ORIGINAL ARTICLE

Comparative study of efficacy of reduction of blood loss by tranexamic acid and epsilon aminocaproic acid for orthopedic femoral surgeries

Maitreyee Mukherjee, MD[1], Chandan Biswas, MD[2], Sajib Chatterjee, MS[3], Bijoy Kumar Bandyopadhyay, MD[4]

[1]Assistant Professor; [2]Senior Resident
Department of Anesthesiology & Critical Care, R. G. Kar Medical College & Hospital, 1, Kshudiram Bose Sarani, Kolkata, West Bengal 700004, (India)
[3]Department of General Surgery, Nil Ratan Sircar Medical College and Hospital (NRSMCH), 138, Acharya Jagadish Chandra Bose Rd, Sealdah, Raja Bazar, Kolkata, West Bengal 700014, (India)

Correspondence: Dr. Maitreyee Mukherjee, Department of Anesthesiology & Critical Care, R. G. Kar Medical College & Hospital, 1, Kshudiram Bose Sarani, Kolkata, West Bengal 700004, (India); Mobile: 09830415924; E-mail: maitreyee1980.mm@gmail.com

ABSTRACT

Background: Femoral surgeries are always associated with excessive bleeding either in the intra-operative or postoperative period; often requiring blood transfusion. Induced hypotension and antifibrinolytics have been used to decrease blood loss. Agents used in this indication are the serine protease inhibitor aprotinin and the lysine analogues tranexamic acid (TA) and 1-aminocaproic acid. This study was designed to establish the efficacy of reduction of blood loss by TA verses epsilon-aminocaproic acid (EACA).

Methodology: The study was prospective, randomized and double blinded. 60 patients with written consent undergoing open femoral shaft surgeries were randomly allocated in Group T (receiving initial dose of 5.4 mg/kg of TA in intravenous route given over 20 min, followed by an infusion of 5 mg/kg/h till the end of the surgery) and Group E receiving initial dose of 100 mg/kg of EACA in intravenous route over 20 min, followed by an infusion of 1g/h till the end of surgery. Intra-operative and postoperative blood loss, intra-operative and postoperative blood transfusion, postoperative hemoglobin (Hb) on day 5 and any adverse effects were recorded.

Results: Intra-operative blood loss (mean ± SD) was 323.28 ± 45.282 ml in Group T and 411.67 ± 41.384 ml in Group E ($p < 0.001$). Postoperative blood loss was 134.48 ± 42.476 ml in Group T and 130.00 ± 44.721 ml in Group E. Intra-operative blood transfusion was 0.10 ± .310 units in Group T and 0.33 ± .479 units in Group E ($p = 0.03$). None required postoperative blood transfusion. Hb on day 5 was 9.74 ± 2.435 Gm in Group T and 10.62 ± 1.561 Gm in Group E ($p = 0.1$). No adverse effects were noted in both groups.

Conclusion: Tranexamic acid significantly reduces intra-operative blood loss and the requirement of blood transfusion during open femoral shaft surgeries, but the differences are not statistically significant in the postoperative period.

Citation: Mukherjee M, Biswas C, Chatterjee S, Bandyopadhyay BK. Comparative study of efficacy of reduction of blood loss by tranexamic acid and epsilon aminocaproic acid for orthopedic femoral surgeries. Anaesth Pain & Intensive Care 2016;20(4):417-421

Received: 11 Aug 2016; **Reviewed:** 15 Nov 2016**; Corrected:** 25 Nov 2016**; Accepted:** 10 Dec 2016

INTRODUCTION

Femoral surgeries are most often associated with excessive blood loss in the perioperative period. Such surgeries need much exposure and hence adequate hemostasis is necessary to avoid blood loss. There is not only invasion of the soft tissues, where the control of bleeding is easily achieved by

compression or cauterization, but also the non-compressible domains of the bone framework, where hemostasis is difficult to achieve.[1,2] The usual outcome is blood loss, which needs blood transfusion in the intra and postoperative period.[3] Blood transfusion has its innate complications in the immediate and near future.[4] The delayed and/or non-availability of blood and blood products entails further research into methods to allay blood transfusion and use alternate methods to reduce blood loss in the perioperative period and its associated hazards.[5] This has serious implications of the wellbeing of the patient, morbidity and healing process.

Various methods have been used to decrease blood loss like induction of hypotension and use of antifibrinolytics. Agents used in this indication are the serine protease inhibitor

aprotinin and the lysine analogues tranexamic acid (TA) and 1-aminocaproic acid.

Prevention of blood loss by the use of antifibrinolytic agents has been proved by several studies in different types of surgeries such as cardiovascular surgeries[6], hepatic surgeries[7], knee replacement surgeries,[1,2,3,5] total hip replacement[8,9] and spinal fusion surgeries[10] Both TA and epsilon-aminocaproic acid (EACA) have been found to be effective in reduction of blood loss and requirement of perioperative transfusion of blood products. Hence we designed this study to compare the effects of the antifibrinolytics, TA and EACA, their relative effectiveness in securing hemostasis, reduction of surgical blood loss, reduction of blood transfusion and hence their roles in prevention of associated morbidities during femoral surgeries.

Specific Objectives: Despite numerous clinical trial using TA and EACA in various surgeries, little focus has been laid on orthopedic surgeries for comparing their efficacies. Considering the equipotent dosages of TA and EACA and their requisite concentration in plasma for action, the study was designed to administer either of the two drugs in two different study groups and carry out the following:

1. Compare surgical blood loss and requirement of transfusion of blood or blood products.
2. Observe any adverse effects in either group

METHODOLOGY

The study was designed as a randomized, prospective, double blind study to be conducted on patients undergoing open femoral shaft surgeries in the orthopedic operating rooms at our hospital. After the institutional ethics committee clearance, consenting patients belonging to American Society of Anesthesiologists (ASA) physical status I, II and III of age > 18 years and of either sex, undergoing open femoral shaft surgeries were included in the study.

Patients with known allergy to TA or EACA, with history or evidence of coagulopathy or bleeding disorder (congenital or acquired), with impaired renal or hepatic function and malignancy were excluded. Patients with history of cerebrovascular accidents, history of myocardial ischemia/infarction, coronary artery disease, history of thromboembolic event within one year before surgery, hemoglobin (Hb) less than 8 g/dl, pregnant patients, patients with a history of ocular pathology or ophthalmologic procedures apart from corrective lens implantation were also excluded from the study.

The 60 eligible consenting patients were randomized using computer generated tables and allocated in either in Group T or Group E. The patients in Group T received an initial dose of 5.4 mg/kg of TA IV given over 20 min, followed by an infusion of 5 mg/kg/hour till the end of surgery.

30 patients in Group E received initial dose of 100 mg/kg of EACA given IV over 20 min, followed by an infusion of 1 g/hour till the end of surgery.

All the patients received subarachnoid block at L3-4 vertebral level. The following were documented for comparison; preoperative Hb, perioperative vital parameters, blood loss and blood transfused, and Hb on 5th postoperative day. Adverse effects related to surgical procedure were documented for comparison.

One patient was excluded from Group T for revision of surgery on third postoperative day. Analysis of demographic and recorded parameters was done by relevant statistical tests (IBM SPSS Statistics 20).

All the cases were followed up clinically for any calf muscle tenderness, pain, edema or swelling of limb.

RESULTS

The demographic and physical parameters including age, sex, body mass index (BMI) and ASA physical status were comparable in both the groups. The pre-operative laboratory and vital parameters incorporating pre-operative Hb, blood pressure and pulse rate revealed no significant difference.

Pre-operative Hb level, blood pressure and pulse

Table 1: Demographic and physical parameters

Parameters	Group T (n = 29)	Group E (n = 30)	p-value
Age (Mean ± SD)	42.31 ± 11.20	41.37 ± 10.83	0.743
Sex, N (%)	M 18 (60) F 12 (40)	M 16 (55.17) F 13 (44.83)	NA
BMI (Mean ± SD)	23.99 ± 4.05	24.28 ± 3.57	0.766
ASA I II III	 51.72% 37.93% 10.34%	 53.33% 30.00% 16.67%	NA

Table 2: Pre-operative laboratory and vital parameters (Mean ± SD)

Pre-op parameters	Group T (n = 29)	Group E (n = 30)	p-value
Hb (G)	10.75 ± 1.64	11.25 ± 1.57	0.238
BP (mmHg)	94.69 ± 13.10	94.33 ± 11.15	0.911
Pulse rate (per min)	94.10 ± 13.91	92.00 ± 12.07	0.537

Table 3: Intraoperative blood loss parameters

Transfusion parameters	Group T (n = 29)	Group E (n = 30)	p-value
Blood loss (ml)	323.28 ± 45.28	411.67 ± 41.38	< 0.05
Patients requiring blood transfusion (n)	3	10	
Units transfused (n)	0.10 ± 0.310	0.33 ± 0.479	

Table 4: Comparative intraoperative blood pressure and heart rate (mean ± SD)

Parameter	Group T	Group E	p-value
Blood pressure (mmHg)	83.1 ± 10.12	90.8 ± 13.45	> 0.05
Heart rate (per min)	84 ± 6	86 ± 10	> 0.05

Table 5: Postop blood loss, postop blood transfusion and Hb on day 5

Parameter	Group T	Group E	p-value
Postop blood loss (ml)*	130 ± 44.72	134.48 ± 42.47	> 0.05
Patients requiring postop blood transfusion (n)	2	7	NA
Hb on Day 5 (Gm)*	10.61 ± 1.56	10.0721 ± 1.62	> 0.05

*Mean ± standard deviation

rates were comparable in both the groups (Table 2).

intraoperative blood loss and transfusion requirement was significantly less in Group T compared to Group E. Three patient in Group T required transfusion, whereas 10 patients in EACA group required blood transfusion in postoperative period (Table 3).

Intra operative blood Loss in Group E was higher. Intra-operative blood pressure and heart rate were comparable (Table 4).

The differences in postoperative blood loss and Hb checked on fifth postoperative day were statistically not significant, whereas less number of patients got blood transfusion in Group T (Table 5). No thromboembolic events encountered in any of the study patients.

DISCUSSION

In this study, we investigated the blood sparing efficacy of TA with that of EACA. The intraoperative and postoperative blood loss was significantly lower in Group T compared to EACA group. Less number of patients received blood transfusion in Group T.

Concern regarding complications of heterologous blood transfusion has introduced several strategies for decreasing intraoperative blood loss in clinical practice. Drugs have shown to be capable of reducing blood loss and exposure to allogenic blood products. Studies with aprotinin therapy in orthotropic liver transplantation have produced conflicting results.[12,13]

Desmopressin has proven useful in preventing bleeding in patients with acquired platelet dysfunction, especially in cases of abnormally low maximum amplitude in thromboelastography and a prolonged bleeding time. Antifibrinolytic drugs namely TA and EACA have been used in various surgeries where chances of blood loss is more.[6] It has not been studied in commonly performed orthopedic surgeries like open femoral surgery where huge blood loss is expected.

TS (1,4 amino carboxylic acid) is 7-10 times more potent than EACA and there is large variation in the recommended dose of TA. Murkin et al.[14] describes seizures in cardiac surgery patients after high-dose TA (100 mg/kg total, or loading doses of 25 to 50 mg/kg followed by infusions of 10 to 25 mg/kg/h). The plasma concentration required to suppress fibrinolysis, in vitro, is 10 μg/ml and to suppress plasmin-induced platelet activation is 16 μg/ml.[4] During deciding the dose of TA we have taken reference from a study of Fiechtner[6] who combined her own studies with others to generate a dosing regimen designed to maintain plasma concentrations of > 20 μg/ml throughout cardiac surgery (5.4 mg/kg loading dose followed by 5 mg/kg/h with an additional 20 mg/L bypass pump prime).We, too, used a loading dose of 5.4 mg/kg followed by 5 mg/kg/h till the end of surgery.

With regard to EACA, the dose chosen (100 mg/kg) was midway between doses used in other studies,[16] and the dose recommended was 100 mg/kg followed by a perfusion of 1 G/h till the end of surgery. The reduction in Hb and, the number of patients who received transfusions and the number of units transfused were significantly lower in the Group T compared with the EACA group. These results are similar to those observed in other clinical trials.[2,18]

Aiming for a 'transfusion-free hepatectomy' Wu and colleagues[7] compared prophylactic TA vs placebo in 217 patients undergoing liver tumor resections in a randomized, double-blind fashion. Blood loss was significantly lower in the Group T (P = .0001) and none of the patients required blood transfusion. as opposed to 17 in the placebo group (P = 0.0001).

The major concern with the use of antifibrinolytic agents is their thrombogenic nature. However, evidence, based on one large multicenter randomized controlled trial,[19] strongly supports the use of TA in bleeding trauma patients as a cost-effective empirical treatment with a good risk–benefit ratio, even without evidence of on-going hyperfibrinolysis. A multidisciplinary European guideline for the management of bleeding after major trauma also recommends the use of antifibrinolytic agents, ideally combined with monitoring of fibrinolytic activity by thromboelastometry

Limitations: In our study we did not notice any thromboembolic events, though we did not use echo-doppler or D-dimer study, which is the main limitation of our study.

CONCLUSION

In conclusion, the results of our study show that tranexamic acid is more effective in decreasing intraoperative blood loss and the requirement of blood transfusion in orthopedic open shaft femoral surgeries as compared to epsilon-aminocaproic acid.

Acknowledgements: The authors would like to thank Dr Goutam Choudhury for helping with useful literature for preparing the manuscript and Dr Dipasree Bhattacharya, Prof & HOD for her constant support in the study.

Conflict of interest: Nil

Authors' contribution: All authors took part in conduct of the study, search of literature, and manuscript preparation.

REFERENCES

1. Alshryda S, Sarda P, Sukeik 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;93B:1577-1585. [PubMed] [Free full text] doi: 10.1302/0301-620X.93B12.26989.
2. Camarasa M A, Olle G, Serra-Prat M, Martin A, Sánchez M, Ricós P, et al. Efficacy of Aminocaproic, Tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial: Br J Anaesth 2006;96:576-82. [PubMed] [Free full text] doi: 10.1093/bja/ael057
3. Gautam PL, Katyal S, Yamin M, Singh A. Effect of Tranexamic acid on blood loss and transfusion requirement in total knee replacement in the Indian population: A case series: Indian J Anaesth 2011;55:590-3. [PubMed] [Free full text] doi: 10.4103/0019-5049.90614.
4. Fox MA. Tranexamic acid: how much is enough? Anesth Analg 2010;111:580-1 [PubMed] doi: 10.1213/ANE.0000000000001050.
5. Kakar PN, Gupta N, Govil P, Shah V. Efficacy and safety of tranexamic acid in control of bleeding following TKR: A randomized clinical trial: Indian J Anaesth 2009;53:667-671. [PubMed] [Free full text]
6. Fiechtner BK, Nuttall GA, Johnson ME, Dong Y, Sujirattanawimol N, Oliver WC Jr, et al. Plasma tranexamic acid concentrations during cardiopulmonary bypass. Anesth Analg 2001;92:1131-36. [PubMed]
7. Wu CC, Ho WM, Cheng SB, Yeh DC, Wen MC, Liu TJ, et al. Perioperative parenteral tranexamic acid in liver tumor resection: a prospective randomized trial toward a "blood transfusion"-free hepatectomy. Ann Surg 2006;243:173–80 [PubMed] [Free full text] doi: 10.1097/01.sla.0000197561.70972.73
8. Gandhi R, Evans HMK, Mahomed SR, Mahomed NN. tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Research Notes 2013;6:184-197 [PubMed] [Free full text] doi: 10.1186/1756-0500-6-184.
9. Zhou XD, Tao LJ, Li J, Wu LD. Do we really need tranexamic acid in total hip arthroplasty? a meta-analysis of nineteen randomized controlled trials. Arch Orthop Trauma Surg 2013;133:1017-1027. [PubMed] doi: 10.1007/s00402-013-1761-2.
10. Wong J, Beheiry HE, Rampersaud YR, Lewis S, Ahn H, De Silva Y, et al. Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. Anesth Analg 2008;107:1479–86 [PubMed] doi: 10.1213/ane.0b013e3181831e44.
11. Weber CF, Gorlinger K, Byhahn C, Moritz A, Hanke AA, Zacharowski K, et al. Tranexamic acid partially improves platelet function in patients treated with dual antiplatelet therapy. Eur J Anaesthesiol 2011;28:57–62 [PubMed] doi: 10.1097/EJA.0b013e32834050ab.
12. Massicotte L, Denault AY, Beaulieu D, Thibeault L, Hevesi Z, Roy A. Aprotinin versus tranexamic acid during liver transplantation: impact on blood product requirements and survival. Transplantation 2011;91:1273–8 [PubMed] doi: 10.1097/TP.0b013e31821ab9f8.
13. Gurusamy KS, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. Cochrane Database Syst Rev 2011;12:CD009052 [PubMed] [Free full text] doi: 10.1002/14651858.CD009052.pub2.
14. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 2010;110:350–3 [PubMed] doi: 10.1213/ANE.0b013e3181c92b23.
15. Breuer T, Martin K, Wilhelm M, Wiesner G, Schreiber C, Hess J, et al. The blood sparing effect and the safety of aprotinin compared to tranexamic acid in paediatric cardiac surgery. Eur J Cardiothorac Surg 2009;35:167–71 [PubMed] [Free full text] doi: 10.1016/j.ejcts.2008.09.038.
16. Martin K, Breuer T, Gertler R, Hapfelmeier A, Schreiber C, Lange R, et al. Tranexamic acid versus varepsilon-aminocaproic acid: efficacy and safety in paediatric cardiac surgery. Eur J Cardiothorac Surg 2011;39:892–7 [PubMed] [Free full text] doi: 10.1016/j.ejcts.2010.09.041.
17. 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;92:2503–2513. [PubMed] [Free full text] doi: 10.2106/JBJS.I.01518.
18. Greilich PE, Jessen ME, Satyanarayana N, Whitten CW, Nuttall GA, Beckham JM, et al. The effect of epsilon-aminocaproic acid and aprotinin on fibrinolysis and blood loss in patients undergoing primary, isolated coronary artery bypass surgery: a randomized, double-blind, placebo controlled, noninferiority trial. Anesth Analg 2009;109:15–24 [PubMed] doi: 10.1213/ane.0b013e3181a40b5d.
19. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23–32. [PubMed] [Free full text] doi: 10.1016/S0140-6736(10)60835-5.

★★★★★