# Local infiltration of analgesia and tranexamic acid is safe and efficacious in reducing blood loss and comparable to intra-articular tranexamic acid in total knee replacements

Harish Sivasubramanian[1], MBBS, MRCS, Cheryl Marise Peilin Tan[1], MBBS, Lushun Wang[1], MMed, FRCSEd

[1]Department of Orthopaedic Surgery, Ng Teng Fong Hospital, National University Health System, Singapore

**Correspondence:** Dr Tan Peilin Cheryl Marise, Medical Officer, Department of Orthopaedic Surgery, Ng Teng Fong Hospital, 1 Jurong East Street 21, Singapore 609606. cherylfrancescatan@gmail.com

More information, including how to cite online first accepted articles, can be found at: http://www.smj.org.sg/accepted-articles

**ABSTRACT**

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

**Methods:** 63 patients who underwent a unilateral primary total knee replacement procedure were divided into 2 groups: 42 patients in the IA TXA delivery group, 21 patients in the PA TXA group. 1g of TXA was utilized for all patients. All patients had pericapsular infiltration consisting of 0.5ml of Adrenaline, 0.4ml of Morphine, 1g of Vancomycin, 1ml of Ketorolac and 15ml of Ropivacaine. Outcomes for blood loss, and surrogate markers for immediate functional recovery were measured.

**Results:** 54.0% of the patients were female, 46.0% male. The mean drop in post-operative Hb levels in the PA and IA group was 2.0g/dL and 1.6 g/dL respectively, and statistically insignificant (p=0.10). The mean HCT drop in the PA and IA group was 6.1% and 5.3% respectively and statistically insignificant (p=0.58). The POD 1 and discharge day flexion angles, POD 1 and POD 2 VAS scores, gait distance on discharge, and length of hospitalization stay were largely similar in both groups.

**Conclusion:** Our study shows that both IA and PA TXA with analgesic components are 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**

Post-operative blood loss is a major concern in total knee arthroplasty (TKA). Considerable blood loss is often observed, ranging from 1000 to 1500ml after knee replacements, and patients often require a blood transfusion.[1] Allogenic blood transfusions are a costly procedure, and are 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 literature to reduce blood loss, including the use of tranexamic acid (TXA). TXA inhibits the conversion of plasminogen to plasmin, thereby preventing fibrinolysis, hence causing fibrin clot stabilisation.[3,4] Multiple modalities of TXA deliverance have been described.[5] Multiple medical co-morbidities such as cardiac and renal disease can affect its use, 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 post-operative drains are preferred or required.[9] Furthermore, the long-term effect of TXA on metal and polyethylene is not known, meaning future implant-related issues could be a real possibility.[9]

A Boolean search of the PubMed and the NLM databases using the terms 'peri-articular' and 'tranexamic acid' show that the peri-articular (PA) mode of infiltration of TXA is a method that has been not well covered in the literature. Theoretically, infiltrating the peri-articular capsular tissues directly addresses the source of bleeding as well as avoids the systemic toxicity associated with 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 terms of reducing post-operative blood loss, compared to IA TXA as it addresses sites of potential blood loss directly. Our second hypothesis was that addition of TXA into the peri-capsular tissues will not affect the analgesic efficacy of the local anaesthetic cocktail and this combination will have minimum side effects. Our study aims to compare the effects of IA and PA TXA with analgesic components in reducing blood loss and improving immediate post-operative pain relief and functional outcomes in unilateral primary total knee replacement (TKA) patients.

**METHODS**

Patient records were accessed retrospectively via computerised patient data collection systems. Appropriate ethical and Institutional Review Board (IRB) clearance was obtained before such access was conducted (Ref: 2018/00954).

This retrospective cohort study was conducted to include operated patients from July 2017 to July 2018. 87 patients were initially identified. The inclusion criteria were patients with symptomatic primary osteoarthritis of the knee, failed conservative treatment necessitating a primary total knee replacement. Exclusion criteria were history of previous venous thromboembolism prior to 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 pre-operative haemoglobin levels of < 9 g/dL (Fig. 1). After the application of inclusion and exclusion criteria (Fig. 1), the records of 63 patients who had undergone a primary, unilateral total knee replacement were accessed. Two groups were created: one was a group of patients with PA TXA and local capsular infiltration of analgesia, and the other was a group of patients with IA TXA with local capsular infiltration of analgesia. 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 a knee replacement under a single surgeon at a tertiary medical centre. Patients with significant co-morbidities had been referred for pre-operative anaesthetic optimization, but otherwise, all went through the same pre-operative procedures. The same technique had been reproduced in all patients: 55 patients (87.3%) underwent a general anaesthesia and 8 patients (12.7%) underwent a spinal; all of them without the adjunct of a nerve block. Intravenous 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. A cemented fixed bearing prosthesis was used in all cases. The TKAs were conventional, with posterior stabilised (PS) implants, and the intramedullary canal not being covered. A routine patelloplasty was performed for all patients and none of the patellae were replaced. Patelloplasty refers to a circumferential denervation of the patella with electrocautery and excision of osteophytic overgrowth of the patella. Intra-operative haemostasis was not routinely performed by the surgeon with the tourniquet deflated. IA and PA TXA was administered prior to deflation of the tourniquet in all cases. All patients had a local infiltration of analgesia into the peri-articular region before closure. The analgesic regime consisted of Adrenaline 0.5ml, Morphine 0.4ml, Vancomycin 1g, Ketorolac 1ml and Ropivacaine 15ml. The regions of the capsule that the cocktail was delivered include: medial and lateral capsule, quadriceps and the tibial soft tissue release sites (Fig. 2a-d). The amount administered was divided equally amongst the 4 regions. No infiltration was given to the posterior aspect of the capsule. The dose of TXA given was higher than the only reported RCT study of PA TXA in the literature (750mg vs 1g).[7] In the intra-articular (IA) group, 1g of TXA was delivered via an intra-articular injection after capsular closure. In the (PA) group, 1g of TXA was injected into the same peri-articular quadrants as the analgesic cocktail before closure. The amount

administered was also divided equally amongst the 4 regions. No drains were used, and all patients had bulky dressings applied post-operatively.

The outcomes measured were broadly divided into two categories to correlate with the objectives of this study: blood loss and immediate functional outcomes. Post-operative day (POD) 1 haemoglobin (Hb) and haematocrit (Hct) counts, 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 pre-operative figures. Flexion angle on POD 1 and discharge day, gait distance on discharge, Visual Analog Score (VAS) POD1 and VAS POD 2, and length of inpatient stay were used to assess functional outcomes. All flexion angles were measured by the physiotherapist on POD1 and discharge day using goniometers and were done only after removal of bulk dressings. Gait distance is measured by the same physiotherapist on POD1 and on discharge using calibrated measurement devices for each stride of the patient. VAS scores were explained to patients via the use of descriptive charts and recorded by the team doctors and / or the 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 hematomas, hemarthrosis, 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 < 8.5g/dL was used unless the patient was symptomatic, or had cardiovascular comorbidities necessitating the 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 on a mean of 6 months from the date of surgery (range 3months to 1 year), where particularly emphasis was placed on identifying complications related to the administration of TXA.

All the data collected were analysed to ascertain normal distribution before analysis was performed. The skewness and the kurtosis of the data collected had a normal distribution. Hence, the data was analysed using parametric statistical tests. Continuous data was analysed using the unpaired Student's t-test to analyse the significance of any difference between the mean values of the 2 normally distributed groups. The unpaired Student t-test was used as the 2 groups that were analysed were independent of each other. This value is expressed in mean with standard deviation in the presented tables. All statistical analyses were performed using SPSS computerised software (IBM Corporation). P-values $< 0.05$ were considered statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (include name of committee + reference number) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**RESULTS**

87 patients from the period of July 2017 to July 2018 were identified. Patient's data that were to be analysed were only selected after the application of inclusion and exclusion criteria. 63 patients were included for analysis. 34 of the patients were female (54.0%) and 29 were male (46.0%). The mean age was 66.4 years (range from 49.2 to 86.4) (Table I). 42 were given IA

tranexamic acid and 21 were given PA tranexamic acid. All of them received peri-articular anaesthetic cocktail infiltration.

The absolute drop in POD 1 Hb for the PA group was slightly higher than the IA group. The mean drop in POD 1 Hb in the IA group was 1.6 g/dL while the mean drop in POD 1 Hb of the PA group was 2.0 g/dL, which were not statistically significant (p=0.10) (Table II). There were 0 intra-operative transfusions amongst both groups and there were 2 patients who were transfused post-operatively in the IA group and 1 in the PA group. This was also not statistically significant (p=0.83). All of the three patients who were transfused postoperatively had pre-existing cardiovascular disease which required their Hb to be at or above the level of 9 g/dL. The absolute drop in POD 1 Hct in the IA group was 5.3 % compared to 6.1% in the PA group, which was also not statistically significant (p=0.58) (Table II). Only 14 patients had POD 2 and 7 had POD 3 Hb and Hct checks, hence sufficient numbers were not obtained for any meaningful analysis to be conducted.

The mean POD 1 and POD2 VAS score are shown in Table III and were not statistically significant (p=0.50 and p=0.98 respectively). The mean POD 1 flexion angle was 63.2 degrees in the IA group compared to 63.8 degrees in the PA group and were also not statistically significant. The mean discharge day flexion angle in the IA and PA groups (Table III) were also not statistically significant (p=0.11). The mean discharge day gait distance in the IA group was 29.2m with the help of walking aids and a therapist. This was in comparison to the PA group where the mean was 34.1m. This difference was not significant (p=0.4, ~~SD 0.20 to 0.45~~). The mean length of inpatient hospitalization stay in the IA group was 4.1 days compared to 4.3 days in the PA group.

The patients had been followed up on a mean of 6 months from the date of surgery (range 3months – 1 year). There were no complications, particularly related to that of local TXA administration, such as symptomatic venous thromboembolism, skin necrosis,

hemarthrosis or subcutaneous hematomas, nerve or vessel injuries or seizures detected 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 POD1, 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 in minimising blood loss, and can be used together with local capsular infiltration of analgesia in a simple, combined procedure to reduce pain and increase early functional outcomes.

TXA, as an anti-fibrinolytic agent, has shown significant recent promise in lowering post-operative blood loss in various surgical and medical procedures. Even though there is literature evaluating IV and IA TXA, there is a paucity regarding PA TXA, and the best route of administration remains a matter of contention: Maniar et al reported that IA TXA, compared to no intervention, reduced blood loss but Sarzaeem et al found that IV administration led to less blood loss than topical IA irrigation.[12,13] However, Chen et al, in a double-blinded, randomised controlled trial, showed that IV and IA TXA had comparable effects on transfusion indices and perioperative blood loss with no differences in post-operative limb swelling as a complication.[14] Furthermore, in an editorial evaluating the current evidence, Chen et al conclude that even though there is no consensus in the literature with regards to the ideal route of administration, IA TXA can be recommended in patients whom IV TXA is cautioned, since the efficacy of IA TXA in reducing perioperative blood transfusion incidence is not inferior to IV TXA, and does not have additional safety concerns.[15]

A theoretical potential complication of IV TXA includes venous thromboembolism. Some studies, on the other hand, have suggested that administration of IV TXA does not

necessarily correlate with an increased risk of venous thromboembolism.[16,17] However, Raveendran et al in his systemic 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 notes that the median sample size of the studies that analysed such adverse effects was too low to detect a difference in such rare events.

PA or IA administration has theoretical benefits of limiting systemic toxicity and benefits of locally increased concentrations (in comparison to IV TXA), and hence it has been considered a safe alternative, especially in consideration of the complications associated with IV TXA as mentioned in the paragraph above.[19] TXA stabilises clot formation and promotes microvascular haemostasis, thereby decreasing haemorrhage after surgical haemostasis has been achieved.[20] There are, however, limitations of IA TXA that have also been described in the literature. The effects of direct contact of TXA with polyethylene and the other implant components are unknown, and risks of implant damage cannot be ruled out.[9] In addition, there is a dose dependent toxic effect of IA TXA on cartilage, tendon and synovial tissue.[21] IA TXA requires the surgeon to clamp the drain postoperatively (where the surgeon prefers to use a drain). IA TXA 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]

PA administration of TXA has not been well established in literature, with only 1 study analysing a dosage of 750mg of TXA. A Boolean search of the PubMed and the 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 peri-articular vs intra-articular TXA administration together with periarticular analgesic administration. PA TXA allows selective administration of TXA into potential sites of bleeding

and avoids the possible pitfalls of IA as described in the paragraph above.[6] Our results show that post-operative Hb and Hct values dropped more in the peri-articular group, but this difference was not significant. Our results, in terms of Hb concentration preservation, are similar when compared to current literature: Aguilera et al (IV), Mao et al (IA), Georgiadis et al (IA), and Wong et al (IA).[8,19,22,23]

PA 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 post-operative 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 intra-articular haemorrhage, such as haemorrhage from bone after osteotomy or intra-medullary bleeding post insertion of the femur guide. The literature also shows a dose-dependent toxic effect of TXA on cartilage, tendon and synovial tissue and this should ultimately play a role in the surgeon's decision.[21] Hence, a PA route of administration should also be weighed not only against IA, but also IV and even a combination of IA/PA and IV.

Local infiltration of analgesia into these peri-articular tissues has, however, shown promise with studies showing a reduction in immediate pain and improvement in functional outcomes.[24-27] No other study, to the authors' knowledge via 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 prior. Peri-articular analgesic infiltration avoids the potential side effects with conventional modes of analgesia such as opioids - 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.[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.[32,33]

Furthermore, the author of this study only routinely infiltrated 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 et al, in his double-blinded, randomized controlled trial, showed that routine infiltration of the posterior capsule is not required to attain good post-operative pain relief.[11] However, the authors of this study do acknowledge that injecting the posterior capsule with TXA can also prevent significant bleeding from the posterior knee bone cuts.

Post-operative anaemia increases the risk of wound complications, longer hospital stay and poor functional recovery.[34] Our results also show that immediate post-operative pain scores, mean length of hospitalisation and mean gait distance were similar between both groups. This may suggest that local tissue concentrations of 1g of TXA do not affect the viability of the anaesthetic agents. There were also no significant adverse effects in either group on a mean of a 6-month follow-up period. Specifically, there were no complications relating to the use of TXA such as skin necrosis, symptomatic venous thromboembolism, subcutaneous hematomas, hemarthrosis, and nerve or vessel injuries from peri-articular infiltration. Hence, the results suggest that TXA can be administered into peri-capsular tissue immediately after analgesic infiltration and have equal efficacy in both reducing post-operative blood loss, and improving immediate post-operative pain scores and function, in comparison to the more commonly used combination of intra-articular TXA and pericapsular anaesthetic infiltration. Our study suggests that peri-articular TXA and analgesia can be administered in an easy 2-step procedure after implant insertion with minimal immediate adverse reactions.

1g of TXA was injected into peri-articular tissues in this study. Pinsornsak et al used a 750mg dose in the injection of pericapsular tissues with TXA.[9] Although the advantage of

using this higher dose is uncertain, this study suggests that 1g can be safely injected into tissues but further studies are also needed to ascertain the optimal dose for peri-articular injections and if toxicity and indeed efficacy is dose-related.

There are limitations to this study. This is a retrospective analysis with modest numbers which only analyses 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 sex, age, height, weight, BMI, preoperative Hb, HCT and presence of anti-platelet medications, there was insufficient matching of the number of patients between both groups, and the 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 anti-platelets were not excluded by this study. The potential increased blood loss from patients on anti-platelets could have been a confounding factor in the final analysis. The amount of 'effective' or 'working' dose of TXA via peri-articular infiltration was also not analysed by this study, and this could be an area for future research. In addition, only 14 patients had POD 2 and 7 had POD 3 Hb and Hct checks, hence sufficient numbers were not obtained 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 POD1, 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 intra-articular injections, and this study shows that this method did not result in any significant clinical differences in terms of blood loss. However, further randomised control trials 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 total knee replacement patients, LIAT (Local Infiltration of Analgesia and Tranexamic Acid) proves to be a simple yet promising modality in ensuring

reduced postoperative blood loss and maximising pain relief and functional outcomes. Although further, more powered studies are needed 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.

**REFERENCES**

1.      Karam JA, Bloomfield MR, DiIorio 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.      Pabinger I, Fries D, Schöchl 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, 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, et al. Safety of intravenous 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 Musculoskelet Disord 2016; 17:313.

10.   Spreng UJ, Dahl V, Hjall A, Fagerland 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, 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; 470:2605-12.

13.   Sarzaeem MM, Razi M, Kazemian G, et al. 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 IH, et al. Intravenous 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.    Alshryda S, Sarda P, Sukeik M, et al. 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, Abrishami A, El Beheiry H, 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, 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, et al. Toxicity of tranexamic acid (TXA)
       to intra-articular tissue in orthopaedic surgery: a scoping review. Knee Surg Sports
       Traumatol Arthrosc 2020 Aug 29. https://doi.org/.10.1007/s00167-020-06219-7. [Epub
       ahead of print]

22.    Aguilera X, Martinez-Zapata MJ, Bosch A, 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, Chinachoti T, Amornyotin S, et al. A randomized placebo-controlled trial of oral ramosetron for prevention of post operative nausea and vomiting after intrathecal morphine in patients undergoing gynecological surgery. J Med Assoc Thai 2016; 99:455-61.

29. Lauretti GR, Righeti CCF, Mattos AL. Intrathecal ketorolac enhances intrathecal morphine analgesia following total knee arthroplasty. J Anaesthesiol Clin Pharmacol 2013; 29:503-8.

30. Shanthanna H, Huilgol 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, 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, 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 Arthrosc 2012; 20:594-9.
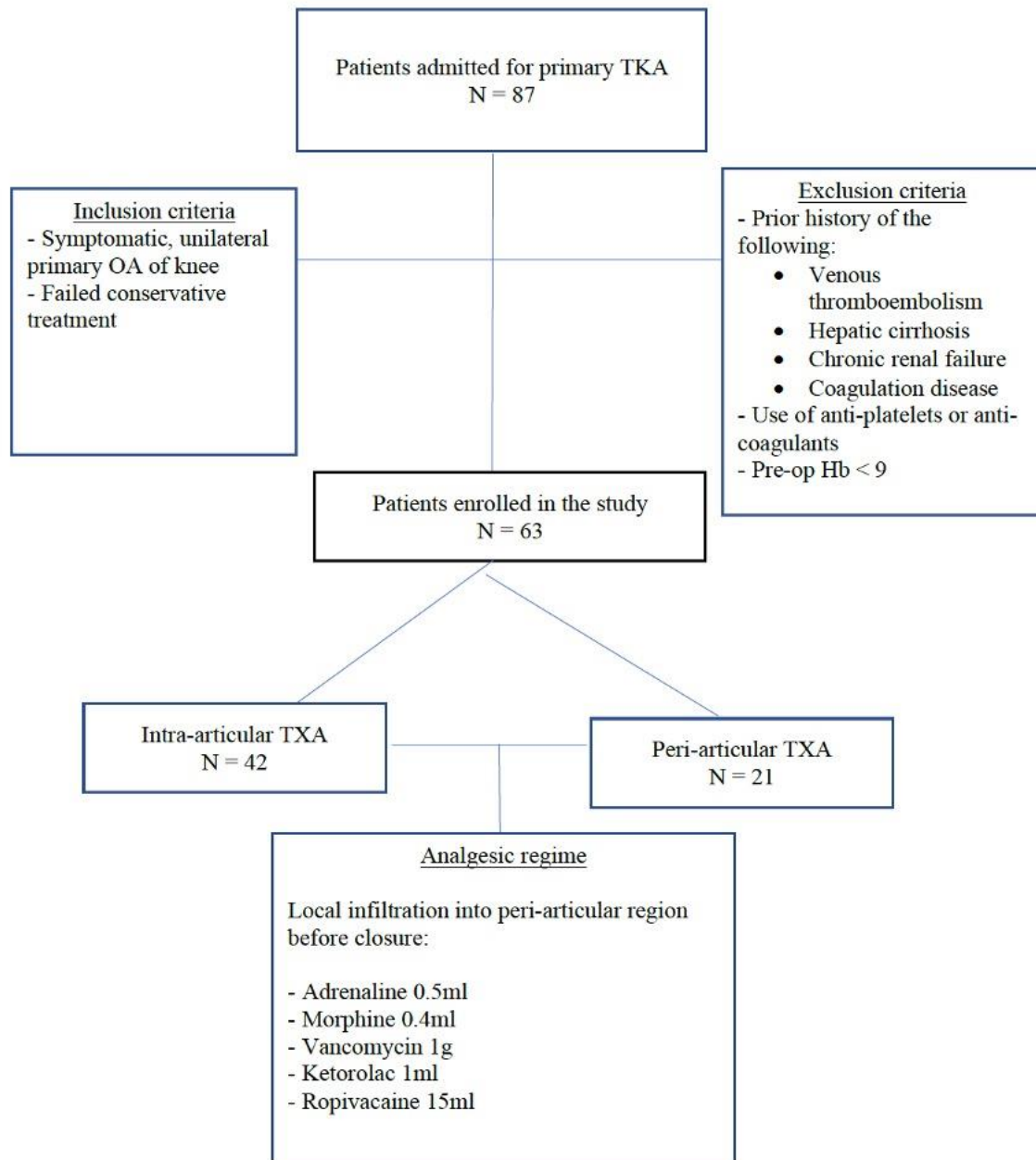
**Fig. 1** Selection process of patient records that were analysed.

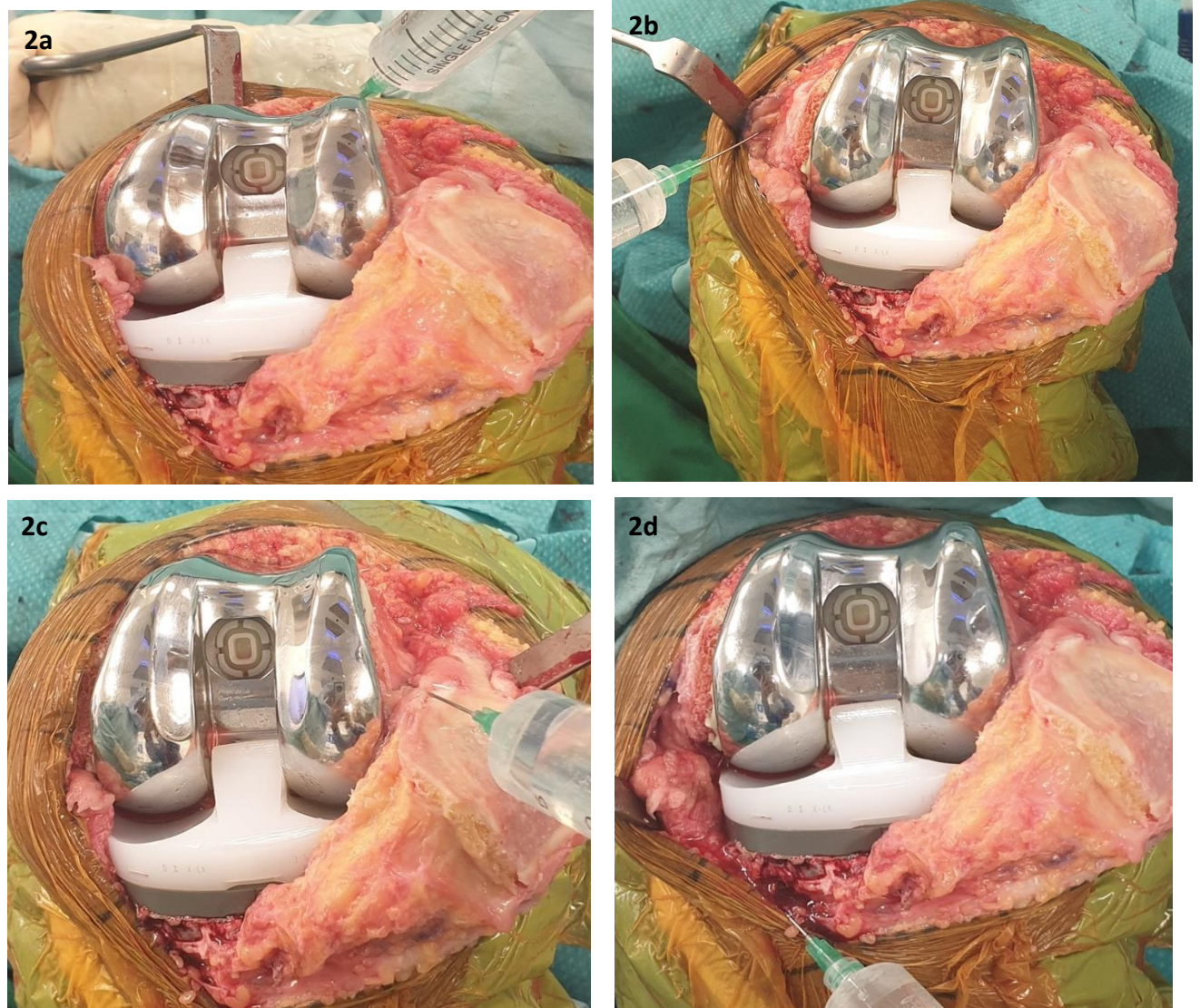TKA: total knee arthroplasty; OA: osteoarthritis; Hb: haemoglobin; TXA: tranexamic acid

**Fig. 2a–d** Peri-articular infiltration of TXA into the quadriceps region, medial capsule, lateral capsule and tibial soft tissue.

**Table I. Patient demographics.**

| Demographic | Peri-articular group (n = 21) | Intra-articular group (n = 42) | p-value |
|---|---|---|---|
| Gender (number of male/female) | 9/12 | 20/22 | 0.42 |
| Age (Yr) | 65.5 | 66.8 | 0.31 |
| Height (cm) | 167.5 | 164.8 | 0.12 |
| Weight (kg) | 57.4 | 58.2 | 0.58 |
| BMI (kg/m$^2$) | 20.6 | 21.5 | 0.23 |
| Preoperative Hemoglobin (g/dL) | 12.7 | 12.5 | 0.17 |
| Preoperative Hematocrit (%) | 38.2 | 38.4 | 0.69 |

Values expressed as mean. BMI: body mass index


**Table II. Blood loss efficacy.**

| Outcome | Peri-articular group | Intra-articular group | p-value |
|---|---|---|---|
| Drop in Hb (POD1) | 2.0 g/dL | 1.6 g/dL | 0.10 |
|    a. % drop | 14.9% | 11.9% | 0.22 |
| Drop in Hct (POD1) | 6.1% | 5.3% | 0.58 |
|    a. % drop | 15.4% | 12.6% | 0.44 |
| Post-operative transfusions | 1 | 2 | 0.83 |

Values expressed as mean. Hb: hemoglobin; Hct: hematocrit; POD1: postoperative day 1


**Table III. Immediate functional outcomes.**

| Outcome | Peri-articular group | Intra-articular group | p-value |
|---|---|---|---|
| Flexion angle (degree) | | | |
|    a. POD 1 | 63.8 | 63.2 | 0.92 |
|    b. Discharge day | 90.3 | 83.6 | 0.11 |
| VAS score | | | |
|    a. POD 1 | 4.3 | 5.4 | 0.50 |
|    b. POD 2 | 4.4 | 4.3 | 0.98 |
| Gait distance on discharge (m) | 34.1 | 29.2 | 0.40 |
| Length of hospital stay (day) | 4.3 | 4.1 | 0.67 |

Values expressed as mean.