK. What is the ideal route of administration of tranexamic acid in TKA? A randomized controlled trial. Clin Orthop Relat Res. 2017;475:1987-1996. doi: 10.1007/s11999-017-5311-z
18. Lin SY, Chen CH, Fu YC, Huang PJ, Chang JK, Huang HT. 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. doi: 10.1016/j.arth.2014.12.001.
19. Dorji Y, Singh CM, Mishra AK, Sad D. Efficacy of combined use of intravenous and intra-articular versus intra-articular tranexemic acid in blood loss in primary total knee arthroplasty: A randomized controlled study. JAJS. 2021;8(2) 134-138. https://doi.org/10.1016/j.jajs.2020.12.006
20. Zhang YM, Yang B, Sun XD, Zhang Z. Combined intravenous and intra-articular tranexamic acid administration in total knee arthroplasty for preventing blood loss and hyperfibrinolysis: A randomized controlled trial. Medicine (Baltimore). 2019;98(7):e14458. doi:10.1097/MD.0000000000014458.
21. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Safety of Tranexamic Acid in Total Joint Arthroplasty: A Direct Meta-Analysis. J Arthroplasty. 2018;33(10):3070-3082.e1. doi: 10.1016/j.arth.2018.03.031.