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Effects of high-dose tranexamic acid in total hip replacement: A prospective, double-blind, randomized controlled study

Total kalça protez ameliyatlarında yüksek doz traneksamik asitin etkileri: Prospektif, çift-kör, randomize kontrollü çalışma

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Abstract

Aim: Different studies support the use of tranexamic acid (TA) to decrease the rate of transfusions in total hip replacement. This study aimed to investigate the effects of high-dose TA in total hip replacement.

Methods: Sixty American Society of Anesthesiologist (ASA) class I-III 60 adult patients were randomly assigned into 2 groups as group TA and group control (C) for this study. While, TA was administered at dose of 50 mg/kg to group TA, the group C received 100 cc normal saline (NS). In all subjects, blood samples were taken pre-surgery and 24 hours after the operation in order to study hemoglobin (Hgb), hematocrit (Hct), platelet count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, D-dimer, blood urea nitrogen (BUN), creatinine, and cystatin-c. The amount of intraoperative bleeding and number of given packed of red blood cell (PRBCs) were recorded.

Results: The amount of blood loss and number of PRBCs given were significantly lower, and Hgb values at discharge were significantly higher in group TA compared with group C. In group TA postoperative cystatin-c levels, compared with the preoperative period, were significantly low. The length of hospital stay was significantly short in group TA.

Conclusion: TA was given intravenously before incision reduces intraoperative blood loss and the use of PRBCs in total hip replacement. This approach also provided higher Hgb values at discharge. The provision of TA shortened length of hospital stay and did not negatively affect renal function.

Keywords: Tranexamic acid, Total hip replacement, Blood transfusion

Öz

Amaç: Farklı çalışmalar total kalça protezi ameliyatlarında transfüzyon oranını azaltmak için traneksamik asit (TA) kullanımını desteklemektedir. Bu çalışmada total kalça protezi ameliyatında yüksek doz TA'nın etkilerinin araştırılması amaçlanmıştır.

Yöntemler: Bu çalışma için American Society of Anesthesiologist (ASA) sınıf I-III 60 yetişkin hasta, grup TA ve grup kontrol (C) olarak 2 gruba ayrıldı. TA grubuna 50 mg / kg'dan traneksamik asit, kontrol grubu (C grubu) hastalarına ise 100 cc normal salin (NS) uygulandı. Tüm olgularda hemoglobin (Hgb), hematocrit (Hct), trombosit sayısı, protrombin zamanı (PT), parsiyel tromboplastin zamanı(PTT), fibrinojen, D-dimer, kan üre azotu (BUN), kreatinin ve sistatin-c değerlerinin çalışılması için hastalardan operasyondan 24 saat önce ve sonra kan örnekleri alındı. İntraoperatif kanama miktarları, transfüze edilen eritrosit süspansiyonu (PRBC) sayısı kaydedildi.

Bulgular: Grup TA'da kan kaybı miktarı verilmiş olan eritrosit süspansiyonu sayısı grup C'ye göre istatistiksel olarak anlamlı düşük bulundu. Taburculuktaki hemoglobin değerleri grup TA'da grup C'ye göre istatistiksel olarak anlamlı yüksek bulundu. TA grubunun postoperatif sistatin-c değerleri preoperatif periyottaki değerlerinden istatistiksel olarak anlamlı düşük bulundu. TA grubunun hastanede kalış süreleri istatistiksel anlamlı olarak düşük bulundu.

Sonuç: Total kalça protezi ameliyatlarında insizyondan önce uygulanan 50 mg/kg traneksamik asit intraoperatif kan kaybı miktarını ve verilen eritrosit süspansiyon sayısını azaltır. Aynı zamanda bu yaklaşımla taburculukta daha yüksek hemoglobin değerleri sağlanır. Bu prosedür böbrek fonksiyonlarını etkilemediği gibi hastanede kalış sürelerinin de kısalmasına neden olur.

Anahtar kelimeler: Traneksamik asit, Total kalça protezi, Kan transfüzyonu

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Introduction

Total hip replacement (THR) is associated with a significant amount of blood loss, often requiring allogenic blood transfusions. Our current population is aging; more and more people are living longer and maintaining active lifestyles, leading to more patients undergoing THR. With the anticipated increase in THR surgery, a strain will be placed on the already limited supply of allogenic blood. Moreover, allogenic blood transfusions are not risk-free. Patients can receive blood-borne pathogens, sustain immunologic reactions, become coagulopathic, be overtransfused, and become volume overloaded. One of the ways to decrease these complications is the use of antifibrinolytic agents. Recent studies showed that therapy with aggressive crystalloid infusion and the use of packed red blood cells (PRBCs) early in resuscitation induced early coagulopathy and increased bleeding [1,2].

Antifibrinolytic drugs are used to provide hemostasis, decrease bleeding, and allogenic blood transfusions. Tranexamic acid (TA) exerts its antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules and thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Although plasmin can still be formed under these circumstances, it is unable to bind to and degrade fibrin. Suppression of fibrinolysis by tranexamic acid is manifested in surgical patients by reductions in blood levels of D-dimer, but the drug has no effect on blood coagulation parameters [3].

The effectiveness of antifibrinolytic drugs has been investigated in cardiovascular, hepatic, orthopedic, and many other operations. TA has been shown to decrease bleeding for some specific orthopedic procedures [4,5]. High-dose TA administration is often used in cardiovascular surgery. We thought that high-dose administration of TA for THR could be effective on both intraoperative blood loss and the need for intraoperative and postoperative PRBCs.

Materials and methods

The study protocol was approved by the Medical Ethics Committee of Erciyes University Hospital. Written, informed consent was obtained from the patients.

We investigated 60 patients who were American Society of Anesthesiologist (ASA) physical status I to III, aged between 18 and 75 years, and were scheduled to undergo primary THR with combined spinal-epidural anesthesia.

The indications for surgery were primary osteoarthritis (n=51), femoral neck fracture (n=4), and rheumatoid arthritis (n=5). All patients' hips were replaced by a cemented prosthesis using the posterior approach. A subfascial drain was used in all patients and removed 24 hours later.

We performed the study as randomized, double-blind and placebo controlled; accordingly, the patients were assigned into two groups. The patients were assigned as TA group and control (C) group using the coin toss method. The TA group (n=30) received a total dose of 50 mg/kg TA (Transamine® %10 ampule) mixed in normal saline (NS); total volume of 100 ml via infusion, which started 15 minutes prior to the skin incision and took a total time of 30 minutes, meaning that it continued during part of the surgery. Group C (n=30) received NS in place of TA in the same manner and the same volume.

Patients were excluded if they had a history of drug sensitivity; coagulopathy; thrombocytopenia; hepatic or renal failure; deep vein thrombosis (DVT) or embolism; severe aortic or mitral valve stenosis; neurologic or cerebrovascular disease; if they had received aspirin or platelet antiaggregant treatment in the week before surgery, or nonsteroidal anti-inflammatory agents in the 2 days before surgery. Patients were also excluded if their preoperative plasma creatinine was greater than 130 μmol litre-1; they had a history of myocardial infarction or chronic arteriopathy; had unstable angina in the previous 12 months; or their mental states prevented them from understanding the study proposal. Eligible patients were informed of the objectives and procedure of the study and were required to give written informed consent before being enrolled.

The patients received no premedication on the day of the procedure. Demographic information and ASA status were recorded preoperatively for all patients. Monitoring included electrocardiography, pulse oximetry, noninvasive blood pressure, respiratory rate, and urine output through a Foley catheter.

After the patients were placed sitting position or in the lateral decubitis position, a lumbar epidural catheter was inserted in the L3-L4 or L4-L5 interspaces and combined spinal-epidural anesthesia was performed. Bupivacaine 0.5% was used for the spinal injection. The TA and NS solutions for all patients were prepared by the same anesthesia technician and administered by the same anesthesiologist. The duration of surgery, hospital length of stay, quantity of infused fluids, and transfused blood or blood products were recorded. During surgery, the loss of about 1000 mL blood was replaced with NS and/or 6% hydroxyethyl starch (Voluven®). Pre-surgery and 24-hour postoperative blood samples were taken from all patients to measure hemoglobin (Hgb), hematocrit (Hct), prothrombin time (PT), partial thromboplastin time (PTT), platelet count, blood urea nitrogen (BUN), creatinine, fibrinogen, D-dimer and cystatin-c values.

Intraoperative blood loss and intraoperative and postoperative numbers of given PRBCs was measured by same anesthesiologist who was unaware of each patient's group assignment. The patient's groups were learned by anesthesiologist only at the end of the study. Intraoperative blood loss was measured as the difference between the weights of used gauze and the original unused gauze, plus the difference between the volume accumulated in suction bottles and the volume of irrigation. The decision to give PRBCs was made by the anesthesiologist in view of the patients' age, cardiovascular status, and the amount of blood loss. Usually, blood loss under 1000 mL was replaced intraoperatively with NS and/or 6% hydroxyethyl starch. The decision to transfuse a patient for the postoperative period was made by the duty physician after the clinical assessment of anemia in orthopedic ward. A Hgb level of less than 8 g/dL−1 was considered a transfusion trigger except in patients who could have poor tolerance to these levels because of associated conditions such as chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented signs, symptoms, or both of hypoxia such as tachycardia, dyspnea, or syncope. The transfusion trigger was placed at less than 10 g/dl for these patients.

For thromboprophylaxis, all patients received 40 mg enoxaparin (Clexane®, Lovenox®) subcutaneously, starting the day before surgery and continuing for 7-10 days.

Postoperative bleeding from the drain was not included in the calculation. However, observational information about postoperative bleeding was taken from the duty orthopedic doctor.

Statistical analysis

Data were analyzed using SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA). Variables were checked using the Kolmogorov-Smirnov test. The independent samples t-test and Mann-Whitney U test were used in the analysis of quantitate data, the paired-sample t-test and Wilcoxon test were used for repeated measures, and the Chi-square test was used in the analysis of qualitative data. Differences were considered statistically significant if $P< 0.05$. Power analysis was used to determine the sample size. Based on a previous study, power analysis was performed according to the "peroperative blood loss amount" parameter. The number of cases was calculated as 26 for each group at 95% power, 95% safety margin ($\alpha = 0.05$, $\beta = 0.95$) [6].

Results

Age, sex, height, weight, ASA physical status, and the duration of surgery were similar between the groups. The length of hospital stay was significantly shorter in the group TA than in the C group ($p < 0.05$) (Table 1).

Intraoperative blood loss was significantly less in the group TA than in the group C (600mL vs 1450mL; $p < 0.05$) (Table 2). The amount of PRBCs given intraoperatively and postoperatively was significantly less in the group TA than in the group C ($p < 0.05$) (Table 2). Hemoglobin and Hct values were similar between the two groups before surgery and 24 hours after surgery; however, Hgb values were higher at hospital discharge in the group TA than in the group C (Table 3).

No significant differences were noted between the two groups with regards platelet count, PT, PTT, BUN, creatinine or fibrinogen values either before or 24 hours after surgery. Also, no significant differences were noted for D-dimer and cystatin-c values between the two groups (Table 3, 4). At the same time, D-dimer values were significantly higher in group C for postoperative period than intraoperative period. Furthermore, cystatin-c values were significantly lower in group TA for postoperative period than intraoperative period. We encountered no clinical venous thromboembolic events in either group.

Table 1: Demographic data, durations of surgery and lengths of hospital stay of the groups

	Group TA (n=30)	Group K (n=30)
Age (years)	53.5±12.7	54.6±14.9
Weight (kg)	79.0±11.4	72.8±11.8
Gender (M/F)	21/9	19/11
Height (cm)	166.6±8.8	164.6 ±9.1
ASA (I/II/III)	10/18/2	17/12/1
Duration of surgery (minute)	135 (60-225)	135 (60-210)
Length of hospital stay (days)	5 (4-6) *	7 (5-10)

Demographic data: mean ± standard deviation or number of patients. Length of hospital stay and duration of surgery: median (minimum–maximum). *p < 0.05

Table 2: Blood loss and transfusion

Parameter	Group TA (n=30)	Group K (n=30)
Intraoperative blood loss (m L)	600(200-1700)*	1450(400-3000)
Numbers of given PRBCs		
intraoperative	0 (0-1) *	1 (0-5)
postoperative	0 (0-1) *	1 (0-6)

Values are median (minimum–maximum). PRBCs: packed of red blood cells, *p < 0.05

Table 3: Red blood cell and coagulation data

Parameter	Group TA (n=30)	Group K (n=30)
Hemoglobin (gr/dl)		
Before surgery	14.1± 1.6	13.2 ± 1.9
24 hours after surgery	11.2± 1.2	10.6 ± 1.5
At discharge	10.8± 1.1	*10.1 ± 0.7
Hematocrit (%)		
Before surgery	42.9± 5.2	40.1 ± 5.3
24 hours after surgery	33.8± 3.4	31.9 ± 4.2
Platelet count (10^9/L)		
Before surgery	270 ± 63	272 ± 80
24 hours after surgery	207 ± 43	192 ± 51
PT (sec)		
Before surgery	11.2± 0.9	11.5 ± 1.1
24 hours after surgery	13.2± 1.9	13.3 ± 1.8
PTT(sec)		
Before surgery	27.0± 3.1	29.7 ± 7.3
24 hours after surgery	29.3± 3.6	31.2 ± 4.4
Fibrinogen (mg/dL)		
Before surgery	349 ± 76	349 ± 112
24 hours after surgery	438 ± 79	400 ± 113
D-dimer (mcg/L)		
Before surgery	2178 ± 6524	1307 ± 2229
24 hours after surgery	2130 ± 1975	2873 ± 2909

Values are mean ± SD. *P < 0.05.Group TA versus Group K

Table 4: Indicators of renal function's data

Parameter	Group TA (n=30)	Group K (n=30)
BUN (mg/dL)		
Before surgery	14.7± 4.4	16.0 ± 6.4
24 hours after surgery	11.2± 4.4	13.5 ± 7.1
Creatinine (mg/dL)		
Before surgery	0.79 ± 0.14	0.78 ± 0.23
24 hours after surgery	0.71 ± 0.18	0.70 ± 0.22
Cystatin-c (mg/dL)		
Before surgery	0.9± 0.2	0.9 ± 0.3
24 hours after surgery	0.8± 0.3	0.9 ± 0.3

Values are mean ± SD. Group TA versus Group K

Discussion

Orthopedic surgery, where the nature of the procedures makes it impossible to fully cauterize the exposed bone surfaces, blood loss tends to be significant, particularly for total joint replacement of hip and knee, often requiring extensive dissections through fibrotic, muscular, and bony tissues [7]. However, allogeneic blood is a scarce and expensive resource as well as having risks of viral disease transmission, immunologic and allergic reactions. These handicaps have led to the development of different methods to reduce or avoid allogeneic blood transfusion, such as restrictive transfusion protocols, use of autologous blood and administration of pharmacological agents. Although strategies to reduce perioperative blood loss during major surgery have been available for many years, they began to be used routinely only when the complications of transfusion became evident [8].

Many studies have reported different doses and methods of administration of TA. Commonly, 10 to 20 mg/kg is injected as an initial bolus dose, and then either the same amount is again injected after a few hours or a continuous infusion is provided during surgery of total hip replacement [9-12].

The clinical benefit of high doses of TA was first demonstrated in dose–response trials of adults undergoing cardiac surgery. Dose of 100 mg/kg was more effective than 50 mg/kg and equally effective to 150 mg/kg in a trial [13].

Timing is one of the important points about administration of TA because TA acts on the early phase of the fibrinolytic cascade, before binding of plasminogen to the fibrin surface, and a reduction of %80 in the activity of tissue plasminogen activator is needed to suppress fibrinolysis [14]. Lemay et al. reported that a 10 mg/kg IV bolus dose and continuous infusion of 1 mg/kg per hour may produce a therapeutic plasma concentration of TA. At the end of the study

they found that TA is not effective on intraoperative and total blood loss but is effective on decreasing frequency of blood transfusion [15]. In this study TA had administrated just before skin incision and TA might have reached effective plasma concentration after binding of fibrin to plasminogen which prevents binding of TA to plasminogen. In our study administration of TA had started 15 minutes before skin incision and found effective on decreasing intra operative blood loss and allogenic blood transfusions. In another study TA had administrated at the end of the surgery and found ineffective on blood loss [16].

The other important point about TA is effective plasma concentration, which is not known for in vivo inhibition of fibrinolysis. In vitro studies show that 10-15 mg/L concentrations of TA at plasma decrease the tissue plasminogen activator at a ratio of %80 [17]. Associated with this condition a study had executed with Garneti et al. [18] who reported that one IV bolus injection at a dose of 10 mg/kg before surgery is not effective on blood loss. As a different from other many studies about TA, transfusion of PRBCs were higher in group TA than control group.

Fibrinolytic activity is biphasic after surgery. Fibrinolytic activity which is increased in the initial phase is terminated after approximately 1 hour and then a deceleration occurs in fibrinolytic activity because of increased Plasminogen activator inhibitor (PAI) release. Fibrinolytic activity increases again after about 24 hours later [8,19]. TA was administered as IV bolus in the Ekbäck et al.'s study [20] and maintained with infusion. At the end of the study TA was found effective on blood loss. They also have studied D-dimer values which were significantly less in group TA than control group. We have also studied D-dimer values and changes of D-dimer values were not differing preoperatively or postoperatively in our group TA. This condition is correlated with higher expectation of fibrinolytic activity in group K, to which TA was not administered, than in our group TA.

Many studies which were executed in total hip replacement reported that TA is effective on postoperative blood loss [8-12,21]. Three study have reported that TA is effective on intraoperative blood loss which we detected [3,20,22]. In our study; intraoperative mean blood loss was recorded 600 mL (200-1700 mL) in group TA, despite that, 1450 mL (400-3000 mL) in group K which means TA is effective on intraoperative blood loss.

The major concern with antifibrinolytic agents is that their use may increase the risk of thrombosis [23,24]. In one study, whole-body enhanced CT was undertaken postoperatively to detect not only deep vein thrombosis but also pulmonary embolization, and they found that TA administration did not increase the incidence of either deep vein thrombosis or pulmonary embolization, as reported by other studies [11,12,22,25]. Tranexamic acid, being a potent antifibrinolytic drug, stabilizes a clot that has already formed and prevents further clot formation [26,27]. Hourlier et al. [28] compared effect of administration of TA as bolus and infusion and they also found that TA is safe in both applications.

No study has been found in the literature on the effects of TA on renal functions. In our study renal functions have been evaluated via cystatin-c values. Serum creatinine and urine output are known as insensitive and nonspecific parameters for renal function evaluation. Thus, a great variety of bio-markers has been identified and then applied in the clinical settings in recent years [29]. Among the potential markers, serum cystatin-c performs a consistent accuracy in various conditions. In our study we found that postoperative cystatin-c values were significantly lower than preoperative cystatin-c values in group TA.

Although there are many studies which evaluate the effectiveness of TA, there is no consensus about dose regime and time of administration for TA. TA effectiveness varies for different surgical types. High dose TA administration is often used in cardiovascular surgery. We thought that high dose administration of TA for total hip replacement can be effective on both intraoperative blood loss and needs of intraoperative and postoperative PRBCs. As result of our study we found that high dose administration of TA reduces intraoperative blood loss and needs of intraoperative and postoperative PRBCs in total hip replacement.

Conclusion

Administration of 50 mg/kg TA via infusion which starts 15 minutes prior to skin incision and takes time total of 30 minutes reduces intraoperative blood loss and needs of intraoperative and postoperative PRBCs. Also this approach provides higher Hgb values at discharge and shorter length of hospital stay. And it does not affect renal functions negatively. New studies are needed on the effectiveness, cost, and reliability of TA.

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