ROLE OF INTRA-GASTRIC TRANEXAMIC ACID IN MANAGEMENT OF ACUTE UPPER GASTROINTESTINAL BLEEDING

Hossein Saidi[1]*, Shayan Shojaie[1], Yaser Ghavami[1], Amirhossein Mirafzal[2], Mohamad Tahmasbi Sisakht[3] and Mehran Sotudehnia[4]

[1]Emergency Medicine Management Research Center, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, IRAN
[2]Assistant Professor, Emergency Department, Kerman University of Medical Sciences, Kerman, IRAN
[3]Emergency medicine, Clinical Research Development Unit, Yasuj University of Medical Sciences, Yasuj, IRAN
[4]Emergency medicine management Research center, Sina Hospital, Tehran university of Medical Sciences, Tehran, IRAN

ISSN 0976-3104

ABSTRACT

Background and Aims: *There are controversies about the safety and haemostatic efficacy of systemic Tranexamic Acid (TA) in patients with Upper Gastrointestinal Bleeding (UGIB). The goal of this study was to determine the efficacy of a single dose of TA, administered topically, on bleedings from benign peptic lesions.* ***Methods:*** *We assessed the effects of intra-gastric administration of TA on 131 patients presenting with hematemesis, melena, or both in a prospective double-blind randomized placebo-controlled trial. TA was administered at a dose of 1 gram diluted in 250 cc of saline solution via nasogastric tube. Our primary outcome parameter was the amount of blood needed for transfusion (units of packed cells).* ***Results:*** *UGIB-related mortality rate was seen to be lower in TA treated group, but the difference did not reach the level of significance (p=0.150). Transfusion requirements were significantly higher in patients not receiving TA (p<0.001). The number of re-bleeding episodes was 4 (6%) in TA group and 12 (18.8%) in placebo group (p=0.033). There was also a significant difference between the 2 groups in the number of emergency endoscopies; Six (9%) in TA group vs. 14 (21.9%) in the placebo group (p=0.040).* ***Conclusions:*** *We believe that intra-gastric administration of TA is safe, cost effective, well tolerated and can be performed easily. Further investigation is needed to evaluate the efficacy and safety of this new method for management of acute UGIB .Since we had some limitations in our sample size, additional evidence is needed before any treatment recommendations can be made.*

KEY WORDS
Upper Gastrointestinal Bleeding, TranexamicAcid, Peptic Ulcer, Antifibrinolytic Drug, Topical

INTRODUCTION

Despite advances in diagnosis and treatment of upper gastrointestinal bleeding (UGIB), the mortality and morbidity rates are still high [1, 2]. Bleeding peptic ulcers are responsible for about half of all upper gastrointestinal hemorrhages [3, 4].

Tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid; TA), a potent anti-fibrinolytic agent, has been found to bind to lysine binding sites of plasmin and plasminogen [5]. It saturates the lysine binding sites of human plasminogen, displacing plasminogen from the fibrin surface, which leads to inhibition of fibrinolysis [6]. Systemic TA appears to be effective in diminishing blood loss in various pathological conditions such as menorrhagia [7, 8], gastric and duodenal ulcers [9, 10], orthopaedic surgery [11, 12], intraoperative and postoperative bleeding in cardiac surgery [13, 14], bleeding from traumatic injuries [15].

Received: 7 November 2016
Accepted: 12 December 2016
Published: 30 January 2017

There are some reports about complications of systemic TA administration. It increased the risk of thromoembolic events [16, 17], and seizure [18, 19] in susceptible patients. However, topical TA has been successfully used to control bleeding in urologic, gynaecologic, oral, otolaryngeal surgeries [20-22] and total knee arthroplasty [23]. Topical application of TA in patients undergoing primary coronary artery bypass grafting led to a significant reduction in postoperative blood loss without adding extra risk to the patient too [24]. Also, topical TA significantly reduced mean blood losses after minor oral surgeries in patients receiving oral anticoagulants without discontinuation of anticoagulation regimen [25].

To our knowledge, there is no report of a controlled trial of topical intra-gastric anti-fibrinolytic therapy in UGIB. The goal of the current study was to determine the efficacy of a single dose of TA, administered topically, to control bleedings from benign peptic lesions.

MATERIALS AND METHODS

Study design

We assessed the effects of intra-gastric administration of TA on acute UGIB in a prospective double-blind randomized placebo-controlled trial in 131 patients with hematemesis, melena, or both by a random number sequence. After eligible subjects received detailed explanations about the protocol, informed consent is obtained. This study is conducted in concordance with the principles of the Declaration of Helsinki. Approval for the conduct of this study was obtained from the Research Ethics Committee and Institutional Review Board of Tehran University of Medical Sciences (Ethic code: 90/d/2781/130). This trial has also been registered at International Clinical Trials Registry Platform (registration number: IRCT201201148721N1at http://www.who.int/ictrp).

***Corresponding Author**
Email: drhsaidi@yahoo.com

Setting and selection of participants

This study was conducted at Hazrat Rasool General Hospital. All patients with an initial clinical diagnosis of UGIB were primarily recruited. Endoscopic examination was performed in all recruited patients within 24 hours of presentation and consequently, any patient without a demonstrable benign gastric or duodenal lesion was excluded from the study.Patients would not be eligible for inclusion in this study if they were pregnant or lactating women, patients having a gastrointestinal malignancy, patients having a history of thromboembolism, myocardial infarction, ischemic cerebrovascular accident, end stage renal disease, allergy to TA, ongoing anticoagulation therapy, congenital or acquired coagulopathy, or patients being reluctant to enroll in this study. A total of 272 patients entered the trial and 141 were excluded, leaving 64 placebo treated and 67 TA treated patients for analysis [Fig. 1]. The most common reason for exclusion was having no gastric or duodenal source of bleeding identified at endoscopy.

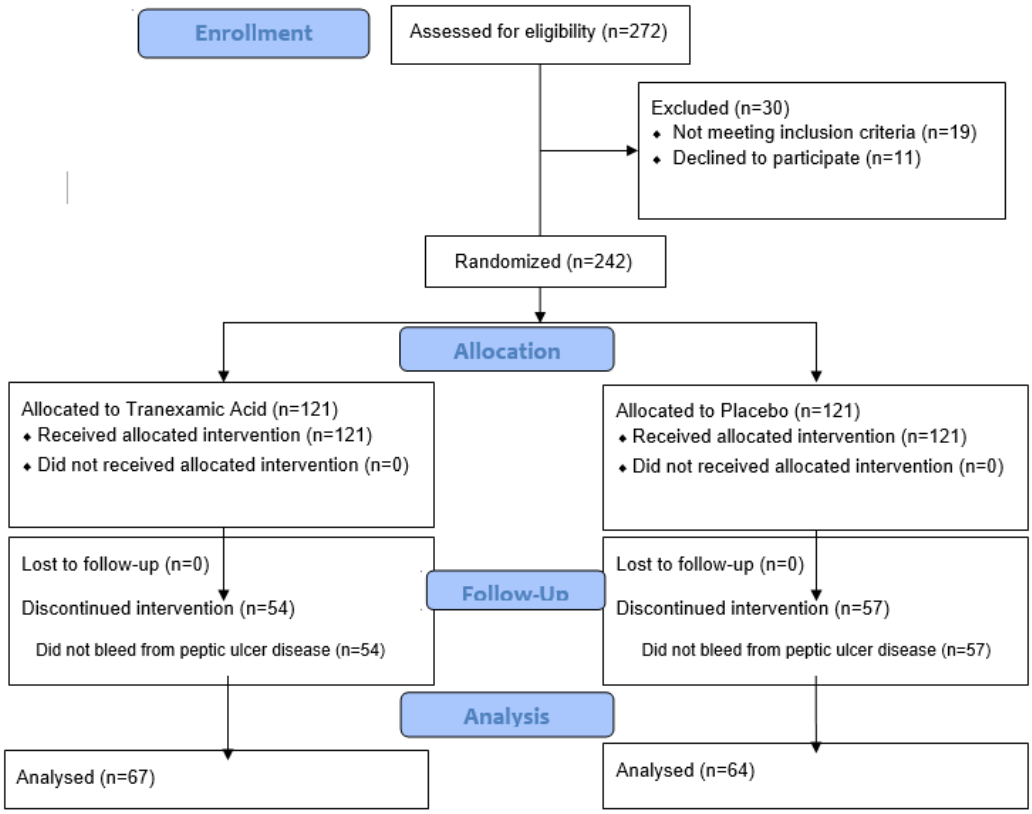

Fig. 1: The overall patient selection process

Outcomes

Our primary outcome parameter was the amount of blood needed for transfusion (units of packed RBCs); secondary outcome parameters included rebleeding events, need for surgical intervention, postoperative 30-day mortality rates, and occurrence of deep vein thrombosis (DVT).

Intervention

Participants were randomized to receive either TA or placebo in addition to the usual conventional treatment. All patients underwent resuscitation with crystalloids, insertion of nasogastric tube and gastric lavage with saline and intravenous pantoprazole. Also patients with UGIB presenting to ED were managed in consultation with department of gastroenterology. TA (Tranexip: Caspian Tamin Co., Rasht, Iran) was administered at a dose of 1 gram diluted in 250 ml of saline solution via nasogastric tube started in the first 30 minutes of patients' arrival at the ED. TA or placebo (physiologic saline) for infusion was prepared by the institution's pharmacy in two 250cc bags indistinguishable in shape and color identified only by random numbers, with the constituents unknown to the administering emergency resident. The placebo group received the same treatment protocol as the TA group except for the infusion of normal saline solution not containing TA. The randomization codes were known only to the pharmacist in charge and revealed only at the end of the study. Rebleeding was defined as bleeding after a silent period of more than six hours, or hypotension (<100 mm Hg systolic blood pressure) associated with a drop in the hemoglobin concentration of 2 g/dl or more and/or endoscopic evidence of fresh rebleeding. Although a hemoglobin level less than7 g/dl was the starting point for packed RBC transfusion, some other factors

also play roles, such as a clinical assessment of shock, hematocrit level, amount of blood loss, age, presence or absence of symptoms, underlying cardiopulmonary status and clinical judgment of ED attending physician. The number of PRBC units used for blood transfusion for each patient was counted up to the time of discharge from hospital: One unit of PRBC was equal to 250ml of this product. In-hospital mortality was recorded and all patients were followed for 4 weeks. Basic data, laboratory study, and endoscopy findings were obtained and recorded. A Doppler ultrasound study of lower limb veins was performed anytime there was a clinical suspicion for DVT (swelling and/or tenderness of calf muscles and/or unexplained postoperative hypoxemia). Rockall score was calculated for each participant at the beginning of treatment and after the endoscopy [26]. Surgical intervention was considered when intervention by endoscopic techniques failed or was contra-indicated.

Data analysis

The statistical analyses were performed by Statistical Package for Social Sciences (SPSS) for Windows 16.0 (SPSS Inc., Chicago, IL, USA). To test the normality of the distribution of the continuous variables, the Kolmogorov-Smirnov test was performed. Descriptive statistics are given by means and standard deviations for normally distributed data. Categorical data are subsumed by absolute and relative frequencies. In analytical statistics, Nominal or ordinal variables were compared between groups by chi-square test and Fisher's exact test, depending on the expected cell counts of the corresponding crosstabs. In addition, unpaired Student *t* test was used when the variables fulfilled the presumption of normal distribution (only age), whereas the Mann-Whitney *U* test was used when the variables were not normally distributed. The Spearman rank order correlation was used to test correlations between transfusion requirements and age. The results of the two-sided tests were considered significant if the p value was less than 0.05. As there were no previously published data, we used the data of previous studies evaluating the effects of intravenous or oral form of TA to estimate the sample size. The null hypothesis was defined as there is no statistically meaningful difference in amount of blood needed for transfusion between those who either did or did not receive TA, and the alternative hypothesis was that the amount of blood transfusion of those who received TA was less than that of those not treated with TA. The Altman's nomogram was used to calculate the sample size; for a power being equal to 90%, the sample size would be 130. We included 272 patients initially because our estimate for the proportion of episodes caused by peptic ulcers was approximately 50% of all UGIB events.

RESULTS

A total of 272 patients with UGIB were admitted to our ED during the study period, of which 131 (48.16%) were diagnosed to bleed from peptic ulcers. Sixty-seven patients were allocated to TA and 64 to placebo. The average age of participants was 64.25 years (± 13.92 years). The treatment group and the placebo group were well comparable regarding gender, age, *Helicobacter pylori* infection, endoscopy findings, Rockall score, and laboratory values; no statistically significant difference was found [Table 1].

Table 1: Presentation of findings on admission and post intervention findings in the participants Data are presented as incidence (%), mean ± standard deviation. PRBC: Packed Red Blood Cell

Variables	All Participants (n=131) Number of patients (%) or mean±*SD*	TA Group (n=67) Number of patients (%) or mean±*SD*	Placebo Group (n=64) Number of patients (%) or mean±*SD*	*P* value
Findings on Admission				
Age (years)	64.25±13.92	63.83±13.60	64.70±14.34	P=0.723
Male Gender	82(62.6%)	41(61.2%)	41(64.1%)	P=0.857
Rockall Score	3.48±1.57	3.52±1.60	3.43±1.55	P=0.759
H.pylori	91 (69.46)	45 (67.16)	46 (71.8575)	P=0.078
Post Intervention Findings				
Mortality	13 (9.9%)	4 (6%)	9 (14.1%)	P=0.150
Rebleeding	16 (12.2%)	4 (6%)	12 (18.8%)	P=0.033
Emergency Endoscopy	20 (15.3%)	6 (9%)	14 (21.9%)	P=0.040
Units of PRBC	2.32±1.47	1.77±1.08	2.90±1.61	P<0.001

Mortality– There were 13(9.92%) cases expired (30-day mortality) in our study population; 4 in TA group

(5.97%) and 9 in placebo group (14.06%). UGIB-related mortality was reduced in TA treated patients but the difference did not reach the level of significance. (p=0.150)
During the study no emergency surgery for UGIB was done in our hospital. Thromboembolic complications (arterial or venous thrombosis) were seen in neither of the groups within 30 days. No other side effects were observed during treatment with intra-gastric TA.

Transfusion- Transfusion requirements (as units of PRBC) were higher in patients not receiving TA. Patients in TA group received 1.77 (SD=1.08) units averagely but the average amount of packed RBCs received by placebo group was 2.9 (SD=1.61) units. This difference was significant statistically. (p<0.001)

Rebleeding- During the follow-up period (4 weeks after initiation of the treatment), the rebleeding frequencies differed between the two groups significantly. The rebleeding episodes were 4 (6%) in TA group and 12 (18.8%) in placebo group. (OR=3.635; 95% CI= 1.106 - 11.943; p=0.033)

Emergency Endoscopy- Significant difference was found in the rate of emergency endoscopies between the two groups. There were 6 (9%) emergency endoscopies in patients received TA whereas patients treated with placebo underwent 14 (21.9%) emergency endoscopies. (OR=2.847; 95% CI 1.019 - 7.949; p=0.040). In addition, patients' age were significantly correlated with transfusion requirements. (Spearman correlation coefficient: 0.711, $P = 0<0.001$)

DISCUSSION

The dosage used for topical administration of TA is much lower and effects are shorter than that used in oral or intravenous routes [9, 27]. The results of this study indicate that topical intra-gastric TA may be as an aid to conventional treatment and illustrates a novel application for TA in patients bleeding from benign lesions in stomach or duodenum. Although we did not measure the plasma level of TA to determine the degree of its systemic absorption, the prompt response of the patients to direct administration suggests that the beneficial effects probably originates from topical influence of TA.

Blood products can expose the patient to the risks of blood-borne diseases, graft-versus-host reactions, and acute hemolytic reactions, all of which increase patient mortality [28, 29]. Therefore, reducing blood loss and consequent transfusions are important priorities in acute UGIB. In our study, the use of intra-gastric TA reduced the risk of exposure to allogenic blood products.

Systemic TA in UGIB: The effect of TA is uncertain in the treatment of acute UGIB [30, 31]. Gluud et al performed a systematic review and evaluated seven double-blind randomized trials. They concluded that no significant differences were found on bleeding, surgery, transfusion requirements and also mortality between TA and placebo group. They stated that systemic TA could not be recommended for UGIB [31].

Topical TA: TA has been used topically in different pathological situations. Topical application of TA in patients undergoing coronary artery bypass operations efficiently has reduced postoperative bleeding [24, 32, 33]. De Bonis and colleagues did not detected TA in any of the blood samples blindly collected from 24 patients underwent coronary artery surgery to verify whether any systemic absorption of the drug occurred [32]. Wong and colleagues assessed the efficacy and safety of the topical application of TA on postoperative blood loss in patients undergoing primary unilateral total knee arthroplasty. They found that topical application of TA directly in the surgical wound reduced postoperative bleeding by 20-25% compared with placebo, with no clinically important increase in complications being identified in the treatment groups [23]. Some studies showed minor oral surgery, such as single tooth extraction or implant placement in patients on anticoagulant agents can be performed safely without any modification of the ongoing anticoagulant therapy when local haemostatic measures such as TA mouthwashes or gauzes saturated with TA were applied, thus minimizing costs and reducing discomfort for patients [34-36]. Results of another study indicated that the mean intra-operative bleeding rate in TA group was significantly lower than that of placebo group in endoscopic sinus surgery [37]. Topical TA has also been successfully used to control bleeding in parotid surgery [38], hemophiliacs undergoing oral surgery [39] and lung surgery [40].

Mechanisms: Fibrinolytic activity in the upper gastrointestinal tract may be a factor contributing to hemorrhage that often complicates gastroduodenal ulcers and erosions [41]. Fibrinolytic activity has been described in the margins of peptic ulcers [42]. Fibrin is readily degraded by gastric juice and duodenal juice. Gastric juice is particularly potent and a haemostatic fibrin clot in the stomach must be regarded as a potential substrate for its action [41].

TA has a plausible mode of action in UGIB. It is a plasminogen inhibitor, and plasminogen activators have been found in the gastric and duodenal mucosa. Cox et al reported that plasminogen activator and free plasmin were present in gastric venous blood obtained at operation in a higher proportion of patients with peptic ulcer than in a control group [43]. In addition, TA has been shown to inhibit the fibrinolytic action of pepsin [41]. This effect is independent of changes in PH, which may have particular relevance for patients who are critically ill and whose gastric contents may remain acidic despite treatment with histamine H2 receptor antagonists [44]. On the other hand, gastric juice from patients with bleeding ulcers was found to have a plasmin-like fibrinolytic activity [45]. Antifibrinolytic treatment and an increase in gastric PH are

possibly the necessary combination for successful haemostatic treatment [42]. The fibrinolytic activation was more pronounced in the wound than in the general circulation. TA inhibited fibrinolysis in blood from the wounds, but had no effect on fibrinolysis in plasma from peripheral venous circulation. The diminished postoperative blood loss in patients treated with TA is probably induced by decreased fibrinolysis in the wound. TA, by reducing local fibrinolysis, decreases plasminogen consumption and thus maintains a higher plasminogen level in the wounds [46].

The principle for the potential effectiveness of TA includes the following activities: local inhibition of fibrinolytic activity in bleeding lesions, inhibition of fibrinolytic activity of pepsin [41, 43], stabilization of haemostatic clots [47], and specific systemic improvement of haemostatic impairment [48].

Limitation: We did not measure the plasma level of TA in patients. The number of the patients was relatively small and the inclusion criteria were strictly tight.

CONCLUSION

We believe that intra-gastric use of TA is safe, cost effective, well tolerated and can be performed easily. The present study suggests that TA may reduce transfusion requirements and rebleeding events. Obviously, further investigation is needed to evaluate the efficacy and safety of this new method for management of acute UGIB and because of limitations in the sample size, additional evidence is needed before any treatment recommendations can be made. Further studies must be carried out to clarify whether this topical effect could also be seen in patients with malignant lesions.

CONFLICT OF INTEREST
There is no conflict of interest.

ACKNOWLEDGEMENTS
None

FINANCIAL DISCLOSURE
None

REFERENCES

[1] Palmer K.[2007] Acute upper gastrointestinal haemorrhage. Br Med Bull; 83:307–24.
[2] Hawkey GM, Cole AT, McIntyre AS, Long RG, Hawkey CJ. [2001]Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. Gut; 49(3):372-379.
[3] Weickert U, Riemann JF. The management of bleeding ulcers. Internist (Berl). 2006; 47(6):596-601.
[4] Chung IK, Lee DH, Kim HU, Sung IK, Kim JH. [2009] Korean College of Helicobacter and Upper Gastrointestinal Research; Korean Association of Gastroenterology. Guidelines of treatment for bleeding peptic ulcer disease. Korean J Gastroenterol 54(5):298-308.
[5] Longstaff C. [1994] Studies on the mechanisms of action of Aprotonin and Tranexamic acid as plasmin inhibitors and antifibrinolytic agents. Blood Coagul Fibrinolysis 5:537–542.
[6] Verstraete M.[1985] Clinical application of inhibitors of fibrinolysis. Drugs 29:236
[7] Leminen H, Hurskainen R. [2012]Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety.Int J Womens Health.4:413-421.
[8] Lukes AS, Moore KA, Muse KN. [2010]Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. Obstet Gynecol ; 116(4):865-875.
[9] Cormack F, Chakrabarti RR, Jouhar AJ, Fearnley GR. Tranexamic Acid in Upper Gastrointestinal Haemorrhage. The Lancet 1973; 301(7814): 1207-1208.
[10] Gluud LL, Klingenberg SL, Langholz SE. [2008] Systematic review: tranexamic acid for upper gastrointestinal bleeding. Aliment Pharmacol Ther 27(9):75275-7528.
[11] March GM, Elfatori S, Beaulé PE.[2013] Clinical experience with tranexamic acid during primary total hip arthroplasty.Hip Int. 21;23(1):72-79.
[12] Irisson E, Hémon Y, Pauly V, Parratte S, Argenson JN, Kerbaul F.[2012] Tranexamic acid reduces blood loss and financial cost in primary total hip and knee replacement surgery.Orthop Traumatol Surg Res. 98(5):477-483.
[13] Kojima T, Gando S, Morimoto Y, et al. [2001]Systematic elucidation of effects of tranexamic acid on fibrinolysis and bleeding during and after cardio-pulmonary bypass surgery. Thromb Res, 104:301.
[14] Brown R, Thwaites B, Mongan P. [1997]Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: A double-blind, randomized, placebocontrolled trial. Anesth Analg, 85:963-970.
[15] CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, et al. [2010]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. 376(9734):23-32.
[16] Ovrum E, Holen EA, Abdelnoor M, Oystese R, Ringdal ML.Tranexamic acid (Cyklokapron) in not necessary to reduce blood loss after coronary artery operations. J Thorac Cardivasc Surg 1993; 105:78–83.
[17] Krivokuca I, Lammers JW. [2011]Recurrent Pulmonary Embolism Associated With a Hemostatic Drug: Tranexamic Acid. Clin Appl Thromb Hemost, 17(1): 106-107.
[18] Ichikawa J, Kodaka M, Nishiyama K, et al. [2013]A case of postoperative convulsive seizure following tranexamic acid infusion during aortic valve replacement.Masui. 62(2):186-189.
[19] 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(2):350-353.
[20] Versraette M. Clinical application of inhibitors of fibrionolysis. Drugs 1985; 29:236–261.
[21] Valsecchi A. Further notes on the topical use of Tranexamic acid in the treatment of gynaecological haemorrhage. Minerva Ginecol 1980; 32:825–30.
[22] Sindet-Pedersen S, Ramtro G, Bernvil S, Blomback M.[1989] Haemostatic effect of tranexamic acid

mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med; 320:840–843.
[23] Wong J, Abrishami A, El Beheiry H, et al. [2010]Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am, 92(15):2503-2513.
[24] Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L. [2009] Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. J Cardiothorac Surg 4:25.
[25] Bacci C, Berengo M, Favero L, Zanon E.[2011] Safety of dental implant surgery in patients undergoing anticoagulation therapy: a prospective case-control study. Clin Oral Implants Res; 22(2): 151-156.
[26] Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996; 38(3):316-21.
[27] Engqvist A, Broström O, von Feilitzen F, et al. [1979]T ranexamic acid in massive haemorrhage from the upper gastrointestinal tract: a double-blind study. Scand J Gastroenterol. 14(7):839-844.
[28] Regan F, Taylor C.[2002] Recent developments. Blood transfusion medicine. BMJ; 325:143-147.
[29] Chiavetta JA, Herst R, Freedman J, Axcell TJ, Wall AJ, van Rooy SC.[1996] A survey of red cell use in 45 hospitals in central Ontario, Canada. Transfusion, 36:699-706.
[30] Morgan A, Jeffrey-Smith A.[2012] BET 1: should tranexamic acid be given to patients who are having an upper gastrointestinal bleed?Emerg Med J. 29(9):773-777
[31] Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding.Cochrane Database Syst Rev. 2012 Jan 18;1:CD006640.
[32] De Bonis M, Cavaliere F, Alessandrini F, et al. [2000] Topical use of tranexamic acid in coronary artery bypass operations: A double-blind, prospective, randomized, placebo-controlled study. J Thorac Cardiovasc Surg; 119(3):575-580.
[33] Aoki M, Okawa Y, Goto Y, Ogawa S, Baba H. [2012] Local administration of tranexamic acid in off-pump coronary artery bypass.Asian Cardiovasc Thorac Ann. 20(6):658-662.
[34] Madrid C, Sanz M. What influence do anticoagulants have on oral implant therapy? A systematic review.Clin Oral Implants Res. 2009 Sep; 20 Suppl 4:96-106.
[35] Bacci C, Maglione M, Favero L, et al. [2010]Management of dental extraction in patients undergoing anticoagulant treatment. Results from a large, multicentre, prospective, case-control study.Thromb Haemost.; 104(5):972-975.
[36] Carter G, Goss A. [2003]Tranexamic acid mouthwash — A prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 32(5):504-507.
[37] Jabalameli M, Zakeri K. [2006]Evaluation of Topical Tranexamic Acid on Intraoperative Bleeding in Endoscopic Sinus Surgery. Iran J Med Sci; 31(4): 221-223.
[38] Coker N, Higgins DJ. [2000]Tranexamic acid applied topically to achieve haemostasis. Anesthesia 55: 600-601.
[39] Patatanian E, Fuqate SE. [2006] Hemostatic Mouthwashes in Anticoagulated Patients Undergoing Dental Extraction. Ann Pharmacother 40(12): 2205-10.
[40] Dell'Amore A, Caroli G, Nizar A, et al.[2012] Can topical application of tranexamic acid reduce blood loss in thoracic surgery? A prospective randomised double blind investigation.Heart Lung Circ. 21(11):706-10.
[41] Low J, Dodds AJ, Biggs JC.[1980] Fibrinolytic activity of gastroduodenal secretions - a possible role in upper gastrointestinal haemorrhage. Thromb Resh 17(6): 819-830.
[42] Von Holstein C, Eriksson S,Kallen R. [1987]Tranexamic acid as an aid to reducing blood transfusion requirements in gastric and duodenal bleeding. BMJ 294:7-10.
[43] Cox HT, Poller L, Thomson JM.[1985] Gastric fibrinolysis: a possible aetiological link with peptic ulcer. Lancet 1967; i: 1300-2.
[44] More DG, Raper RF, Munro IA, Watson CJ, Boutagy JS, Shenfield GM. Randomized prospective trial of cimnetidine and ranitidine for control of intragastric pH in the critically ill. Surgery 97:215-24.
[45] Buhr H, Encke A, Seufert R. Untersuchungen zur lokalen Fibrinolyse des Magens. Ckiurg; 49:431-5.
[46] Benoni G, Lethagen S, Fredin H. [1978] The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. Thromb Res 1997; 85(3):195-206.
[47] Mannucci PM. [1998]Hemostatic drugs. N Engl J Med; 339:245-253.
[48] Mezzano D, Tagle R, Panes O, et al.[1996] Hemostatic disorder of uremia: the platelet defect, main determinant of the prolonged bleeding time, is correlated with indices of activation of coagulation and fibrinolysis. Thromb Haemost 76:312–321