Effects of local infiltration of analgesia and tranexamic acid in total knee replacements: safety and efficacy in reducing blood loss and comparability to intra-articular tranexamic acid

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Abstract

Introduction: The use of periarticular (PA) tranexamic acid (TXA) and its efficacy in comparison with intra-articular (IA) TXA have not been well explored in the literature. This retrospective cohort study aimed to compare the effects of IA and PA TXA with analgesic components in reducing blood loss and improving immediate postoperative pain relief and functional outcomes in patients after unilateral primary total knee arthroplasty (TKA).

Methods: A total of 63 patients underwent TKA, and they were divided into the IA TXA delivery group (n = 42) and PA TXA delivery group (n = 21). All patients were administered 1 g of TXA. They also received pericapsular infiltration consisting of 0.5 mL of adrenaline, 0.4 mL of morphine, 1 g of vancomycin, 1 mL of ketorolac and 15 mL of ropivacaine. Outcomes for blood loss and surrogate markers for immediate functional recovery were measured.

Results: Of the 63 patients, 54% were female and 46% male. The mean drop in postoperative haemoglobin levels in the PA and IA groups was 2.0 g/dL and 1.6 g/dL, respectively, and this was not statistically significant (P = 0.10). The mean haematocrit drop in the PA and IA groups was 6.1% and 5.3%, respectively, and this was also not statistically significant (P = 0.58). The postoperative day (POD) 1 and discharge day flexion angles, POD 1 and POD 2 visual analogue scale (VAS) scores, gait distance on discharge and length of hospitalisation stay were largely similar in the two groups.

Conclusion: Our study showed that both IA and PA TXA with analgesic components were equally efficient in reducing blood loss and improving immediate postoperative pain relief and functional outcomes.

Keywords: Functional outcomes, local infiltration of analgesia, total knee arthroplasty, tranexamic acid

INTRODUCTION

Postoperative blood loss is a major concern in total knee arthroplasty (TKA). Considerable blood loss of 1,000–1,500 mL is often observed after knee replacements, and patients often require a blood transfusion.[1] Allogenic blood transfusions are costly and commonly associated with multiple complications such as increased risk of infection, transfusion-related acute lung injury and transfusion-associated sepsis.[2] There are several strategies that have been described in the literature to reduce blood loss, including the use of tranexamic acid (TXA). Tranexamic acid inhibits the conversion of plasminogen to plasmin, thereby preventing fibrinolysis, and results in fibrin clot stabilisation.[3,4] Multiple modalities of TXA delivery have been described.[5] However, the use of TXA can be affected by medical comorbidities such as cardiac and renal diseases, and only a small percentage of the drug reaches targeted tissues via this method.[6‑8] Topical TXA in the form of intra-articular (IA) TXA has a superficial, limited duration of contact with bleeding surfaces and cannot be used in...
surgeries where the use of postoperative drains is preferred or required.\[^9\] Furthermore, the long-term effect of TXA on metal and polyethylene is not known, and thus, future implant-related issues could be a real possibility.\[^9\]

A Boolean search of the PubMed and the National Library of Medicine (NLM) databases using the terms ‘peri-articular’ and ‘tranexamic acid’ showed that the periarticular (PA) mode of infiltration of TXA has been not well covered in the literature. Theoretically, infiltrating PA capsular tissues directly addresses the source of bleeding and avoids the systemic toxicity associated with intravenous (IV) TXA administration.\[^9,10\] Local infiltration of anaesthetic agents into the pericapsular tissue has been shown to provide good immediate pain relief and improved functional outcomes while maintaining maximum muscle control for early weight-bearing and range-of-motion exercises, in comparison to other modalities such as peripheral nerve blocks and spinal anaesthesia.\[^11\]

Our first hypothesis was that PA TXA is more effective in reducing postoperative blood loss as compared to IA TXA, as it addresses sites of potential blood loss directly. Our second hypothesis was that the addition of TXA into the pericapsular tissues will not affect the analgesic efficacy of the local anaesthetic cocktail and this combination will have minimum side effects. Our study aimed to compare the effects of IA and PA TXA with analgesic components in reducing blood loss and improving immediate postoperative pain relief and functional outcomes in unilateral primary TKA patients.

**METHODS**

Patient records were accessed retrospectively via computerised patient data collection systems. Approval was obtained from the National University Health System Institutional Review Board before the records were accessed (Reference: 2018/00954). The study adhered to the principles of the Declaration of Helsinki.

This retrospective cohort study was conducted to include operated patients from July 2017 to July 2018. Eighty-seven patients who underwent TKA were initially identified. The inclusion criteria were patients with symptomatic primary osteoarthritis of the knee who failed conservative treatment, necessitating primary TKA. Exclusion criteria were history of previous venous thromboembolism before surgery, hepatic cirrhosis, chronic renal failure, any underlying disease of coagulation, allergy to TXA or the constituents in the local anaesthetic preparation, concurrent use of anticoagulants, and preoperative haemoglobin (Hb) levels <9 g/dL. After applying the inclusion and exclusion criteria [Figure 1], the records of 63 patients who had undergone primary unilateral TKA were accessed. The patients were divided into two groups — patients who received PA TXA and patients who received IA TXA; both groups had local capsular infiltration of anagelsia. The independent variable was the mode of delivery of TXA, and the dependent variables were blood loss and functional outcomes (pain score, flexion angles, gait distance and length of hospitalisation stay).

All patients had undergone TKA under a single surgeon at a tertiary medical centre. Patients with significant comorbidities had been referred for preoperative anaesthetic optimisation, but otherwise, all went through the same preoperative procedures. The same technique had been reproduced in all patients: 55 (87.3%) patients underwent general anaesthesia and eight (12.7%) patients underwent spinal anaesthesia, all without the adjunct of a nerve block. Intravenous (IV) antibiotics was given on induction. An inflatable tourniquet was used with standard cleaning and draping procedure. A medial parapatellar approach was used in all patients and a cemented fixed-bearing prosthesis was used in all cases. The TKA procedures were conventional, with posterior stabilised implants, and the intramedullary canal not covered. A routine patelloplasty was performed for all patients, and none of the patellae was replaced. Patelloplasty refers to a circumferential denervation of the patella with electrocautery and excision of osteophytic overgrowth of the patella. Intraoperative haemostasis was not routinely performed by the surgeon with the tourniquet deflated. Both IA and PA TXA was administered before deflation of the tourniquet in all cases. All patients had a local infiltration of analgesia into the PA region before closure. The analgesic regime consisted of adrenaline 0.5 mL, morphine 0.4 mL, vancomycin 1 g, ketorolac 1 mL.
and ropivacaine 15 mL. The regions of the capsule that the cocktail was delivered included the medial and lateral capsule, the quadriceps and the tibial soft tissue release sites [Figure 2]. The amount administered was divided equally among the four regions. No infiltration was given to the posterior aspect of the capsule. The dose of TXA given was higher than the dose used in the only reported randomised controlled trial (RCT) of PA TXA in the literature (1 g vs. 750 mg).[7] In the IA group, 1 g of TXA was delivered via an IA injection after capsular closure. In the PA group, 1 g of TXA was injected into the same PA quadrants as the analgesic cocktail before closure. The amount administered was also divided equally among the four regions. No drains were used, and all patients had bulky dressings applied postoperatively.

The outcomes measured were broadly divided into two categories to correlate with the objectives of this study: blood loss and immediate functional outcomes. Postoperative day (POD) 1 Hb and haematocrit (Hct) counts and POD 2 Hb and Hct counts were used as markers of blood loss. The drop in Hb was calculated by deducting the POD 1/POD 2 Hb values from the preoperative figures. Flexion angle on POD 1 and discharge day, gait distance on discharge, visual analogue scale (VAS) POD 1 and VAS POD 2, and length of inpatient stay were used to assess functional outcomes. All flexion angles were measured by the physiotherapist on POD 1 and on discharge day using goniometers, these measurements were done only after removal of bulk dressings. Gait distance was measured by the same physiotherapist on POD 1 and on discharge day using calibrated measurement devices for each stride of the patient. The VAS scores were explained to patients using descriptive charts and recorded by the team doctors and/or anaesthetists. Length of hospital stay was measured until the discharge day from the acute hospital and did not include stays in the community hospital for rehabilitation. Secondary outcomes that were measured in the total knee pathway included possible complications from local infiltration of the agents, mainly skin necrosis, symptomatic venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), subcutaneous haematomas, haemarthrosis, and nerve or vessel injuries. These were routinely recorded as part of the care plan follow-up for all TKA patients.

A restrictive transfusion threshold of Hb <8.5 g/dL was used unless the patient was symptomatic or had cardiovascular comorbidities necessitating Hb to be above a certain level as documented by the cardiologists. None of the patients were placed on chemical DVT prophylaxis, but all had intermittent pneumatic calf compression pumps on POD 0. Physiotherapy was started on POD 1, and patients were discharged when medically well and deemed safe by our physiotherapy team. The patients were followed up for a mean duration of 6 months (range 3 months–1 year) from the date of surgery; in particular, emphasis was placed on identifying complications related to the administration of TXA.

The data collected followed a normal distribution. Hence, the data were analysed using parametric statistical tests. Continuous data were analysed using unpaired Student’s t-test to find the significance of any difference between the mean values of the two normally distributed groups. Unpaired Student’s t-test was used as the two groups that were analysed were independent of each other. This value is expressed as mean and standard deviation (SD) in the presented tables. All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY, USA). A P value < 0.05 was considered as statistically significant.

RESULTS
A total of 87 patients who were admitted for primary TKA between July 2017 to July 2018 were identified for the study. After application of the inclusion and exclusion criteria, 63 patients were included for analysis; 34 (54.0%) were female and 29 (46.0%) were male. The mean age of patients was 66.4 (range 49.2–86.4) years [Table 1]. Of the 63 patients, 42 were given IA TXA and 21 were given PA TXA. All patients received PA anaesthetic cocktail infiltration.

In terms of blood loss efficacy, the absolute drop in POD 1 Hb in the PA group was slightly higher than in the IA group. The mean drop in POD 1 Hb in the PA and IA groups was not statistically significant (2.0 g/dL [14.9%] vs. 1.6 g/dL [11.9%], \( P = 0.10 \)). There was no intraoperative transfusion in both groups. Two patients underwent postoperative transfusion in the IA and one patient in the PA group, which was statistically insignificant (\( P = 0.83 \)). All three patients who were transfused postoperatively had pre-existing cardiovascular disease, which required their Hb to be ≥ 9 g/dL. The absolute drop in POD 1 Hct in the PA and IA groups was statistically insignificant.
(6.1 g/dL [15.4%] vs. 5.3 g/dL [12.6%], P = 0.58). Of the patients, only 14 and 7 had POD 2 and POD 3 Hb and Hct checks, respectively; hence, there were insufficient numbers for any meaningful analysis to be conducted.

For immediate functional outcomes, the mean POD 1 and POD 2 VAS scores of the PA group was 4.3 and 4.4, respectively, and that of the IA group was 5.4 and 4.3, respectively; these were not statistically significant (P = 0.50 and 0.98, respectively). The mean POD 1 flexion angle of the PA and IA groups was statistically insignificant (63.8° vs. 63.2°, P = 0.92). The mean discharge day flexion angle of the PA and IA groups was also statistically insignificant (90.3° vs. 83.6°, P = 0.11). The mean discharge day gait distance in the IA group was 29.2 m, achieved with the help of walking aids and a therapist. This was comparable to the PA group, where the mean distance was 34.1 m. This difference was not statistically significant (P = 0.40, SD 0.20 to 0.45). The mean length of inpatient hospitalisation stay in the IA group was 4.1 days as compared to 4.3 days in the PA group.

The patients were followed up for a mean duration of 6 months (range 3 months–1 year) from the date of surgery. There were no complications, particularly related to those of local TXA administration, such as symptomatic venous thromboembolism, skin necrosis, haemarthrosis or subcutaneous haematomas, nerve or vessel injuries, or seizures in either group at the end of follow-up.

A post hoc power analysis was done. There was 68% power when looking at the outcomes for blood loss (drop in Hb), 2.1% for outcomes of flexion angle on POD 1, 22.6% for VAS score and 55.3% for gait distance on discharge.

**DISCUSSION**

The main findings of this study were that PA administration of TXA is as effective as IA administration in minimising blood loss and they can be used together with local capsular infiltration of analgesia in a simple, combined procedure to reduce pain and increase early functional outcomes.

As an antifibrinolytic agent, TXA has shown significant recent promise in lowering postoperative blood loss in various surgical and medical procedures. Even though there is literature evaluating IV and IA TXA, there is a paucity of studies on PA TXA, and the best route of administration remains a matter of contention. Maniar et al.\(^{[12]}\) reported that IA TXA, as compared to no intervention, reduced blood loss, but Sarzaeem et al.\(^{[13]}\) found that IV administration led to less blood loss than topical IA irritation. However, Chen et al., in a double-blinded RCT, showed that IV and IA TXA had comparable effects on transfusion indices and perioperative blood loss, with no differences in postoperative limb swelling as a complication.\(^{[14]}\) Furthermore, in an editorial evaluating the current evidence, Chen et al. concluded that even though there is no consensus in the literature with regards to the ideal route of administration, IA TXA can be recommended for patients in whom IV TXA is contraindicated, since the efficacy of IA TXA in reducing perioperative blood transfusion incidence is not inferior to that of IV TXA and it does not have additional safety concerns.\(^{[15]}\)

A theoretically potential complication of IV TXA is venous thromboembolism. However, some studies have suggested that administration of IV TXA does not necessarily correlate with an increased risk of venous thromboembolism.\(^{[16,17]}\) Raveendran and Wong, in their systematic review and meta-analysis of 7,383 patients, showed that there are too few highly powered trials to concretely establish this notion.\(^{[18]}\) The study reported that the median sample size of the studies that analysed such adverse effects was too low to detect a difference in such rare events.

Both PA and IA administration have theoretical benefits of limiting systemic toxicity and leading to locally increased concentrations of the drug (in comparison to IV TXA), and hence, they are considered safe alternatives, especially in consideration of the complications associated with IV TXA as mentioned above.\(^{[19]}\) Tranexamic acid stabilises clot formation and promotes microvascular haemostasis, thereby decreasing haemorrhage after surgical haemostasis has been achieved.\(^{[20]}\) However, limitations of IA TXA have also been described in the literature. The effects of direct contact of TXA with polyethylene and other implant components are unknown, and the risks of implant damage cannot be ruled out.\(^{[9]}\) In addition, there is a dose-dependent toxic effect of IA TXA on the cartilage, tendon and synovial tissue.\(^{[21]}\) Intra-articular TXA requires the surgeon to clamp the drain postoperatively (where the surgeon prefers to use a drain). It has the theoretical risk of soft tissue leakage, particularly in knees where extensive releases have been performed. The relatively extended period of being supine may reduce the effectiveness of topical TXA in addressing bleeding from the anterior aspect of the knee.\(^{[8]}\)

Periarticular administration of TXA has not been well established in the literature, with only one study analysing a
dosage of 750 mg of TXA. A Boolean search of the PubMed and NLM databases using the terms ‘peri-articular’ and/or ‘tranexamic acid’ and/or ‘analgesia’ showed that no study had analysed the effect of increased PA dosages or compared the efficacy of PA versus IA TXA administration together with PA analgesic administration. Periarticular TXA allows selective administration of TXA into potential sites of bleeding and avoids the possible pitfalls of IA as described above.\textsuperscript{[9]} Our results show that postoperative Hb and Hct values dropped more in the PA group, but this difference was not significant. In terms of Hb concentration preservation, our results are similar to those reported in the current literature: Aguilera \textit{et al.} (IV),\textsuperscript{[22]} Mao \textit{et al.} (IA),\textsuperscript{[8]} Georgiades \textit{et al.} (IA)\textsuperscript{[23]} and Wong \textit{et al.} (IA).\textsuperscript{[19]}

Periarticular TXA has theoretical advantages in its mode of action in comparison to IA TXA. Firstly, it directly addresses the source of bleeding, especially from the surgical approach and soft tissue releases, during the peak period of bleeding after surgery. It can also work in the immediate postoperative period on the anterior structures in the knee, where a relatively longer period of being supine may otherwise affect the distribution of IA TXA. However, PA TXA is effective for soft tissue haemorrhage but not for IA haemorrhage, such as haemorrhage from the bone after osteotomy or intramedullary bleeding postinsertion of the femur guide. The literature also shows a dose-dependent toxic effect of TXA on the cartilage, tendon and synovial tissue, and this should ultimately play a role in the surgeon’s decision.\textsuperscript{[21]} Hence, PA route of administration should be weighed not only against IA, but also against IV and even a combination of IA/PA and IV route of administration.

Local infiltration of analgesia into these PA tissues has, however, shown promise with studies showing a reduction in immediate pain and improvement in functional outcomes.\textsuperscript{[14‑27]} To our knowledge, no study using a Boolean search using the terms ‘peri-articular’ and/or ‘tranexamic acid’ and/or ‘analgesia’, had shown that TXA can be injected in tissues that have already been injected with local anaesthetic infiltration previously. Periarticular analgesic infiltration avoids the potential side effects of conventional modes of analgesia (e.g. opioids), such as nausea, sedation, urine retention and respiratory depression. Well-established techniques, such as spinal anaesthesia and intrathecal morphine, have the potential risks of epidural bleeding, spinal headache and hypotension.\textsuperscript{[28‑31]} Peripheral nerve blocks, although free of the above mentioned side effects and risks, can lead to transient neurological deficits, hence impairing immediate mobilisation and physiotherapy.\textsuperscript{[32,33]}

Furthermore, we have routinely infiltrated only the medial and lateral capsule, the quadriceps and the sites of soft tissue releases. The posterior capsule was not injected in view of the theoretical risk of neurovascular injury to the structures in the popliteal fossa. Pinsornsak \textit{et al.}, in their double-blinded RCT, showed that routine infiltration of the posterior capsule is not required to attain good postoperative pain relief.\textsuperscript{[11]} However, we acknowledge that injecting the posterior capsule with TXA can also prevent significant bleeding from the posterior knee bone cuts.

Postoperative anaemia increases the risk of wound complications and leads to longer hospital stay and poor functional recovery.\textsuperscript{[13]} Our results also show that immediate postoperative pain scores, mean length of hospitalisation and mean gait distance were similar between the groups. This may suggest that local tissue concentrations of 1 g of TXA do not affect the viability of the anaesthetic agents. There were also no significant adverse effects in either group during a mean follow-up period of 6 months. Specifically, there were no complications related to the use of TXA, such as skin necrosis, symptomatic venous thromboembolism, subcutaneous haematoma, haemarthrosis, and nerve or vessel injuries from PA infiltration. Hence, the results suggest that TXA can be administered into the pericapsular tissue immediately after analgesic infiltration and has equal efficacy in both reducing postoperative blood loss and improving immediate postoperative pain scores and function, in comparison to the more commonly used combination of IATXA and pericapsular anaesthetic infiltration. Our study suggests that PA TXA and analgesia can be administered in an easy two-step procedure after implant insertion, with minimal immediate adverse reactions.

In our study, 1 g of TXA was injected into PA tissues. Pinsornsak \textit{et al.} used a dose of 750 mg TXA in the injection of pericapsular tissues.\textsuperscript{[9]} Although the advantage of using a higher dose is uncertain, this study suggests that 1 g can be safely injected into tissues, but further studies are needed to ascertain the optimal dose for PA injections and if toxicity and efficacy are dose related.

There are limitations to this study. This is a retrospective analysis with modest numbers, which analysed only immediate outcomes; hence, uncommon side effects such as symptomatic DVT and PE may not have been identified. Even though we compared patients between the groups in terms of gender, age, height, weight, body mass index, preoperative Hb, Hct and presence of antiplatelet medications, there was insufficient matching of the number of patients between the groups, and the \textit{P} values should ideally approach 0.99 to demonstrate that the differences between them were not significant. Another possible limitation of this study was that patients who were on antiplatelets were not excluded in this study. The potential increase in blood loss in the patients on antiplatelets could have been a confounding factor in the final analysis. The amount of ‘effective’ or ‘working’ dose of TXA via PA infiltration was also not analysed in this study, and this could be an area for future research. In addition, only 14 patients had POD 2
and seven patients had POD 3 Hb and Hct checks, and hence, there were insufficient numbers for any meaningful analysis to be conducted. The post hoc analysis also showed only 68% power when looking at the outcomes for blood loss (drop in Hb), 2.1% for outcomes of flexion angle on POD 1, 22.6% for VAS score and 55.3% for gait distance on discharge.

There are certain theoretical benefits of direct capsular infiltration as opposed to IA injections, and our study shows that this method did not result in any significant clinical differences in terms of blood loss. However, further RCTs with larger numbers are required to ascertain the long-term outcomes and adverse effects.

In conclusion, while our study has shown no difference in outcomes between PA and IA TXA administration in TKA patients, local infiltration of analgesia and TXA proves to be a simple yet promising modality in ensuring reduced postoperative blood loss and maximising pain relief and functional outcomes. Although more studies are needed in future to establish the safety and efficacy of this method, early results from this pilot study are promising and this dual modality, local infiltration technique can be considered an option by the arthroplasty surgeon.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Karam JA, Bloomfield MR, Dilorio TM, Irizarry AM, Sharkey PF. Evaluation of the efficacy and safety of tranexamic acid for reducing blood loss in bilateral total knee arthroplasty. J Arthroplasty 2014;29:501-3.
2. Vamvakas EC, Blajchman MA. Transfusion-related mortality: The ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood 2009;113:3406-17.
3. Dunn CJ, Goa KL. Tranexamic acid: A review of its use in surgery and other indications. Drugs 1999;57:1005-32.
4. Phabinger I, Fries D, Schöch H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr 2017;129:303-16.
5. Ralley FE, Berta D, Binns V, Howard J, Naudie DDR. One intraoperative dose of tranexamic acid for patients having primary hip or knee arthroplasty. Clin Orthop Relat Res 2010;468:1905-11.
6. 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;35:1639-45.
7. Franchini M, Mengoli C, Marietta M, Marano G, Vaglio S, Pupella S, et al. Safety of intraoperative tranexamic acid in patients undergoing majororthopaedic surgery: A meta-analysis of randomised controlled trials. Blood Transfus 2018;16:36-43.
8. Mao Z, Yue B, Wang Y, Yan M, Dai K. A comparative, retrospective study of peri-articular and intra-articular injection of tranexamic acid for the management of postoperative blood loss after total knee arthroplasty. BMC Musculoskelet Disord 2016;17:438.
9. Pinsornsak P, Rojanavijitkul S, Chumchuen S. Peri-articular tranexamic acid injection in total knee arthroplasty: A randomized controlled trial. BMC Musculoskeletal Disord 2016;17:313.
10. Spreng UJ, Dahl V, Hjal J, Lagerland MW, Ræder J. High-volume local infiltration analgesia combined with intravenous or local ketorolac-morphine compared with epidural analgesia after total knee arthroplasty. Br J Anaesth 2010;105:675-82.
11. Pinsornsak P, Nangnual S, Boontanapibul K. Multimodal infiltration of local anaesthetic in total knee arthroplasty; is posterior capsular infiltration worth the risk? A prospective, double-blind, randomised controlled trial. Bone Joint J 2017;99-B:483-8.
12. Maniar RN, Kumar G, Singh T, Nayak RM, Maniar PR. Most effective regimen of tranexamic acid in knee arthroplasty: A prospective randomized controlled study in 240 patients. Clin Orth Relat Res 2012;470:2605-12.
13. Sarrazcem MM, Razi M, Kazemian G, Moghaddam ME, Rasi AM, Karimi M. Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. J Arthroplasty 2014;29:1521-4.
14. Chen JY, Chin PL, Moo H, Pang HN, Tay DK, Chia SL, et al. Intra-articular versus intra-articular tranexamic acid in total knee arthroplasty: A double-blinded randomised controlled noninferiority trial. Knee 2016;23:152-6.
15. Chen JY, Chia SL, Lo NN, Yeo SJ. Intra-articular versus intravenous tranexamic acid in primary total knee replacement. Ann Transl Med 2015;3:33.
16. Alishyda S, Sarda P, Suveik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic acid in total knee replacement: A systematic review and meta-analysis. J Bone Joint Surg Br 2011;93:1577-85.
17. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: A meta-analysis. J Bone Joint Surg Am 2012;94:1153-9.
18. Raveendran R, Wong J. Tranexamic acid reduces blood transfusion in surgical patients while its effects on thromboembolic events and mortality are uncertain. Evid Based Med 2013;18:65-6.
19. Wong J, Abrihamsi 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 Joint Surg Am 2010;92:2503-13.
20. Reust DL, Reeves ST, Abernathy JH 3rd, Dixon JA, Gaillard WF 2nd, Mukherjee R, et al. Temporally and regionally disparate differences in plasmin activity by tranexamic acid. Anesth Analg 2010;110:694-701.
21. Bolam SM, O’Regan-Brown A, Paul Monk A, Musson DS, Cornish J, Munro JT. Toxicity of tranexamic acid (TXA) to intra-articular tissue in orthopaedic surgery: A scoping review. Knee Surg Sports Traumatol Arthrosoc 2021;29:1862-71.
22. Aguilera X, Martinez-Zapata MJ, Bosch A, Urrutia G, González JC, Jordan M, et al. Efficacy and safety of fibrin glue and tranexamic acid to prevent postoperative blood loss in total knee arthroplasty: A randomized controlled clinical trial. J Bone Joint Surg Am 2013;95:2001-7.
23. Georgiadis AG, Muh SJ, Silverton CD, Weir RM, Laker MW. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. J Arthroplasty 2013;28(8 Suppl):78-82.
24. Li C, Qu J, Pan S, Qu Y. Local infiltration anesthesia versus epidural analgesia for postoperative pain control in total knee arthroplasty: A systematic review and meta-analysis. J Orthop Surg Res 2018;13:112.
25. Kasture S, Saraf H. Epidural versus intra-articular infusion analgesia following total knee replacement. J Orthop Surg (Hong Kong) 2015;23:287-9.
26. Niemeläinen M, Kalliovalkama J, Aho AJ, Moilanen T, Eskelinen A. Single periarticular local infiltration analgesia reduces opiate consumption until 48 hours after total knee arthroplasty. A randomized placebo-controlled trial involving 56 patients. Acta Orthop 2014;85:614-9.
27. Affas F, Nygårds EB, Stiller CO, Wretenberg P, Olofsson C. Pain control after total knee arthroplasty: A randomized trial comparing local infiltration anesthesia and continuous femoral block. Acta Orthop 2011;82:441-7.
28. Wangnamthip S, Chinchotii T, Amornotin S, Wongtangman K, Sukantar N, Noitasang P. A randomized placebo-controlled trial of oral ramosefet for prevention of post operative nausea and vomiting after intraartefinal morphine in patients undergoing gynecological surgery. J Med Assoc Thai 2016;99:455-61.
29. Laurret GR, Righetti CCF, Mattos AL. Intrathecal ketorolac enhances post
intrathecal morphine analgesia following total knee arthroplasty.
J Anaesthesiol Clin Pharmacol 2013;29:503-8.
30. Shanthanna H, Huigol M, Manivackam VK, Maniar A. Comparative study of ultrasound-guided continuous femoral nerve blockade with continuous epidural analgesia for pain relief following total knee replacement. Indian J Anaesth 2012;56:270-5.
31. Nakamura M, Kamei M, Bito S, Migita K, Miyata S, Kumagai K, et al. Spinal anesthesia increases the risk of venous thromboembolism in total arthroplasty: Secondary analysis of a J-PSVT cohort study on anesthesia. Medicine (Baltimore) 2017;96:e6748.
32. Liu SS, Zayas VM, Gordon MA, Beathie JC, Maalouf DB, Paroli L, et al. A prospective, randomized, controlled trial comparing ultrasound versus nerve stimulator guidance for interscalene block for ambulatory shoulder surgery for postoperative neurological symptoms. Anesth Analg 2009;109:265-71.
33. Kent CD, Bollag L. Neurological adverse events following regional anesthesia administration. Local Reg Anesth 2010;3:115-23.
34. Li B, Wen Y, Liu D, Tian L. The effect of knee position on blood loss and range of motion following total knee arthroplasty. Knee Surg Sports Traumatol Arthrosoc 2012;20:594-9.