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## Comparison of Two Doses of Tranexamic Acid on Bleeding and Surgery Site Quality During Sinus Endoscopy Surgery

### Porównanie wpływu dwóch dawek kwasu traneksamowego na krwawienia i jakości pola operacyjnego podczas endoskopowego zabiegu chirurgicznego zatok

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;  
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#### Abstract

**Background.** One of the main concerns in sinus surgery is blood loss due to the high vasculature of the mucosa. Tranexamic acid (TA) is an antifibrinolytic agent which reduces bleeding following certain surgical procedures.

**Material and Methods.** This randomized double-blinded clinical trial was performed on 70 patients with class I and II ASA (American Society of Anesthesiologists) who were scheduled for endoscopic sinus surgery under general anesthesia. The average ages of the patients were 18 to 50 years old. Thirty-five patients (group A) received 5 mg/Kg of TA, and another 35 patients (group B) received 15 mg/Kg of TA. The mean arterial pressure (MAP), diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) were documented. Also, the amount of blood loss and satisfaction scores were obtained from the surgeon in 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup>, 120<sup>th</sup> and 180<sup>th</sup> minutes. All the data was analyzed by SPSS-15 software with *T*-test.

**Results.** A total of 52 males and 18 females participated in the study. There were no significant differences between the mean age, MAP, DBP, SBP and HR during surgery between groups. Blood loss was 272.74 ± 25.77 mL 242.89 ± 51.77 mL in the group A and B respectively (*P* < 0.003). The surgeon was more satisfied with the surgical field of the group B than the group A (mean scores 4 (3–5) vs. 3 (1–5) respectively, *P* < 0.005). Surgery period and need for supplement drug to control bleeding in group B was significantly less than in group A (*P* < 0.05). But there was no significant difference between the two groups in terms of side effects.

**Conclusions.** Administration of 15 mg/Kg TA intravenously is more effective than 5 mg TA to achieve hemostasis and improving the quality of surgical field, surgeon satisfaction, less surgery period and bleeding volume during endoscopic sinus surgery without any significant side effects (*Adv Clin Exp Med* 2012, 21, 6, 773–780).

**Key words:** tranexamic acid, bleeding, surgical field quality, endoscopic sinus surgery.

#### Streszczenie

**Wprowadzenie.** Jednym z głównych problemów w chirurgii zatok przynosowych jest utrata krwi z powodu dużego unaczynienia błony śluzowej. Kwas traneksamowy (TA) jest środkiem antyfibrynolitycznym, który zmniejsza krwawienie po niektórych zabiegach chirurgicznych.

**Material i metody.** Do randomizowanego badania klinicznego z podwójnie ślełą próbą włączono 70 chorych klasy I i II wg ASA (Amerykańskie Stowarzyszenie Anestezjologów), u których wykonano planowy zabieg chirurgii endoskopowej zatok w znieczuleniu ogólnym. Wiek pacjentów wynosił 18–50 lat. 35 chorych (grupa A) otrzymało 5 mg/kg TA, a kolejne 35 osób (grupa B) otrzymało 15 mg/kg TA. Zmierzono średnie ciśnienie tętnicze (MAP), ciśnienie rozkurczowe (DBP), ciśnienie skurczowe (SBP) i częstość akcji serca (HR). Ponadto udokumentowano ilość utraconej krwi i uzyskano ocenę satysfakcji od chirurga w 30., 60., 90., 120. i 180. minucie. Wszystkie dane analizowano za pomocą oprogramowania SPSS-15 i testu *T*.

**Wyniki.** Łącznie 52 mężczyzn i 18 kobiet wzięło udział w badaniu. Nie stwierdzono istotnych różnic w średnim wieku, MAP, DBP, SBP i HR podczas operacji między grupami. Utrata krwi wynosiła  $272,74 \pm 25,77$  ml i  $242,89 \pm 51,77$  ml odpowiednio w grupie A i B ( $p < 0,003$ ). Chirurg był bardziej zadowolony z pola operacyjnego w grupie B w porównaniu z grupą A (średnie wyniki 4 (3–5) vs 3 (1–5);  $p < 0,005$ ). Czas operacji i konieczność stosowania dodatkowego leku hamującego krwawienie były mniejsze w grupie B niż w grupie A ( $p < 0,05$ ). Nie było znaczącej różnicy między grupami pod względem działań ubocznych.

**Wnioski.** Podawanie 15 mg/kg TA dożylnie jest bardziej skuteczne niż 5 mg TA w celu osiągnięcia hemostazy, poprawy jakości pola operacyjnego, większej satysfakcji chirurga, skrócenia czasu zabiegu chirurgicznego i ograniczenia wielkości krwawienia podczas endoskopowego zabiegu chirurgicznego zatok, bez żadnych istotnych działań ubocznych (*Adv Clin Exp Med* 2012, 21, 6, 773–780).

**Słowa kluczowe:** kwas traneksamowy, krwawienie, jakość pola chirurgicznego, endoskopowa chirurgia zatok.

The purpose of anesthesia is not only hypnosis but also a combination of safe analgesia, amnesia and the immobilization of patients during a surgery. But another important duty of anesthesiologists is to prepare a suitable situation to make an appropriate surgery field for better visibility of the surgery site, thus lowering the risk of possible injuries to other adjacent organs and also decrease the time of operation [1]. Chronic rhino sinusitis and polyps are common diseases. Sinus surgeries are commonly done by endoscopic techniques [2]. Bleeding during endoscopic surgeries is a common inevitable complication and a major concern for both anesthesiologists and otolaryngologists [3]. In endoscopic sinus surgery local anesthesia has been replaced by general anesthesia, because general anesthesia immobilizes the surgery site, gives the opportunity for better care of respiratory tract and better analgesia and respiration. But the most important limitation in this method is more bleeding [4, 5]. The most important source of bleeding during endoscopic sinus surgeries are the capillaries [6]. Also, mean arterial pressure (MAP) can influence the severity of bleeding [7, 8]. Controlled hypotension is a way to decrease bleeding during surgery; this will be reached by using drugs like nitroprusside sodium, nicardipine, nitroglycerin, beta blockers and also a high dose of anesthesia drugs like halothane, Isoflurane and propofol. Nasal decongestant like oxymetazoline, cocaine and adrenaline [9, 10], lidocaine combined with adrenaline [11] and fibrin glue (that is composed of biologic coagulants like thrombin, fibrinogen and cryoprecipitate) can also be used for this purpose. Although the volume of bleeding during endoscopic surgeries is low, considering the limited environment of surgery and limitation in visibility of surgery site by endoscope, even low amounts of bleeding can interfere with surgeon visibility [12, 13]. Then, the surgeon will have to use suction frequently and this will increase the risk of further manipulation of field and also more bleeding and longer surgery duration [14]. It can cause limitations in seeing the surgery site and increase the risk of possible injuries to other adjacent organs, such as the vasculature of the eye

and intracranial complications [15, 16]. There are several suggested ways to prevent bleeding during endoscopic surgeries and its related problems but there is no method of choice for this purpose. Methods like head elevation [1], vasoconstrictor drugs [17], controlled hypotension [18] and the use of only intravenous anesthesia techniques have been suggested. For most patients, a combination of these methods is suggested. But in a lot of patients, bleeding remains uncontrolled and further action is needed. One of the popular ways to prevent such problems is administering antifibrinolytic agents, such as tranexamic acid. This product prevents plasminogen linking with fibrin to make plasmin and stabilizes the formed clot [19]. Tranexamic acid has dose dependent complications, such as nausea, vomiting, headache, blurred vision and vertigo. Although there are some reports on thrombosis formation by using this product but evidence for risk of such complication are low [20, 21]; and generally this drug is safe [20, 22]. This drug has been used for hemophiles, von Willebrand factor deficiency [22, 23], primary menorrhagia [20], GI bleeding [22], urinary tract surgeries [24], cardiothoracic surgeries [25] and thrombocytopenia [26].

Antifibrinolytic effect of tranexamic acid is about 5–10 times more than aminocaproic acid. The half-life of the drug is about two hours (with dose administered 1 gram).

Considering the dose dependent complications of tranexamic acid and high cost of the drug, the authors compared two doses of tranexamic acid on bleeding and surgery site quality during sinus endoscopic surgery.

## Material and Methods

This randomized, double blinded clinical trial was done during April 2011–February 2012 in Shahid Sadoughi Hospital, Yazd, Iran. After confirmation of university institutional ethics committee, the study was registered in Iranian registry of clinical trials (<http://irct.ir>) as IRCT201203242963N7. A total of 70 patients who were candidates for en-

Endoscopic sinus surgery participated in this study. Considering  $P < 0.05$  as significant, test power of 80%,  $d = 1.5$  and based on previous studies, thirty five patients were needed for each group. Patients were allocated to groups by random selection with table of random numbers. The flow of the study is indicated in Figure 1. A written consent was obtained from the patients.

All patients were in ASA (American Society of Anesthesiologists) class I and II, with no airway complications, systemic diseases or known psychological diseases.

Patients received no medication 24 hours before surgery. Patients had no history of sensitivity to anaesthesia or any other drugs used in this study.

Patients with a history of coagulation disease or use of anti coagulants, and patient with a history of stroke, coronary artery diseases, hypertension, deep vein thrombosis, pulmonary embolism and peripheral vascular diseases were excluded from this study.

The anesthesia protocol was the same for both groups. After monitoring, fentanyl (2 µg) and lido-

caine (1.5 mg) and midazolam (0.02 mg/kg) were administered. Anesthesia induction was by propofol (2.5 mg/kg) and atracurium (0.5 mg/kg). After intubation, anesthesia maintenance was by propofol infusion (100 µg/kg/min) and remifentanyl (0.1 µg/kg/min). Ventilation control was by NO 50% and O<sub>2</sub>. After surgery muscle relaxation was reversed by neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. Before surgery 3 ml/kg isotonic liquid was infused, and also during surgery maintenance serum was administered according to patients' weight and bleeding. If bleeding remained uncontrolled, TNG (5 µgr/min) was infused till MAP = 60 mm Hg was reached.

For first group (A) 5 mg/kg and for second group (B) 15 mg/kg tranexamic acid was diluted with 100 ML normal saline and administered during 10 minutes infusion. Drug is colorless and then researcher and surgeon were unaware of injected drug. Drug volume integration was done by a pre operation nurse and also labeled. Researcher diluted drug with normal saline to reach 100 ml of liquid and after that drug was injected during first

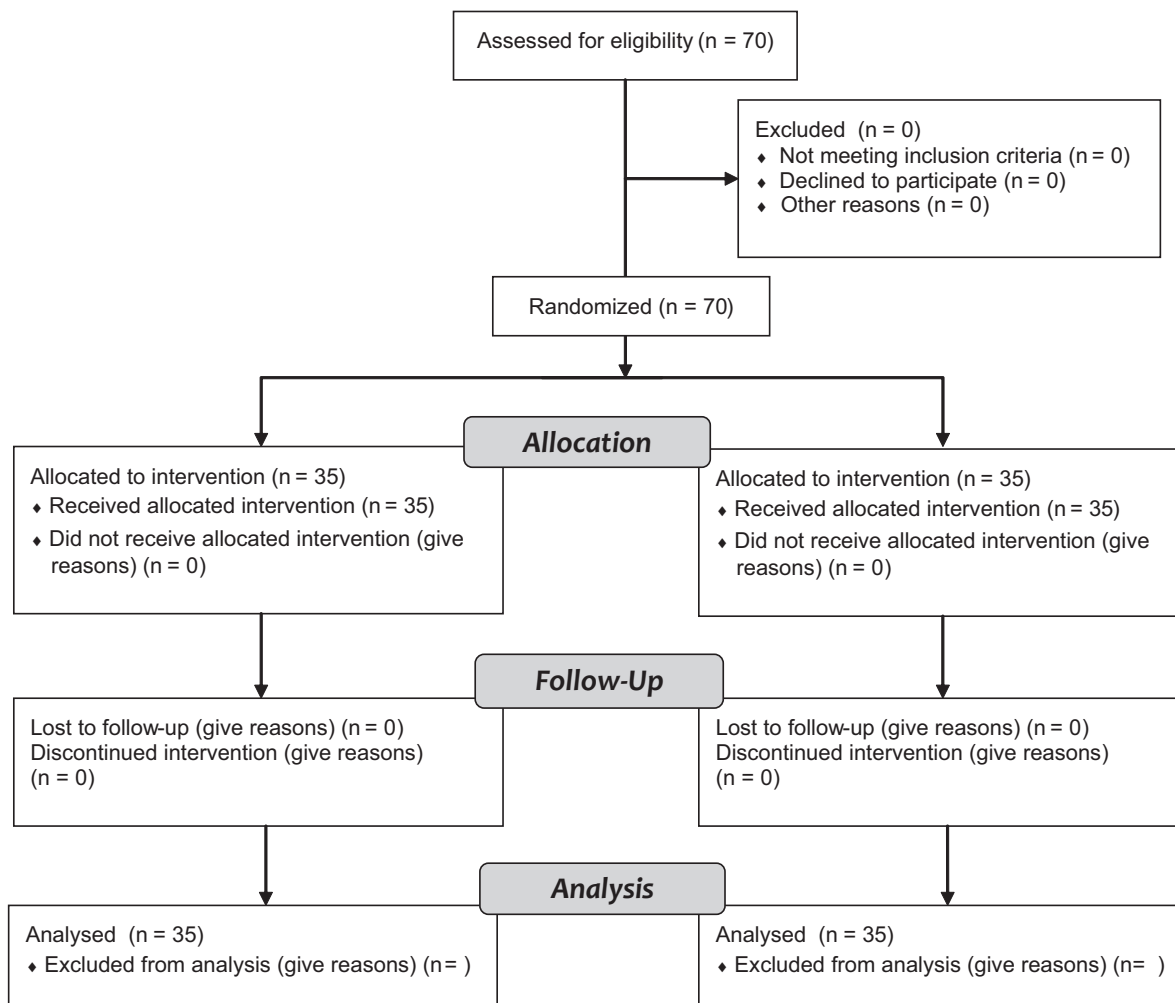


Fig. 1. Flow of the study

Ryc. 1. Algorytm badania

**Table 1.** Boezaart Grading Scale for Scoring of Surgical Field Bleeding**Tabela 1.** Skala Oceny Krwawienia Pola Chirurgicznego Boezaarta

Assessment (Ocena)
No bleeding (cadaveric conditions)
Slight bleeding – no suctioning required
Slight bleeding – occasional suctioning required
Slight bleeding – frequent suctioning required.
Bleeding threatens surgical field a few seconds after suction is removed
Moderate bleeding – frequent suctioning required.
Bleeding threatens surgical field directly after suction is removed.
Severe bleeding – constant suctioning required.
Bleeding appears faster than can be removed by suction; surgical field severely threatened and surgery usually not possible.

10 minutes after anesthesia induction. The researcher and surgeon were unaware about patients' group.

The data was registered in a questionnaire which consisted of demographic variable (age, sex and weight), medical history of patients, laboratory test before operation, volume of bleeding during surgery according to Boezaart' scale (Table 1) at 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup>, 120<sup>th</sup> and 180<sup>th</sup> minutes, satisfaction of surgeon about surgery site (evaluated by five parts' Likert scale (from very bad (1) to very good (5)), surgery time, volume of bleeding and drug side effect after surgery. All registered data were transferred into SPSS-15 software and analyzed by descriptive analysis and T-Test. P-values < 0.05 was considered as significant result.

## Results

A total of 70 patients (35 in group A and 35 in group B) aged 18–50 years old were included in the study. The mean age for group A was  $36.4 \pm 9.53$  and for group B was  $33.7 \pm 8.58$ . There were no significant differences according to age and sex between the two groups ( $P > 0.05$ ).

Also, there were no significant discrepancies between the two group based on Mean Arterial Pressure (MAP), Heart Rate (HR), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at any measured time (before anesthesia induction and 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup>, 120<sup>th</sup> and 180<sup>th</sup> minutes) ( $P > 0.05$ ) (Table 2).

Quality of surgery site based on Boezaart' scale and surgeon satisfaction about surgery site quality based on five parts Likert scale were assessed on 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup>, 120<sup>th</sup> and 180<sup>th</sup> minute. There were

significant differences in these contexts at all measured times ( $P < 0.05$ ) (Tables 3 and 4).

Mean collected blood was  $272.74 \pm 25.77$  ml for group A and  $242.89 \pm 51.77$  ml for group B ( $P = 0.003$ ).

About 71.4% of the patients in group A and 91.4% in group B did not need more drugs to control bleeding ( $P = 0.03$ ). The time of surgery was  $180.86 \pm 17.34$  and  $169.11 \pm 18.82$  minutes in groups A and B respectively ( $P = 0.01$ ).

Only three patients (4.3%) had side-effects in the form of mild Gastro Intestinal complication (GI) (2 cases of group B and one case of group A); in the other 67 cases (95.7%) no complications were reported ( $P = 0.55$ ).

## Discussion

One of the most important concerns in endoscopic sinus surgeries, because of vessel filled area, is bleeding during surgery. Bleeding can have venous, arterial or capillary source and can cause serious complications due the interference with the visibility and quality of surgery field. Tranexamic acid is a hydrophilic antifibrinolytic drug that can be administered orally or intravenously to decrease intra operative bleeding.

In this study the authors did not find any significant difference between study groups according to SBP, DBP and MAP. These results are concomitant with Mottaghi et al. study [27] that compared effect of 500 mg tranexamic acid with placebo. Jebel Ameli et al., who used topical tranexamic acid [28] and Athanasiadis et al. [29] in their studies, had similar conclusions.

According to viewpoint of surgeon about the surgery field quality and visibility, the authors found significant differences between two groups at all measured times ( $P < 0.05$ ). Jebel Ameli et al. [28] in his study compared the quality of surgery field and volume of bleeding with similar scales to the present study and concluded that using tranexamic acid can decrease bleeding and improve quality of surgery field significantly comparing with placebo.

Alimian et al. [30] also compared 10 mg/kg IV tranexamic acid with a placebo. In this study there was a significant difference in terms of bleeding, satisfaction of surgeon about visibility of surgery field and surgery site quality.

Athanasiadis [29] compared patients in three groups. Aminocaproic acid group, 100 mg tranexamic acid group and 1 gr of tranexamic acid group; and concluded that tranexamic acid can reduce surgery site bleeding at 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> minutes after the injection of drug, while aminocaproic acid had no signifi-

**Table 2.** Mean  $\pm$  SD of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) in two groups of study and related P values (T-test)

**Tabela 2.** Średnia  $\pm$  odchylenie standardowe skurczowego ciśnienia tętniczego (SBP), ciśnienia rozkurczowego (DBP) i średniego ciśnienia tętniczego (MAP) w dwóch grupach badanych oraz związane z nimi wartości P (test T)

Group (Grupa)		A	B	P-value
Measured times (Czas zmierzony)				
Before anesthesia induction (Przed wywołaniem znieczulenia)	SBP	134.29 $\pm$ 9,2	136.77 $\pm$ 8.5	0.24
	MAP	88.4 $\pm$ 4.8	85.3 $\pm$ 5.1	0.68
	DBP	88.28 $\pm$ 6.26	86.8 $\pm$ 8.39	0.52
30 <sup>th</sup> minute (30. minuta)	SBP	110.63 $\pm$ 7.6	110.97 $\pm$ 8.7	0.86
	MAP	73.2 $\pm$ 5.1	74.5 $\pm$ 5.6	0.32
	DBP	71.77 $\pm$ 6.89	73.2 $\pm$ 3.31	0.27
60 <sup>th</sup> minute (60. minuta)	SBP	110.69 $\pm$ 8.2	110.4 $\pm$ 8.15	0.88
	MAP	69.25 $\pm$ 3.32	65.2 $\pm$ 6.78	0.41
	DBP	73.08 $\pm$ 8.19	70.14 $\pm$ 7.9	0.3
90 <sup>th</sup> minute (90. minuta)	SBP	102.20 $\pm$ 5.6	101.86 $\pm$ 6.02	0.84
	MAP	63.8 $\pm$ 9.97	61.6 $\pm$ 9.2	0.62
	DBP	80.4 $\pm$ 6.75	79.08 $\pm$ 9.63	0.5
120 <sup>th</sup> minute (120. minuta)	SBP	100.23 $\pm$ 5.88	99.62 $\pm$ 17.31	0.15
	MAP	61.9 $\pm$ 8.6	59.6 $\pm$ 10.36	0.56
	DBP	68.25 $\pm$ 5.34	67.54 $\pm$ 6.35	0.6
180 <sup>th</sup> minute (180. minuta)	SBP	95.28 $\pm$ 3.24	96.68 $\pm$ 9.13	0.39
	MAP	60.7 $\pm$ 6.8	59.7 $\pm$ 8.3	0.1
	DBP	57.94 $\pm$ 1.13	60.85 $\pm$ 5.47	0.17

cant effect. Tranexamic acid is 6–10 times more effective than aminocaproic acid [31–33]. Also Moise [34] in his study concluded that after the administration of 10 mg/kg tranexamic acid, bleeding during surgery will be half of control group.

Mottaghi et al. [27] compared 500 mg of IV tranexamic acid with placebo. Based on the results of this study there were no significant differences according to any variables like SBP, DBP, and MAP, amount of bleeding and surgeon satisfaction. These results did not accept the results of the present study and other similar studies. Researchers in this study attributed this difference to individual differences, differences in tissue destruction, hypertrophy and surgery technique [27]. But also it seems that the dosage of tranexamic acid can be effective in such results. As the authors have compared two different doses in the present study and as the authors concluded, 15 mg/kg of tranexamic acid is much more effective

than 5 mg/kg. Mottaghi et al. of course used higher doses than the present group A study. But the dose of Mottaghi et al. study will be about 10 mg/kg or lower. Of course, in some other studies, such as the Athanasiadis [29] study, results show that even 100 mg of tranexamic acid can be effective and this maybe of individual or surgery technique differences.

The incidence of drug side effects in the present study was low. This result was concomitant to other similar studies [14, 29, 34]. Side effects of systemic anti-fibrinolytics are related to Gastro Intestinal system usually.

About surgery time the present study showed significant differences between two groups. This variable only was assessed in Mottaghi study [27] that was not significant. This can be due to the dosage of the drug. It seems that 500 mg or lower (like the present group A study) have a low effects on surgery time.



**Table 3.** Mean  $\pm$  SD of surgery site quality based on Boezaart scale (0–5) and related P values (T-test)**Tabela 3.** Średnia  $\pm$  SD jakości pola operacyjnego na podstawie skali Boezaarta (0–5) i istotności statystycznej

Mean $\pm$ SD		Mean (Średnia)	SD (Odchylenie standardowe)	P-value
Measured times (Czas zmierzony)				
30 <sup>th</sup> minute (30. minuta)	A	3.28	0.92	0.003
	B	2.62	0.87	
60 <sup>th</sup> minute (60. minuta)	A	3.45	0.78	0.001
	B	2.74	0.98	
90 <sup>th</sup> minute (90. minuta)	A	3.48	0.65	0.001
	B	2.82	0.89	
120 <sup>th</sup> minute (120. minuta)	A	3.31	0.63	0.003
	B	2.68	1.02	
180 <sup>th</sup> minute (180. minuta)	A	2.88	0.63	0.002
	B	2.25	0.98	

**Table 4.** Mean  $\pm$  SD of surgeon satisfaction about surgery site quality based on five parts Likert scale (1–5) and related P values (T-test)**Tabela 4.** Średnia  $\pm$  SD satysfakcji chirurga z jakości pola chirurgicznego na podstawie 5 części skali Likerta (1–5) i związanych z nią wartości P (test T)

Mean $\pm$ SD		Mean (Średnia)	SD (Odchylenie standardowe)	P-value
Measured times (Czas zmierzony)				
30 <sup>th</sup> minute (30. minuta)	A	3.08	1.01	0.017
	B	3.65	0.93	
60 <sup>th</sup> minute (60. minuta)	A	3.2	0.71	0.001
	B	3.77	0.59	
90 <sup>th</sup> minute (90. minuta)	A	3.37	0.68	0.009
	B	3.75	0.44	
120 <sup>th</sup> minute (120. minuta)	A	3.28	0.45	0.032
	B	3.71	0.62	
180 <sup>th</sup> minute (180. minuta)	A	3.48	0.61	0.001
	B	4.02	0.74	

In a meta-analysis of 60 studies, results showed that tranexamic acid and aprotinin could decrease the need for a blood transfusion after coronary artery bypass graft (CABG) compared to aminocaproic acid and desmopressin. Also bleeding during surgery will be reduced by about 40% [22].

In most of the previous studies, tranexamic

acid was compared with placebo, but or study has compared two different doses of tranexamic acid with together. Based on the present study 15 mg/kg tranexamic acid can decrease bleeding during surgery and improve the quality of surgery site and its better visibility by surgeon without considerable complications compared to a 5 mg/kg dose.

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