

Topical versus intravenous administration of tranexamic acid in primary total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trials

Sammy A. Hanna, Anoop Prasad, Joshua Lee, Pramod Achan

Department of Orthopedic and Trauma Surgery, The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom

Abstract

Tranexamic acid (TA) is widely used by orthopedic surgeons to decrease blood loss and the need for transfusion following total hip arthroplasty (THA). Although both intravenous and topical applications are described in the literature, there remains no consensus regarding the optimal regimen, dosage and method of delivery of TA during THA. In addition, concerns still exist regarding the risk of thromboembolic events with intravenous administration. The purpose of this meta-analysis was to compare the efficacy and safety of topical *versus* intravenous administration of TA in THA. A systemic review of the electronic databases PubMed, CENTRAL, EMBASE and Google Scholar was undertaken to identify all randomized controlled trials (RCTs) comparing the topical and intravenous administration of TA during THA, in terms of total blood loss, rate of blood transfusion and incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE) post-operatively. A meta-analysis was performed to evaluate and compare the efficacy and safety of both methods of administration. Of 248 potentially relevant papers, three RCTs comprising (482) were eligible for data extraction and meta-analysis. The results showed a slightly higher amount of blood loss [Mean Difference (MD) – 46.37, P=0.12, 95% confidence interval (CI) – 12.54 to 105.29] and rate of transfusion (Risk Ratio 1.30, P=0.39, 95%CI 0.71 to 2.37) post-operatively in the topical TA group, but both did not reach statistical significance. There were 3 cases (1.2%) of DVT/PE in the intravenous group and one case (0.4%) in the topical group. Topical TA is an effective and safe method to reduce blood loss and the rate of transfusion following primary THA. It has comparative effectiveness to IV administration with slightly less post-operative thromboembolic complications. Larger and better-designed RCTs are required to establish the optimum dosage and regimen for topical use.

Introduction

Primary total hip arthroplasty (THA) is one of the most commonly performed surgical procedures in orthopedic surgery, with more than 70,000 THAs carried out annually in the United Kingdom¹ and 285,000 in the United States.² This is set to continue to rise with a projected increase to 527,000 THAs in the United States by the year 2030.³ Although very successful, THA is often associated with significant blood loss, which is reported to range between 1000 and 2000 mL.⁴ This necessitates blood transfusion for post-operative anemia in up to 37% of patients undergoing primary THA.⁵ Allogeneic blood transfusion remains a concern for patients and healthcare providers because of the potentially serious complications, such as disease transmission, hemolysis, anaphylaxis, and transfusion related acute lung injury and possibly death.⁶⁻⁸ As a result, antifibrinolytic agents, such as tranexamic acid (TA), have emerged as an effective way of reducing blood loss and transfusion following surgical procedures. TA is a synthetic derivative of lysine with a molecular weight of 157 g/mol, which exerts its effect by a reversible interaction with plasminogen.⁹ It binds to the lysin-binding site of plasminogen, which prevents the binding of plasminogen to the fibrin surface. Thus, plasminogen activation is prevented and fibrinolysis is delayed.¹⁰ Although TA was first discovered in 1962,^{11,12} the first study to examine its efficacy in reducing blood loss after total joint arthroplasty was in 1997.¹³ The findings suggested that TA was associated with a significant reduction in blood loss with no increase in venous thromboembolic events following total knee arthroplasty (TKA). The first study demonstrating the efficacy of TA when used during THA was published in 2000.¹⁴ Since then, numerous clinical trials have demonstrated that TA could effectively reduce blood loss in THA with no increase in complications.^{15,16} There remains a lack of consensus, however, regarding the optimal regimen, dosage and method of delivery of TA. In addition, there are still concerns regarding the risk of thromboembolic complications following intravenous (IV) administration.¹⁷ These safety concerns have resulted in an increasing interest in local use, with some authors suggesting a 70% reduction in systemic absorption when TA is used topically.¹⁸ Other proposed advantages of topical administration include the ease of use, providing a higher therapeutic concentration at the bleeding site, limiting blood loss with little or no systemic side effects.^{9,18} It is still not clear, however, if the topical administration of TA is as effective as systemic administration in terms of reducing blood loss and the need for subsequent transfusion following THA. We therefore per-

Correspondence: Sammy A. Hanna, Department of Orthopaedic Surgery, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London, E1 1BB, United Kingdom. E-mail: sammy.hanna@bartshealth.nhs.uk

Key words: Tranexamic acid; total hip arthroplasty; topical; intravenous; transfusion.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 23 July 2016.

Accepted for publication: 27 July 2016.

This work is licensed under a Creative Commons Attribution NonCommercial 4.0 License (CC BY-NC 4.0).

©Copyright S.A. Hanna et al., 2016
Licensee PAGEPress, Italy
Orthopedic Reviews 2016;8:6792
doi:10.4081/or.2016.6792

formed a systematic review and meta-analysis to compare the topical and intravenous administrations of TA in primary THA, specifically assessing the following outcome measures: i) amount of total blood loss; ii) number of blood units transfused; iii) the incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE).

Materials and Methods

The methods used in this review were according to the guidelines published in the Cochrane handbook for systemic review and meta-analysis of interventions.¹⁹ We searched the electronic databases (PubMed, CENTRAL, EMBASE, and Google Scholar) for all randomized controlled trials (RCTs) of patients who had undergone primary THA and received either topical or systemic (IV) tranexamic acid. The search included the following texts to maximize sensitivity and specificity: (total hip arthroplasty OR total hip replacement OR THA OR THR) AND (tranexamic acid). The search date range was between the time of inception of each database and January 2016. The search strategy was designed and agreed by all authors (SAH, AP, JL and PA). The inclusion criteria included: i) RCTs; ii) patients undergoing unilateral primary THA; iii) intervention including topical *versus* systemic (IV) TA administration; iv) reported outcome measures including: amount of total blood loss, blood units transfused per patient, the number of patients receiving a blood transfusion and

the incidence of DVT and PE. The title of the articles and their abstracts were reviewed independently by the first three authors (SAH, AP, JL). Any disagreement was resolved by the senior author (PA). When there were any issues requiring further scrutiny, the full article was obtained and analyzed. The included articles were assessed and scored according to their methodological quality using the Jadad five-point scale for randomized controlled trials.²⁰

Data extraction was performed independently by the first two authors (SAH and AP), who screened the identified articles. We attempted to contact the authors of studies when further information was required. The following data was extracted: demographics, indication for THA, length of follow-up, surgical approach, type of hip prosthesis, method of TA administration, blood transfusion criteria, amount of blood loss, the number of patients requiring blood transfusion, the number of

blood units transfused and the incidence of DVT and PE.

Statistical methods

Dichotomous outcomes such as rate of transfusion and the incidence of DVT/PE were expressed as proportions or risks, with the treatment effect reported as a risk ratio (RR) with 95% confidence interval (CI). Continuous outcomes such as total blood loss and blood units transfused were expressed as a mean \pm standard deviation (SD), with treatment effect being reported as the mean difference (MD). A P value of <0.05 was considered statistically significant. Review Manager (Rev-Man 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to present the study findings. The presence of statistical heterogeneity was assessed using the chi-squared test and I^2 statistics. A P value <0.1 and $I^2 >50\%$ were considered to indicate substantial heterogeneity.

Results

Search results

Figure 1 shows a flow chart of the study selection process. Our initial search identified 248 potentially relevant studies. After screening the titles and abstracts, 241 were excluded. The full text of each of the remaining 7 studies was obtained for further analysis, which resulted in 4 further citations excluded. Three RCTs comparing the efficacy of topical versus systemic administration of tranexamic acid in the context of primary THA were included in this review.²¹⁻²³ Table 1 summarizes the demographic data and Table 2 summarizes the surgical and intervention details in the included studies.

Quality assessment

The quality scores for the three trials using the Jadad²⁰ method are summarized in Table 1.

Table 1. Demographic data in the three selected trials.

Study	Country, year	Power of study	Patients (n)		Age		Male gender (%)		Diagnosis	Approach	Type of implant	Quality score ²⁰
			Top	IV	Top	IV	Top	IV				
Wei <i>et al.</i> ²¹	China, 2014	90%	102	101	60.2	63.6	35 (34)	39 (39)	OA	Posterior	Uncemented	5
Xie <i>et al.</i> ²²	China, 2015	90%	70	70	62.2	59.5	25 (50)	20 (40)	OA and AVN	Posterior	Uncemented	3
North <i>et al.</i> ²³	USA, 2015	80%	69	70	65.7	64.1	39 (57)	38 (54)	OA	Not mentioned	Uncemented	4

Table 2. Surgical and intervention details of the included studies.

Study	Country, year	Intervention		Technique used		Transfusion criteria	Thromboprophylaxis
		Topical TA	IV TA	Topical	IV		
Wei <i>et al.</i> ²¹	China, 2014	3 g TA in 100 mL NS	3 g TA in 100 mL NS	20 mL in acetabulum after preparation; 20 mL in femoral canal after preparation; 60 mL infiltrated into joint after closure of fascia	100 mL given as IV infusion 10 minutes before incision	Hb <9 g/dL at 24 hours post-operatively	Low molecular weight heparini
Xie <i>et al.</i> ²²	China, 2015	3 g TA in 150 mL NS	1.5 g TA	50 mL TA solution in gauze used to soak the acetabulum and femoral canal for 3 minutes after preparation; 50 mL injected into the hip joint through drain tube after closure of fascia	1.5 g TA single IV injection 15 minutes before skin incision	All patients with Hb <7 g/dL; all symptomatic patients with Hb between 7 and 10 g/dL	Mechanical prophylaxis, LMWH (Enoxaparin) (4000IU) until discharge then Rivaroxaban 10 mg (OD) for 30 days
North <i>et al.</i> ²³	USA, 2015	2 g TA in 100 mL NS	2 g TA in 100 mL NS	Placed in hip after component placement and allowed to sit undisturbed for 5 minutes	Two 50 mL doses each over 20 minutes using a pump; one started 10 minutes before incision and the second during closure of fascia	All patients with Hb <7 g/dL; all symptomatic patients with Hb <8 g/dL (no drains used in study)	According to AAOS guidelines: mechanical prophylaxis plus Enoxaparin 40 mg (OD) for 21 days or Rivaroxaban 10 mg (OD) for 35 days or Aspirin 325 mg (BD) for 21 days

TA, tranexamic acid; NS, normal saline; Hb, haemoglobin; AAOS, American Academy of Orthopaedic Surgeons.

The scores demonstrated that the trials were of a high quality (Jadad score ≥ 3). Two studies^{21,23} were double-blinded whereas the Xie and colleagues study was not.²²

Results of meta-analysis

Total blood loss

All three studies (482 patients) provided data on total blood loss. There was moderate statistical heterogeneity between the studies ($P=0.05$, $I^2=66\%$). The meta-analysis (Figure 2) showed a slightly higher amount of total blood loss with topical use, but this did not reach statistical significance (MD = 46.37, $P=0.12$, 95% CI = 12.54 to 105.29).

Rate of blood transfusion

All three studies (482 patients) provided data on the number of patients who required blood transfusion. Twenty-two transfusions (9%) occurred in the topical group compared with 17 transfusions (7%) in the IV group. The summarized estimate of effect size (Figure 3) indicated no statistically significant difference in the risk of transfusion between the groups (RR 1.30, $P=0.39$, 95% CI 0.71 to 2.37) in the absence of statistical heterogeneity ($P=0.83$, $I^2=0\%$).

Thromboembolic complications

All three studies (482 patients) provided data on DVT and PE events. There were 3 cases in the IV group (1.2%) compared with 1 case (0.4%) in the topical group (Figure 4) (RR 0.50, 95% CI 0.09 to 2.71) in the absence of statistical heterogeneity ($P=0.84$, $I^2=0\%$).

Discussion and Conclusions

This review demonstrated no statistically significant differences in total blood loss, rate of transfusion and thromboembolic complications when comparing topical and systemic TA administration in primary THA. Although THA is very successful as a surgical procedure, it may cause significant perioperative bleeding because of the rich blood supply of adjacent soft tissues and the large exposed surface of bone. Some studies have shown that blood loss after THA ranges between 1000 and 2000 mL⁴ with up to 37% of patients requiring blood transfusion.⁵ If not treated, post-operative anemia is associated with a significant increase in morbidity and mortality²⁴ and an increased stay in hospital^{25,26} following total joint arthroplasty (TJA). Addressing post-operative anemia with blood transfusion carries health and cost implications for both patients and

doctors.²⁷ TA was introduced with the aim of reducing post-operative bleeding and the need for blood transfusion following TJA.

Since the first report of its IV administration during TKA back in 1997,¹³ the use of TA in TJA has become well established in the literature.²⁷ It is now widely accepted that IV administration of TA reduces blood loss and the need for transfusion without a significant increase in the rate of adverse events following THA.^{16,27} However, concerns remain regarding the risk of DVT and PE associated with IV administration. In addition, some authors believe that the systemic use of TA results in its distribution throughout the whole circulating volume thus reducing its therapeutic concentration at the operative field.²⁸ In contrast,

topical TA is thought to rapidly reach therapeutic concentration at the site of bleeding with little or no systemic absorption.¹⁸ Despite the numerous published studies and trials, there remains no consensus regarding the most effective regimen, dosage, safety and method of delivery of TA in THA. This review was conducted in an attempt to answer these questions. To our knowledge, this is the first to date specifically evaluating the efficacy and safety of topical administration of TA *versus* intravenous administration in primary THA.

This review demonstrated slightly less bleeding in the IV group, but this did not reach statistical significance. The rate of transfusion was 7% in the IV group and 9% in the topical group, both being significantly less than the

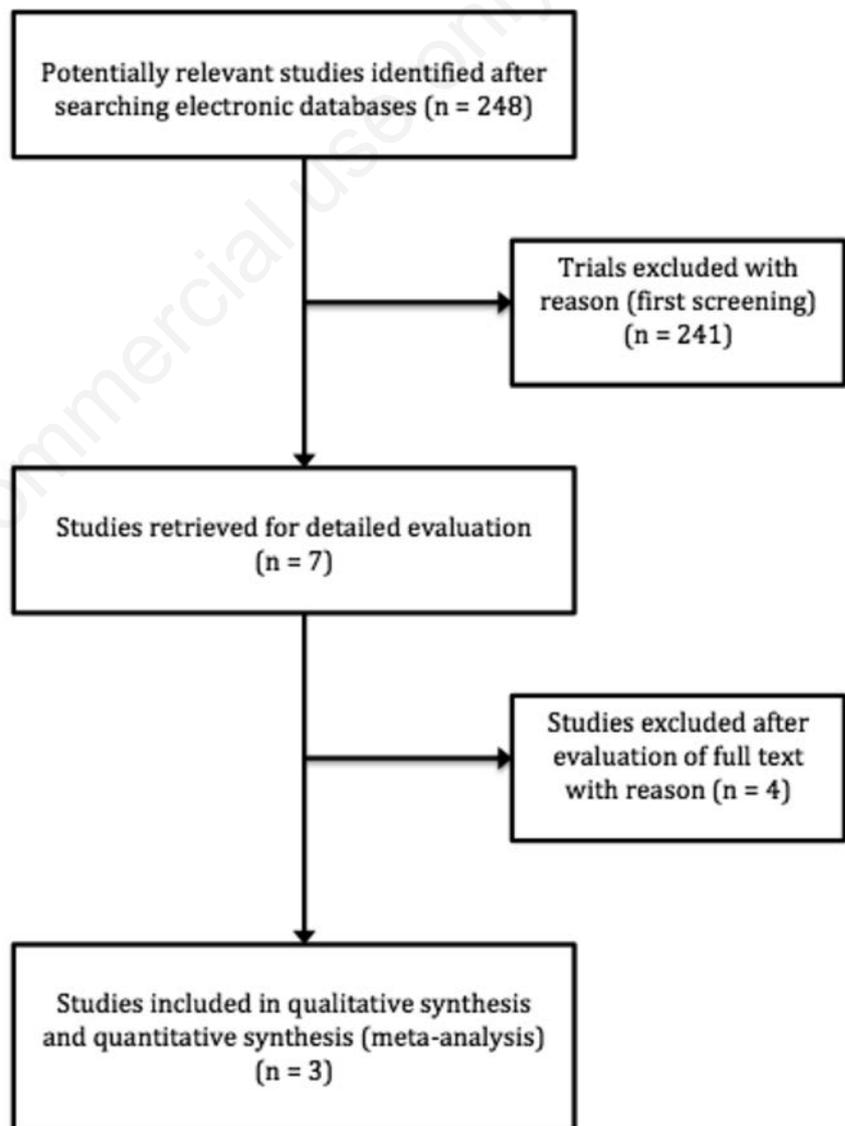


Figure 1. Flowchart of the study selection.

reported rate of 37% following THA without the use of TA.⁵ The risk of DVT/PE with IV TA remains a concern, although this has not been proven clinically. This analysis did not demonstrate a significant difference in the incidence of thromboembolic events between the IV and topical groups (1 case: 0.4% versus 3 cases: 1.2% respectively). It is however difficult to draw accurate conclusions as the number of thromboembolic events were small. In addition, uncertainty still remains because of the difference of DVT and PE screening methods in the studies. Doppler Ultrasound was routinely used in the Wei and colleagues²¹ and Xie and colleagues²² studies but not in the North and colleagues²³ study, where only symptomatic patients were investigated. This may

have resulted in the under diagnosis of thromboembolic events in this study.

The dose and method of topical application differed between the three studies. Wei and colleagues²¹ used 3 g in 100 mL of normal saline; 20 mL were placed in the acetabulum and 20 mL in the femoral canal after preparation and left for a few minutes before inserting the components. The remaining 60 mL were infiltrated into the joint after closure of the fascia. Xie and colleagues²² used 3 g TA in 150 mL normal saline; 50 mL were placed in the acetabulum and 50 mL in the femoral canal (soaked gauze) with the remaining 50 mL injected into the joint after closure of the fascia. North and colleagues²³ used 2 g of TA in 100 mL normal saline. The whole amount was placed in the hip after component

placement and allowed to sit undisturbed for 5 minutes. The dose of IV administration was also different (3, 1.5 and 2 g respectively).²¹⁻²³

Conclusions

In conclusion, the use of topical TA is an effective and safe method to reduce total blood loss and the rate of transfusion following primary THA. It has comparative effectiveness to IV administration with slightly less post-operative thromboembolic complications. Larger and better-designed future RCTs are required to establish the optimum dosage and method of delivery of topical use.

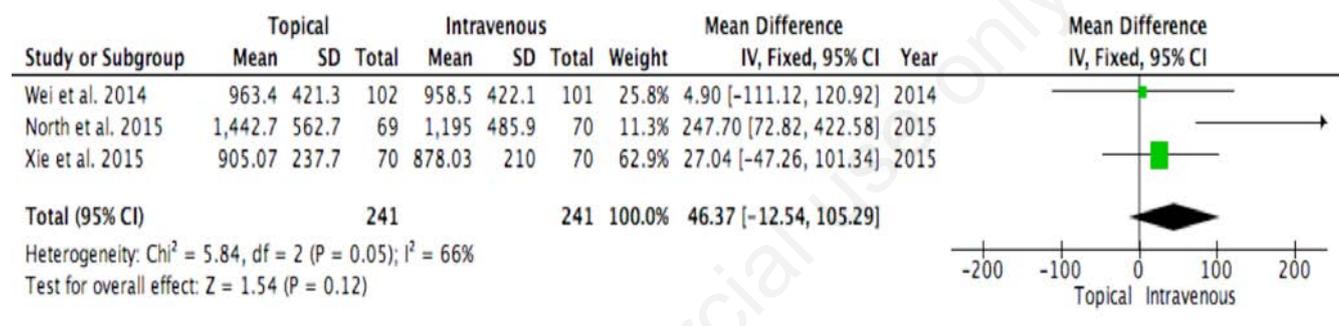


Figure 2. Meta-analysis results for total blood loss total blood loss.

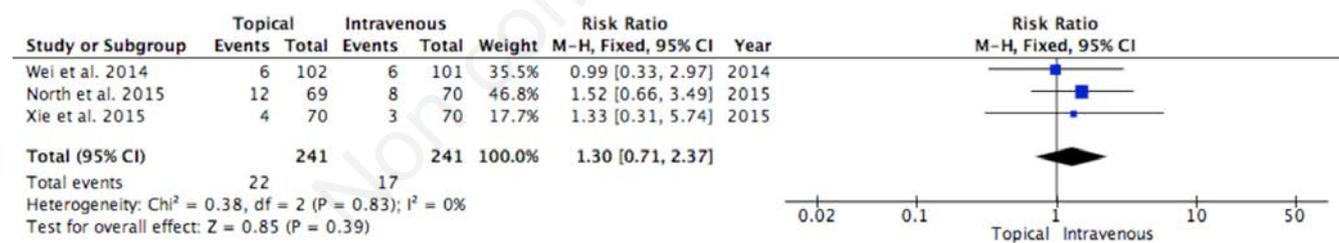


Figure 3. Meta-analysis results for rate of blood transfusion.

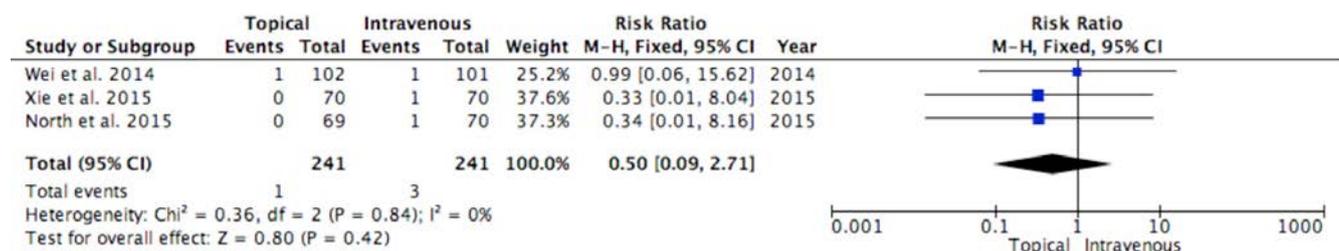


Figure 4. Meta-analysis results for the incidence of deep venous thrombosis/pulmonary embolus.

References

1. National Joint Registry. Annual Report, 2013. Available from: <http://www.njr-centre.org.uk/njrcentre/Reports/PublicationsandMinutes/Annualreports/tabid/86/Default.aspx>
2. American Academy of Orthopaedic Surgeons. Total hip replacement. Available from: <http://www.orthoinfo.aaos.org/topic.cfm?topic=a00377>
3. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007;89:780.
4. Toy PT, Kaplan EB, McVay PA, et al. Blood loss and replacement in total hip arthroplasty: a multicenter study. The preoperative autologous blood donation study group. *Transfusion* 1992;32:63-7.
5. Blumberg N, Kirkley SA, Heal JM. A cost analysis of autologous and allogeneic transfusion in hip-replacement surgery. *Am J Surg* 1996;171:324-30.
6. Madjdpour C, Spahn DR. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. *Br J Anaesth* 2005;95:33-42.
7. Klein HG. Allogeneic transfusion risks in the surgical patient. *Am J Surg* 1995;170:21S-26S.
8. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996;334:1685-90.
9. Dunn CJ, Goa KL. Tranexamic acid. A review of its use in surgery and other indications. *Drugs* 1999;57:1005-32.
10. Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. *Biochim Biophys Acta* 1981;673:75-85.
11. Okamoto S, Sato S, Takada Y, Okamoto U. An active stereo-isomer (trans-form) of AMCHA and its antifibrinolytic (antiplasminic) action in vitro and in vivo. *Keio J Med* 1964;13:177-85.
12. Melander B, Gliniecki G, Granstrand B, Hanshoff G. Biochemistry and toxicology of amikapron; the antifibrinolytically active isomer of AMCHA. (A comparative study with epsilon-aminocaproic acid). *Acta Pharmacol Toxicol (Copenh)* 1965;22:340-52.
13. Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg* 1997;84:839-44.
14. Ekbäck G, Axelsson K, Rytberg L, et al. Tranexamic acid reduces blood loss in total hip replacement surgery. *Anesth Analg* 2000;91:1124-30.
15. Huang F, Wu Y, Yin Z, et al. A systematic review and meta-analysis of the use of antifibrinolytic agents in total hip arthroplasty. *Hip Int* 2015;25:502-9.
16. Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg Br* 2011;93:39-46.
17. 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.
18. 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.
19. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. 2011. Available from: <http://handbook.cochrane.org/>
20. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
21. Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. *J Arthroplasty* 2014;29:2113-6.
22. Xie J, Ma J, Yue C, et al. Combined use of intravenous and topical tranexamic acid following cementless total hip arthroplasty: a randomised clinical trial. 2016;26:36-42.
23. North WT, Mehran N, Davis JJ, et al. Topical vs intravenous tranexamic acid in primary total hip arthroplasty: a double-blind, randomized controlled trial. *J Arthroplasty* 2016;31:928-9.
24. Carson JL, Terrin ML, Jay M. Anemia and postoperative rehabilitation. *Can J Anaesth* 2003;50:S60-4.
25. Bierbaum BE, Callaghan JJ, Galante JO, et al. An analysis of bloodmanagement in patients having a total hip or knee arthroplasty. *J Bone Joint Surg Am* 1999;81:2-10.
26. Triulzi DJ, Vanek K, Ryan DH, Blumberg N. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion* 1992;32:517-24.
27. Kim C, Park SS, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. *J Blood Med* 2015;6:239-44.
28. Alshryda S, Sukeik M, Sarda P, et al. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. *J Bone Joint Surg Br* 2014;96-B:1005-15.