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Original article

Comparison of oral vs. combined topical/intravenous/oral tranexamic acid in the prevention of blood loss in total knee arthroplasty: A randomised clinical trial

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ABSTRACT

Background: Tranexamic acid (TXA) has long been used to reduce blood loss associated with total knee arthroplasty (TKA). Debate remains over the best administration route with limited data comparing regimes including, to date, no studies investigating the equivalence of oral TXA and a combined topical/intravenous (IV) regime. Therefore, the aim of this study was to compare the efficacy and safety of oral TXA to combined topical/IV/oral TXA.
Working hypothesis: We postulated that oral TXA would offer the same efficacy and safety as combined topical/IV/oral regime. We asked: (1) Would blood loss and haemoglobin change be affected? (2) Would complication rates increase?
Patients and methods: Patients were randomised into either the study group (oral TXA regimen) or the control group (combined topical/IV/oral TXA). Both groups were administered three doses of TXA and received the same post-operative venous thromboembolism prophylaxis. Efficacy outcomes including blood loss and haemoglobin (Hb) change were investigated, together with safety outcomes of incidence of deep vein thrombosis and adverse events.
Results: The study ($n=25$) and control ($n=28$) group were comparable at baseline (eg pre-op haemoglobin). No significant difference was found between the study and control group in terms of Hb change (32.9 ± 8.9 vs. 31.8 ± 10.4, $p=0.687$) or blood loss (measured 640.0 ± 291.1 vs. 538.3 ± 270.2, $p=0.173$ and total 1211.5 ± 336.0 vs. 1092.9 ± 341.4, $p=0.214$). No cases of DVT were reported for either group and no statistical differences were found in the incidence of adverse events (nausea, hypotension, constipation) between groups.
Discussion: This study has shown for the first time that an oral TXA regimen is non-inferior to a topical/IV/oral regimen in TKA in efficacy and safety. Utilising oral TXA in place of a combined topical/IV/oral regime can significantly reduce costs without compromising patient outcomes.
Level of evidence: II, Randomised controlled trial.

1. Introduction

In Australia there were 47,087 total knee arthroplasties (TKAs) conducted between 2014–15 for the primary diagnosis of osteoarthritis [1]. TKAs result in blood loss with up to 46% of unilateral procedures requiring blood transfusions [2]. Tranexamic acid (TXA), an antifibrinolytic agent that induces blood clot formation, is commonly used to reduce blood loss and prevent the need for blood transfusions [3].

TXA use during TKA results in significantly reduced blood loss compared to placebo [4] with administration via the intravenous (IV) [5], topical [6] and oral [7] route all effectively reducing blood loss associated with TKA. The combination of topical and IV TXA has been shown superior to IV only protocols in terms of reducing blood loss [8–10] and a recent meta-analysis by Sridharan and Sivaramakrishnan [11] concluded that the combined topical/IV TXA may perform better than other regimes in reduction of blood

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transfusion rates. Comparative studies of oral to IV TXA have shown non-inferiority [12,13] with a meta-analysis by Wang et al. [14] demonstrating no significant difference between oral and IV TXA in terms of blood loss, postoperative haemoglobin (Hb) or transfusion rates. Similarly, a meta-analysis by Guo et al. [15] suggested oral TXA provided reduced drain output and Hb drop with no increased need for blood transfusions, but this was when compared to placebo. Recently, a network meta-analysis by Fillingham et al. [16] did not observe any treatment as superior to oral TXA for TKA and found no clear difference between available TXA administration regimes. Interestingly, these authors [16] estimated no difference in blood loss between an IV/topical and oral TXA regime but this was based on indirect measures due to a lack of available literature on the direct comparison. To date, no reports of a comparison of oral TXA versus a topical/IV/oral combination of TXA have been found in the literature. Therefore, for the first time, this study aimed to demonstrate the non-inferiority of oral TXA versus a topical/IV/oral regimen of TXA in TKA. We asked if:

- blood losses and haemoglobin change would be consistent?
- complication rates would increase including deep vein thrombosis and TXA adverse effects?

2. Patients and Method

2.1. Study population

Approval for this prospective, randomised trial was obtained from two Research and Ethics Committee, namely Greenslopes (17/25) and Griffith University (2017/541) and registered with the Australia and New Zealand Clinical Trial Register (ACTRN12617000617369P).

Patients scheduled for TKA by the collaborating orthopaedic surgeon during the trial period, August 2017 to September 2018, were eligible to participate. Exclusion criteria included bilateral TKA, allergy to TXA, history of bleeding disorders, use of anticoagulants or antithrombotics within 7 days of surgery, inability to take apixaban as post-surgical venous thromboembolism (VTE) prophylaxis, and the presence of contraindications to the use of TXA. All participants were required to be over the age of 18 and able to provide informed consent prior to surgery.

Participants were assigned to one of two groups determined by randomisation using a blocking method. The study group received oral TXA and the control group a mixed topical/IV/oral regime as this was the standard procedure used prior to the commencement of the study at the participating institution. Both groups were administered three doses of TXA (Cyklokapron®, Pfizer, Sydney, Australia). The study group received an oral 1 g dose two hours prior to the commencement of surgery, a second 1 g oral dose two hours post-surgery and a final 1 g oral dose six hours post-surgery. The control group received a 3 g topical application of TXA perioperatively, a 1 g IV dose TXA dose at two hours post-surgery and a final 1 g oral dose six hours post-surgery.

During the study period 48 potential participants were excluded for reasons outlined in Fig. 1. Of the 53 patients that were finally enrolled, 25 (47.2%) were randomised to the study group and 28 (52.8%) to the control group (Table 1). One patient in the study group did not have Hb after surgery recorded but remained included in the study. The demographic characteristics were similar across the two groups, although the study group had a higher number of patients ($n = 20$, 80%) with right-sided surgery compared to the control group ($n = 15$, 53.6%) but there was no significant difference in the duration of surgery or length of stay in hospital between groups (Table 1).

2.2. Surgical Protocol

All surgeries were conducted by the same orthopaedic surgeon. The Attune® Knee System (DePuy Synthes, Sydney, Australia) implants were inserted then balanced, adjusted and cemented in place. The knee was lavaged with aqueous betadine and the topical tranexamic acid applied for five minutes prior to closure of the incision. No tourniquet was used. A suction drain was inserted and removed the morning after surgery.

Pain management initially involved parenteral opioids dosed by nursing staff or patient controlled analgesia depending on patient preference. Pain was managed entirely orally by day two with an anti-inflammatory and opioids (combination of slow release plus immediate release for breakthrough pain). Post-operative protocol included mobilising the patient on the day of surgery and from day two having the patient up and exercising at least twice daily with discharged planned for day 3 or 4. Post-surgery all participants received protocol VTE prophylaxis consisting of apixaban (Eliquis®, Bristol Meyers Squibb, Melbourne, Australia) 2.5 mg twice daily commenced 8 hours post-surgery and continued for 15 days. During the post-operative hospital stay participants were monitored for signs of VTE and a Doppler ultrasound conducted if required. A follow-up bilateral Doppler ultrasound of the legs was conducted six weeks after surgery to exclude evidence of post-surgical deep vein thrombosis (DVT).

2.3. Outcomes

Two primary efficacy outcomes were investigated, namely Hb levels and blood loss. Pre-surgery Hb levels and Hb measured on the day after surgery were used to calculate the Hb change due to surgery. Hb change was used as a primary outcome as it accounts for visible blood loss and also hidden blood loss [17] and guides the need for blood transfusions. Secondly, blood loss volume due to TKA was investigated by measurement of blood lost in the operating theatre by the anaesthetist. Post-operative blood loss was measured by means of a Bellovac drain which remained in place until the day after surgery, the volume of blood in the drain was recorded upon removal. The volume of theatre and drain blood loss was reported as measured blood loss. The Nadler formula [18] was used to calculate blood volume and the Meunier's formula [19] used to calculate and report total blood loss. Blood transfusions were also another efficacy outcome. Pre-operatively, any patients with abnormal iron storage were seen by a haematologist and this was corrected prior to surgery if needed. Intra- and post-operatively, blood transfusion was performed on all patients with a haemoglobin below 80 g/L or at higher haemoglobin levels dependent on patient specific indications as outlined by the National Blood Authority of Australia. Post-operatively patients with acute myocardial or cerebrovascular ischemia and a haemoglobin level inferior to 100 g/L were recommended for transfusion whereas in the absence of these conditions post-operative transfusion was not required with haemoglobin levels > 80 g/L. The primary safety outcome was the incidence of DVT during the post-operative period. A secondary safety outcome was comparison of reported adverse events.

2.4. Statistical analysis

All data was recorded in the IBM SPSS program Statistics 24.0 and this program was used for statistical analysis. A one-way ANOVA was used to compare results between the groups for normalised continuous data. For any continuous data that was not normally distributed a Kruskal-Wallis analysis was used. For discrete data a chi-square test was used to assess significance of differences between groups. Pre-study power analysis determined

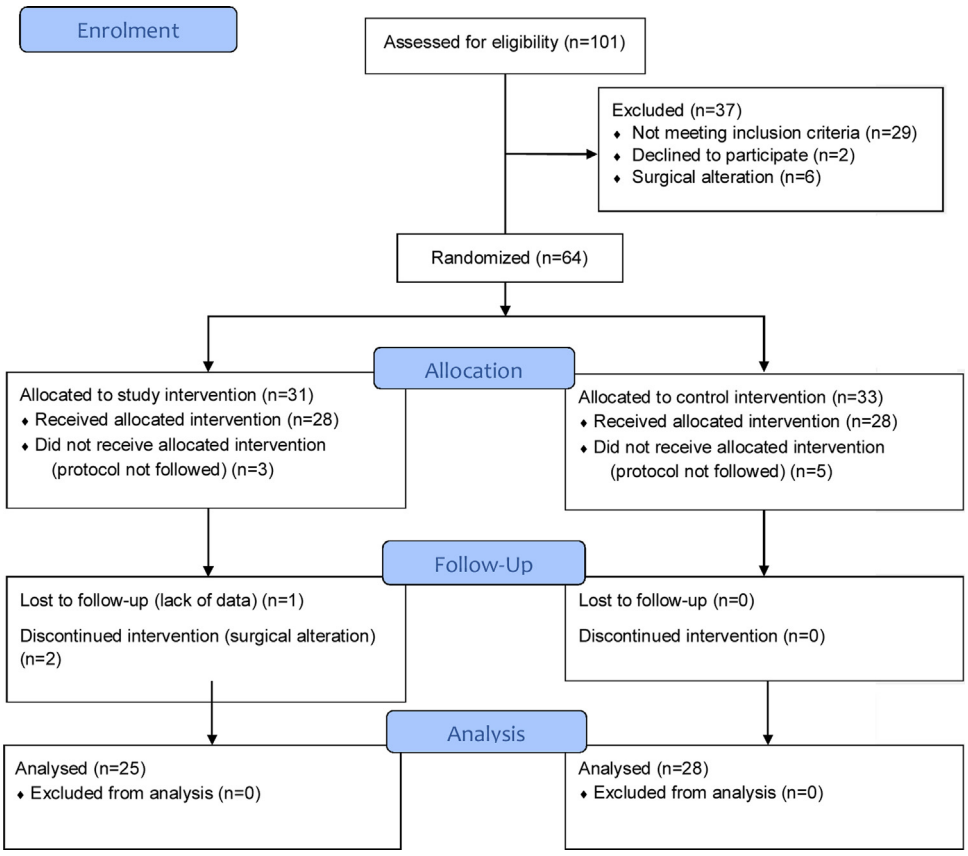

Fig. 1. CONSORT patient screening process.

Table 1
Patient demographics of study and control group. Data shown is number and percentage for gender and surgery side, mean and standard deviation for other variables.

Variable	Study ($n = 25$)	Control ($n = 28$)	p-value
Gender			
Male	14 (56.0)	12 (42.9)	0.289
Female	11 (44.0)	16 (57.1)	0.289
Age (years)	65.4 (8.8)	63.8 (9.7)	0.540
Weight (kilograms)	90.2 (16.72)	86.4 (16.3)	0.414
BMI (kilogram/metre^2)	30.1 (4.8)	30.2 (4.6)	0.943
Hb level (pre-op) (g/L)	142.2 (11.7)	142.0 (13.3)	0.937
Surgery Side			
Left	5 (20.0)	13 (46.4)	0.043
Right	20 (80.0)	15 (53.6)	0.043
Surgery Duration (Minutes)	138.2 (20.8)	140.5 (21.4)	0.694
Intra-operative blood transfusion	0 (0)	0 (0)	

a sample size of 25 patients per group was required to have an 80% chance of detecting a difference in blood loss of 260 mL at 95% confidence interval limitations.

3. Results

No significant difference was found between study and control group in mean Hb change, total blood loss or in measured blood loss (Table 2). One blood transfusion was administered during the study period, being to a patient in the control group.

No cases of DVT occurred during the study period for either group (Table 2). Although not significant, there was a slightly higher incidence of hypotension in the control group (39.3%) than the study group (32.0%). The study group showed a higher incidence of constipation (20.0%) compared to the control group (3.6%) but this did not reach statistical significance.

4. Discussion

This study demonstrated that an oral TXA regimen was non-inferior to a topical/IV/oral TXA regimen when comparing Hb change and blood loss (both measured and total) and incidence of DVT and adverse events. Previously, multiple studies have demonstrated two regimes to be non-inferior including that topical TXA is non-inferior or superior to IV TXA in reducing blood loss due to TKA [20–22] and that the use of oral TXA is non-inferior to IV TXA [12,13,23], but this study was the first to directly compared oral to a combined topical/IV/oral regimen.

This study has several limitations. First, it is possible that we were only able to demonstrate non-inferiority as our comparison was between two active treatments. In addition to this, the active treatments included oral TXA in both groups as it was part of the standard protocol at the hospital to utilise topical, IV and oral

Table 2
Efficacy & Safety outcomes of the study and control groups. Data is shown as mean (standard deviation) for haemoglobin change, blood loss and length of stay and number (percentage) for all other variables.

Variable	Study ($n = 25$)	Control ($n = 28$)	p-value
Efficacy Outcome			
Haemoglobin change (g/L)	32.9 (8.9)	31.8 (10.4)	0.687
Measured blood loss (mL)	640.0 (291.1)	538.3 (270.2)	0.173
Total blood loss (mL)	1211.5 (336.0)	1092.9 (341.4)	0.214
Total blood volume	5296.3 (985.8)	4956.8 (888.1)	0.197
Postoperative blood transfusion	0 (0.0%)	1 (3.6%)	
Length of hospital stay (days)	4.0 (1.1)	4.5 (1.5)	0.169
Safety Outcome			
DVT	0	0	
Potential Adverse Effects			
Seizures	0	0	
Visual disturbances	0	0	
Allergy	0	0	
Acute nausea	9 (36.0)	9 (32.1)	0.7647
Delayed nausea	8 (32.0)	9 (32.1)	0.9938
Headache	1 (4.0)	0	
Diarrhoea	0	0	
Hypotension	8 (32.0)	11 (39.3)	0.5801
Dizziness	0	2 (7.1)	
Constipation	5 (20.0)	1 (3.6)	0.056

administration. This may have biased results by not allowing evaluation between oral and other routes of administration, but this study still demonstrated comparison between routinely used regimens. Second, Hb levels at both 48- and 72-hours post-surgery could have provided further comparison of outcomes between groups and should be collected in future studies. Third, larger numbers of participants may be required to identify any significant differences in blood transfusions. Four, both the study and control groups had no patients showing sonographic evidence of DVT but this may be attributed to the effective use of post-surgical VTE prophylaxis. Therefore, a larger sample size may be required to identify any significant differences between TXA regimes in terms of DVT.

The 1 g oral TXA dose utilised in our study was the same as other studies [12,24,25] although the regimes differed. Similar to Lee et al. [24], our study found no significant difference in both blood loss and Hb utilising a 1 g dose of oral TXA at three time points Previously, Sridharan and Sivaramakrishnan [11] discussed the lack of consensus regarding appropriate dosing of TXA, whilst Fillingham et al. [16] recommended using 2 g oral TXA two hours pre-operatively. In our study a three dose 1 g TXA regime was used. The difference in total blood loss for the study compared to control group was around half the volume at which non-inferiority would not have been demonstrated. This may indicate the oral TXA dose regime may need to include a higher dose so further studies may be required to determine the optimum dosage regime for use of oral TXA in TKA.

Both the oral and the topical/IV/oral TXA regime were similar for the majority of adverse events. Whilst not statistically significant, the control group showed a higher incidence of hypotension than the study group, which is consistent with the literature when TXA is administered intravenously [26]. Conversely, the oral group showed a higher incidence of constipation than the control group. This difference was unexpected as constipation is not a listed adverse effect of TXA [26], however constipation may be attributed to post-operative pain management with opioids (both IV and oral) so it cannot be determined if this side effects was solely due to the administration route of TXA. Previously there have been case reports of anaphylaxis with IV TXA [27,28] and theoretical concerns with topical TXA aggravating staphylococcal infection [29] raising concerns for regimes utilising topical/IV TXA. The comparative adverse effect profiles of the two groups in this study suggests that the oral TXA regimen would be as safe as a topical/IV/oral regimen and potentially minimise the risk of such complications.

One efficacy outcome utilised in this study was incidence of blood transfusions which favoured the use of oral TXA. No patients in the study group required a blood transfusion however one patient in the control group did receive a transfusion during the study period (three days post-op). However, a gastroenterology review concluded that the Hb drop was due to bleeding caused by gastritis and accelerated by apixaban, and therefore this event cannot be reliably used to compare safety between the two regimens.

Costs associated with oral TXA are lower than topical and IV TXA [25]. The benefits of demonstrating non-inferiority of the oral regime compared to the combined topical/IV/oral regime is two-fold. Firstly, it results in significant cost savings to the healthcare facilities and healthcare providers with the IV formulation almost 40-fold more expensive than the equivalent oral dose [30]. Secondly, replacing the combined TXA regime with an oral regime can reduce the burden on nursing staff.

In conclusion, this study demonstrates for the first time in a study population that an oral TXA regime consisting of three 1 g doses at two hours pre-surgery and both two and six hours post-surgery is non-inferior to a topical/IV/oral regime of TXA in TKA in terms of Hb change and blood loss for efficacy and incidence of DVT and adverse events for safety. Replacing the combined topical/IV/oral regime of TXA with an entirely oral TXA regime can reduce cost to healthcare facilities and burden to nursing staff without impacting patient outcomes.

Disclosure of interest

The authors declare that they have no competing interest.

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Author's Contribution

L.K data collection, statistics, manuscript writing; R.R study design, surgery, recruitment, manuscript review; W.D. study design; manuscript review; N.B. data reporting, statistics, manuscript writing.

References

[1] Australian Institute of Health and Welfare 2016 Osteoarthritis. Arthritis series no. 22, Cat no. PHE 186. Canberra Available online: https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/osteoarthritis/contents/what-is-osteoarthritis.(accessed 3 July 2018).

[2] Bong MR, Patel V, Chang E, Issack PS, Hebert R, Di Cesare PE. Risks associated with blood transfusion after total knee arthroplasty. J Arthroplasty 2004;19:281–7.

[3] Dunn C, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57:1005–32.

[4] 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.

[5] MacGillivray RG, Tarabichi SB, Hawari MF, Raoof NT. Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. J Arthroplasty 2011;26:24–8.

[6] Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503–13.

[7] Alipour M, Tabari M, Keramati M, Zarmehri AM, Makhmalbaf H. Effectiveness of oral tranexamic acid administration on blood loss after knee artroplasty: a randomized clinical trial. Transfus Apheresis Sci 2013;49:574–7.

[8] Karaaslan F, Karaoglu S, Mermerkaya MU, Baktir A. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. The Knee 2015;22:131–5.

[9] Wu YG, Zeng Y, Yang TM, Si HB, Cao F, Shen B. The efficacy and safety of combination of intravenous and topical tranexamic acid in revision hip arthroplasty: a randomized controlled trial. J Arthroplasty 2016;31:2548–53.

[10] 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;30:776–80.

[11] Sridharan K, Sivaramakrishnan G. Tranexamic acid in total knee arthroplasty: mixed treatment comparisons and recursive cumulative meta-analysis of randomized. Controlled trials and cohort studies. Basic Clin Pharmacol Toxicol 2018;122:111–9.

[12] Zohar E, Ellis M, Ifrach N, Stern A, Sapir O, Fredman B. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesth Analg 2004;99:1679–83.

[13] Irwin A, Khan SK, Jameson SS, Tate RC, Copeland C, Reed MR. Oral versus intravenous tranexamic acid in enhanced-recovery primary total hip and knee replacement: results of 3000 procedures. Bone Joint J 2013;95–B:1556–61.

[14] Wang F, Zhao K-C, Zhao M-M, Zhao D-X. The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: a meta-analysis. Medicine 2018;97:e2270.

[15] Guo P, He Z, Wang Y, Gao F, Sun W, Guo W, et al. Efficacy and safety of oral tranexamic acid in total knee arthroplasty: a systematic review and meta-analysis. Medicine 2018;97:e0587.

[16] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total knee arthroplasty: a network meta-analysis. J Arthroplasty 2018;33:3090–8.

[17] Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br 2004;86:561–5.

[18] Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962;51:224–32.

[19] Meunier A, Petersson A, Good L, Berlin G. Validation of a haemoglobin dilution method for estimation of blood loss. Vox Sang 2008;95:120–4.

[20] Gomez-Barrena E, Ortega-Andreu M, Padilla-Eguiluz NG, Perez-Chrzanowska H, Figueredo-Zalve R. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. J Bone Joint Surg Am 2014;96:1937–44.

[21] Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2013;21:1869–74.

[22] Soni A, Saini R, Gulati A, Paul R, Bhatty S, Rajoli SR. Comparison between intravenous and intra-articular regimens of tranexamic acid in reducing blood loss during total knee arthroplasty. J Arthroplasty 2014;29:1525–7.

[23] Fillingham YA, Kayupov E, Plummer DR, Moric M, Gerlinger TL, Della Valle CJ. The James A. Rand young investigator's award: a randomized controlled trial of oral and intravenous tranexamic acid in total knee arthroplasty: the same efficacy at lower cost? J Arthroplasty 2016;31:26–30.

[24] Lee QJ, Chang WYE, Wong YC. Blood-sparing efficacy of oral tranexamic acid in primary total hip arthroplasty. J Arthroplasty 2017;32:139–42.

[25] Yuan X, Li B, Wang Q, Zhang X. Comparison of 3 routes of administration of tranexamic acid on primary unilateral total knee arthroplasty: a prospective, randomized, controlled study. J Arthroplasty 2017;32:2738–43.

[26] Australian Medicines Handbook (Online). Adelaide. Australian Medicines Handbook Pty Ltd; 2018 https://amhonline.amh.net.au.

[27] Li PH, Trigg C, Rutkowski R, Rutkowski K. Anaphylaxis to tranexamic acid—a rare reaction to a common drug. J Allergy Clin Immunol Pract 2017;5:839–41.

[28] Bansal R, Nicholas A, Bansal A. Tranexamic acid: an exceedingly rare cause of anaphylaxis during anaesthesia. Case Reports Immunol 2016 [Article ID 7828351, 2 pages].

[29] Kłak M, Änäkkälä N, Wang W, Lange S, Jonsson I-M, Tarkowski A, et al. Tranexamic acid, an inhibitor of plasminogen activation, aggravates staphylococcal septic arthritis and sepsis. Scand J Infect Dis 2010;42:351–8.

[30] Ramsay Pharmacy Services. Merlin Catalogue. Melbourne, Australia: Ramsay Pharmacy Services; 2018.