Acta Medica Alanya

RESEARCh ARTICLE

ARAŞTIRMA

Acta Medica Alanya

2021;5(3): 282-288

DOI:10.30565/medalanya.956769

Heparin titration protocol with tranexamic acid in cardiac surgery: a pilot study

Kalp Cerrahisinde Traneksamik Asit ile Beraber Heparin Titrasyon Protokolü Kullanımına Yönelik Bir Pilot Çalışma

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ABSTRACT

Aim: Postoperative bleeding related to cardiac surgery is a clinically important condition. Consequently, re-exploration and increased blood utilization lead to adverse outcomes. The aim of this pilot study was to assess the effect of a newly adapted blood conservation strategy, including heparin titration protocol along with antifibrinolytics, regarding to mediastinal bleeding, re-exploration for bleeding and blood and blood products utilization.

Methods: This study included 100 patients undergoing cardiac surgery with higher risk for bleeding, such as mitral valve replacement, aortic valve replacement, ascending / arcus aortic surgery, between January 2015 and August 2016. The study group consisted of consecutive patients who underwent new protocol (heparin titration protocol + tranexamic acid). The control group consisted of patients who were administered standard dose heparin(4 mg/kg). Fifty patients in each group (with the new protocol and the standard protocol) were compared by means of amount of heparin applied, blood utilization, mediastinal drainage and rate of re-exploration.

Results: Twenty-eight of the 50 study group patients (56%) received a red blood cell (RBC) transfusion for the first 24 hours. RBC transfusion ≥ 3 units was lower in the study group (34% vs 54%; p=0.044). Moreover, mediastinal drainage and blood utilization was found to be lower at the study group, however re-exploration rates remained similar.

Conclusion: Based on our study results, the suggested heparin titration protocol seemed to be beneficial for reducing postoperative bleeding and blood product usage. We consider that blood utilization protocols like our heparin titration protocol should be established to reduce the need for blood transfusion in cardiac surgery.

Keywords: Cardiac surgery; blood transfusion; drainage; reoperation; heparin; tranexamic acid.

ÖZ

Amaç: Kalp cerrahisi ile ilişkili postoperatif kanama klinik olarak önemli bir durumdur. Sonuç olarak, reeksplorasyon ve artan kan kullanımı olumsuz sonuçlara yol açar. Bu pilot çalışmanın amacı, mediastinal kanama, kanama sebepli reeksplorasyon ve kan-kan ürünü kullanımına ilişkin antifibrinolitikler ile birlikte heparin titrasyon protokolünü içeren yeni uyarlanmış bir kan koruma stratejisinin etkisini değerlendirmektir.

Yöntemler: Bu çalışmaya Ocak 2015 ile Ağustos 2016 tarihleri arasında mitral kapak replasmanı, aort kapak replasmanı, asendan/arkus aort cerrahisi gibi kanama riski daha yüksek kalp cerrahisi geçiren 100 hasta dahil edilmiştir. Çalışma grubu yeni protokol uygulanan ardışık hastalardan oluşmaktadır.(heparin titrasyon protokolü+traneksamik asit) Kontrol grubu ise standart doz heparin (4 mg/kg) uygulanan hastalardan oluşmaktadır.

Her gruptaki 50 hasta (yeni protokol ve standart protokol) uygulanan heparin miktarı, kan-kan ürünü kullanımı, mediastinal drenaj ve reeksplorasyon açısından karşılaştırıldı.

Bulgular: Çalışma grubundaki 50 hastanın 28'i (%56) ilk 24 saat boyunca kırmızı kan hücresi (RBC) transfüzyonu aldı. 3 üniteden fazla RBC transfüzyonu alan hasta sayısı çalışma grubunda daha düşüktü. (%34'e karşı %54; p=0.044). Ayrıca reeksplorasyon oranları benzer olarak bulundu.

Sonuçlar: Sonuç olarak, çalışma sonuçlarımıza göre önerilen heparin titrasyon protokolünün postoperative kanama ve kan ürünü kullanımını azaltmada faydalı olduğu görülmektedir. Kalp cerrahisinde kan transfüzyonu ihtiyacını azaltmak için heparin titrasyon protokolü gibi kan kullanım protokollerinin oluşturulması gerektiğini düşünüyoruz.

Anahtar kelimeler: Kardiyak cerrahi; kan transfüzyonu; drenaj; reoperasyon; heparin; traneksamik asit

Received: 27.06.2021 Accepted: 28.07.2021 Published (Online):31.12.2021

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To cited: Turkcan BS, Ünal EU, Kiriş E, Aytekin B, Aykut A, Akkaya B, Demir A, Aksöyek A, Birincioğlu L. Heparin Titration Protocol with Tranexamic Acid in Cardiac Surgery: A Pilot Study. Acta Med. Alanya 2021;5(3): 282-288 doi:10.30565/medalanya.956769

INTRODUCTION

Cardiac surgical interventions are the greatest blood consuming procedures from the point of view of national blood resources [1]. Cardiac surgery remains at the top of the list for blood and blood product utilization among the other surgeries. Blood remains an indispensable product for most cardiac surgical procedures [2]. However, there has developed a tendency to use less blood in our field as well. According to the Society of Thoracic Surgeons Adult Cardiac Surgery Database 2016 Update, blood transfusion rates decreased by 10-15% between 2009 and 2014 [3]. It was documented that the lowest rates occur in mitral valve repair (34.4%) followed by coronary artery bypass grafting (44.5%) [3]. On the other hand, valve replacement, combined (coronary artery bypass grafting + valve) and aortic surgeries, account for at least 50% or higher blood product utilization, for each procedure type [3, 4]. Therefore, strategies to reduce transfusion rates comes into account for this considerable usage of blood [1].

The main reason for reoperation after cardiac surgery is the mediastinal bleeding, which is one of the main complications and accounts for morbidities [5]. Blood and blood product usage after cardiac surgery increases similarly after mediastinal bleeding and subsequent reoperations. It is well-known that blood transfusion is associated with adverse outcomes such as infection, transfusion-related lung injury, transfusion reactions, increased costs and even increased long term mortality [6-8]. All these devastating outcomes should be managed with blood conservation strategies. The main protocol in our institution was changed towards less usage of blood and blood products in the beginning of 2016. Some modifications, such as a heparin titration protocol and routine usage of tranexamic acid infusion for relatively high-risk patients, as aforementioned, were considered for this reason.

We expect that our newly adopted blood conservation strategy may reduce postoperative bleeding and decreases blood and blood product usage. However, there are limited studies regarding the effect of tranexamic acid and heparin titration protocol use on postoperative bleeding in cardiac surgery in literature. Therefore, the aim of this study was to assess the efficacy of heparin titration protocol, along with antifibrinolytics regarding to mediastinal bleeding, re-exploration for bleeding and blood and blood products utilization.

MATERIALS AND METHODS

This study included 100 patients undergoing cardiac surgery with higher risk for bleeding, such as mitral valve replacement, aortic valve replacement and ascending / arcus aortic surgery, between January 2015 and August 2016. Patients undergoing coronary artery bypass grafting, emergency surgery, pediatric patients and those with a history of any hematological disorder prior to surgery, were excluded from the study. This study complies with the Declaration of Helsinki and ethical approval was granted by the local institutional ethical board. (No: 70, Date: 31/10/2016). The data of the patients were obtained from the hospital automation system and patient files.

As of January 2016, use of tranexamic acid, together with the heparin titration protocol described in detail below, has been routinely used in our clinic. The study group consisted of consecutive patients who underwent this protocol. In this heparin titration protocol, an initial 2 mg/kg bolus (half of measured dosage) was administered and afterwards (5 minutes later) ACT was measured. If it was below sufficient levels (< 480 sec), then 1 mg/kg additional heparin (quarter of measured dosage) was administered and repeated if necessary, until adequate ACT levels were achieved prior to cardiopulmonary bypass (Figure 1). Tranexamic acid infusion is routinely used in our clinic along, with the heparin titration protocol. 10 mg/kg/30 min loading dose after induction and 1 mg/kg/hour infusion until the end of operation. 1 mg/kg tranexamic acid is added to the prime solution as well [9]. The control group consisted of patients who were administered a standard dose of heparin (4 mg/kg).

The following data, including patients' characteristics such as age, gender, body weight were analyzed: diabetes mellitus, hypertension, chronic obstructive lung disease, redo surgery, hematological parameters such as hemoglobin, hematocrit, platelet count, active

partial tromboplastin time (aPTT), international normalized ratio (INR), biochemical analysis results such as urea, creatinine, and operative data such as cardiopulmonary bypass (CPB), crossclamp time, measured heparin dosage, initial heparin dosage and additional heparin dosage. Postoperative intensive care unit (ICU) and hospital stay, duration of ventilator-dependency, the amount of drainage and blood and blood product usage as well as mortality, were also recorded.

Anesthetic management and surgical procedures were performed in a standard manner in both groups. In addition, cardiopulmonary bypass techniques (CPB) (including oxygenator and tubing sets – not heparinized) were similar between the groups. In addition, intraoperative and postoperative transfusion thresholds (hematocrit < 24-25%) were kept to avoid unconditional bias.

Statistical Analysis

The data from the study revealed that the reported tranexamic acid may be as effective as the previously used aprotinin and antifibrinolytic agents can reduce blood utilization by approximately 20-25% [10, 11]. We assumed that 30% relative reduction in blood utilization was significant, and therefore the sample size was found to be 41 patients in each group with type-1 error of 0.05 and with 80% power (type-2 error = 0.20). Power analysis was conducted by the G*Power Software 3.1 (Universität Kiel, Germany).

Continuous variables with normal distribution were expressed as mean ± standard deviation, and categorical variables were expressed as number and percentage. Demographic features and perioperative variables were compared by Mann-Whitney U test and chi-square test. Any p value less than 0.05 was considered statistically significant. All statistical analyses were carried out using the SPSS for Windows 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Age, gender, body weight and other demographics were similar between the groups: the demographic data is summarized in Table 1. The standard measured dosage of heparin was similar between the groups (p=0.987). In the study group, eight patients (16%) achieved adequate ACT levels only with the initial dosage (2 mg/kg heparin). Appropriate ACT levels were achieved in 33 patients (66%) in the study group without full dosage of heparinization (Figure 1). Only three patients (6%) in the control group needed an initial dosage of 1 mg/kg heparin after full dosage of heparin administration. Total administered mean heparin dosage just prior initiation of CPB was also higher in the control group (240 mg vs 305 mg; p<0.001). ACT levels at the initiation of CPB was higher in the control group (560 sec vs. 623 sec, p<0.001) (Table 2). In the study group, 89% of the mean standard measured dosage of heparin was sufficient for initiation of CPB (ACT about 560 sec), whereas in the control group 115% of the mean standard measured dosage was administered (ACT about 623 sec) (p<0.001) (Figure 2).

Table 1. Demographic variables of the groups

Preoperative variables	Study group (n=50)	Control group (n=50)	P value
	Mean±SD or n (%)	Mean±SD or n (%)	
Age (years)	53.20±13.40	57.17±12.94	0.179
Male gender	30 (60%)	30 (60%)	1.000
Body weight (kg)	77.28±15.93	77.20±14.37	0.978
Diabetes mellitus	7(14%)	2(4%)	0.162
Hypertension	15 (30%)	18 (36%)	0.347
Chronic obstructive pulmonary disease	9 (18%)	9 (18%)	0.844
Redo surgery	7 (14%)	4 (8%)	0.394
Acetylsalicylic acid	9(18%)	14 (28%)	0.154
Clopidogrel	1 (2%)	0 (0%)	1.000
LMWH	2(4%)	7(14%)	0.082
Preoperative laboratory values			
Hemoglobin (gr/dl)	13.63±1.42	13.32±1.27	0.238
Hematocrit (%)	42.93±4.03	40.91±3.66	0.053
Platelet (x103/uL)	215.42±42.52	226.06±61.45	0.317
Urea (mg/dl)	36.02±13.58	43.40±18.32	0.010
Creatinine (mg/dl)	0.97±0.18	0.99±0.27	0.715
INR	1.31±0.51	1.63±1.03	0.321
aPTT (sec)	35.46±8.01	36.73±8.92	0.394

aPTT: activated partial thromboplastin time; INR: international normalized ratio LMWH: low molecular weight heparin; SD: standard deviation

On the other hand, protamine administration to neutralize heparin was lower in the control group

(251 mg vs. 315 mg; p<0.001), however the protamin:heparin ratio was similar between the groups (p=0.459).

Table 2. Operation types and variables, administered heparin dosage and ACT levels

Variables	Study group (n=50)	Control group (n=50)	P value
	Mean±SD or n (%)	Mean±SD or n (%)	
Operation types			
Mitral valve replacement	10 (20%)	16 (32%)	0.055
Aortic valve replacement	7 (14%)	0 (0%)	
Aortic surgery	8 (16%)	5 (10%)	
Combined aortic surgery	13 (26%)	14 (28%)	
Combined mitral surgery	12 (24%)	14 (28%)	
Operative variables			
Measured heparin dosage (mg)	270.48±55.76	270.18±50.30	0.978
Initial heparin dosage (mg)	171.10±70.29	280.57±64.68	<0.001
ACT after initial dosage (sec)	412.40±108.18	553.55±169.70	<0.001
Additional heparin dosage (mg)	68.50±53.68	24.43±58.94	<0.001
ACT before CPB (sec)	560.74±122.24	622.75±141.51	0.004
CPB period (min)	139.29±52.23	140.67±46.36	0.569
Cross-clamp period (min)	90.76±35.34	96.98±36.93	0.405
Protamine dosage (mg)	251.00±70.34	314.77±57.65	<0.001
Protamine: heparin ratio	1.07±0.12	1.00±0.07	0.459
Need for additional protamine	9 (18%)	13 (26%)	0.334

ACT: activated coagulation time; CPB: cardiopulmonary bypass; SD: standard deviation

The amount of mediastinal drainage was significantly lower in the study group (505 ml vs 651 ml; p=0.047). Mean red blood cell (RBC) utilization for the first 24 hours was 0.46 units for the study group, whereas 0.89 units were used for the control group (p=0.002). Mean fresh frozen plasma (FFP) utilization for the first 24 hours was significantly higher in the control group (1.87 units vs 1.10 units; p<0.001). Total blood product utilization was found to be significantly higher in the control group (4.92 units vs 5.96 units; p=0.013). Relative reduction in RBC utilization for first 24 hours was 16% (from 66% to 56%; p=0.305). On the other hand, relative reduction in FFP utilization was 22% (from 100% to 78%; p<0.001). For further analysis, blood and blood product utilization was categorized as ≥3 units and < 3 units. RBC utilization for ≥3 units was reduced from 54% to 34% with our new protocol (p=0.044). On the other hand, even if it is not significant, there was a relative reduction of FFP utilization (from 86% to 72%; p=0.086).

Table 3. Postoperative variables

Postoperative variables	Study group (n=50)	Control group (n=50)	P value
	Mean±SD or n (%)	Mean±SD or n (%)	
Amount of drainage (ml/first 24 hours)	505.00±311.55	651.09±435.70	0.047
Packed red cells (units/ first 24 hours)	0.46±0.68	0.89±0.80	0.003
Fresh frozen plasma (units/first 24 hours)	1.10±0.93	1.87±0.93	<0.001
Total blood and blood products (units)	4.92±5.19	5.96±4.16	0.013
Reoperation for bleeding	0 (0%)	1 (2%)	1.000
Prolonged ventilation	3 (6%)	7 (14%)	0.182
ICU stay (days)	1.72±2.29	1.30±0.75	0.579
Hospital stays (days)	6.96±3.32	6.98±3.01	0.246
Mortality	2 (4%)	4 (8%)	0.678

ICU: intensive care unit, SD: standard deviation

There was no significant difference regarding to the other outcomes such as ICU and hospital stay, reoperation for bleeding and mortality between the groups.

DISCUSSION

In the present study, heparin titration protocol, along with tranexamic acid, provided less mediastinal bleeding and less utilization of blood for the open-heart surgery. However, the rate of re-exploration for bleeding remained similar. Mediastinal bleeding after cardiac surgery, subsequently necessitating inevitable blood utilization, can be a devastating complication for the patient. Re-exploration for bleeding occurs in about 4-5% at open heart surgery [12]. Afterwards, re-exploration for bleeding subject patients increased the risk of adverse outcomes [13]. It has been considered that the re-exploration plays a major role in the adverse outcomes, however subsequent need for blood utilization has a quite similar influence on

outcomes [5]. Vivacqua et al. reported that either the transfusion or re-exploration for bleeding, similarly and independently contributes to adverse effects including mortality [5]. Blood transfusion is merely associated with several complications [7,14-16]. Transfusion reactions, postoperative infections, pneumonia, cardiac complications, lung injury, etc., are the unfavorable outcomes after blood utilization [14,17,18]. Koch et al. examined the effect of RBC transfusion at open-heart surgery in detail. They reported a significant relation in several morbidities (such as renal failure, prolonged ventilatory support, serious infection cardiac complications and neurological events) and long-term survival with transfusion of RBCs [14, 15]. Engoren et al. reported that blood transfusions in cardiac surgery were associated with increased long-term mortality [7, 16].

As a matter of fact, therefore, implementation of a blood conservation strategy is essential for the cardiac surgery centers. 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Guideline is a beneficial milestone for effective blood conservation methods [1]. Different strategies, ranging from preoperative period to postoperative period including perfusion strategies, are well documented in this guideline. The BART study shows that the lysine analogs are as effective as aprotinin regarding to risk of bleeding and much safer drugs for early mortality [10]. The STS/ACC 2011 guideline strongly recommends tranexamic acid to reduce total blood loss and decrease the number of patients who require blood transfusion [1]. It remains controversial which dose scheme is more beneficial. A complete review of Hodgson shows that low-dose tranexamic acid protocol can be safely given with low seizure risk [9]. At the beginning of 2016, the blood conservation attempts were gradually put into practice. First, low dose tranexamic acid protocol (10 mg/kg bolus + 1 mg/kg/hour infusion + 1 mg/kg priming) was routinely used for high-risk patients for bleeding. Then, the unpublished encouraging results from a study of heparin titration protocol at aortic dissection patients, this protocol came forward for high-risk patient profile. Some heparin dose regimens were recommended at STS/ACC 2007 blood conservation guidelines [1]. Firstly, patient-specific heparin concentrations seemed to be effective for blood utilization, however the major contribution of this system was the stable heparin concentration, especially during prolonged CPB [19]. Secondly, either protamine titration or empiric low-dose heparin regimens to reduce bleeding and blood transfusion requirements, had controversial results [20, 21]. Thirdly, low doses of systemic heparinization (ACT approximately 300 sec) have a risk of under-heparinization and an increased risk of thrombin generation [22]. However, these recommendations are not out of date and still have validity, although they are not included at the current and revised guideline [1]. In the present study, heparin is titrated by serial ACT measurements and therefore under-heparinization, and especially hyper-heparinization, were avoided.

The gold standard for heparin concentrations is the anti-Xa level assessment that is challenging and is not reliable in an operating room setting. On the other hand, the Hepcon system (Hepcon HMS, Medtronic, MN, USA) provides a calculation of individualized heparin dose response curve that is helpful for bleeding and blood conservation protocols. However, the main cumbersome aspect of this device is the occurrence of potential calculation errors, as the device requires estimation of the patient's blood volume and the device measures total heparin, not just antithrombin III-bound functional heparin. Other potential conflicts are inherent inaccuracy of the device and variances at ex vivo heparin activity [23]. Another method for heparin dosing strategy may be the calculation of heparin via lean body weight [24]. However, this approach should, similarly, be developed with regards to large-scale trials. On the basis of these issues, the method described in our study may be an alternative model for heparin dosing strategy. It was obvious that the 89% of the standard measured heparin dosage is sufficient for adequate ACT levels (>480 sec). More precise titration such as repeated one tenths of the dosage instead of quarters may be concluded with much less heparin usage.

Excessive protamine administration may lead to bleeding [25]. The administered protamine in the study group was considerably lower than the control group. At the same time, the protamine:heparin ratio was similar between the groups, indicating

that adequate protamine was administered with regards to administered heparin.

The amount of blood and blood product usage has been generous in our clinic at recent years. However, attempts at blood conservation strategies offer some differences for the blood utilization. The threshold for transfusion has not change much over the years (hematocrit <24-25%). Whereas there has been a tendency to administer FFP widely. New generation surgical teams and intensivists are more restrictive and careful of the issue. Three or more RBC utilization ratios have dropped from 54% to 34% with this new protocol. In the study group, at least one unit of RBC utilization was 56%, which is comparable with the STS reports on outcome [3].

Limitations

The present study has two major limitations. First, this is a pilot study of a newly generated blood conservation strategy for our clinic. Therefore, the patient population for the study is noticeably small, even though the power of the study was 80%. This was also a single center pilot study, and thus the results should not be expanded to other practices or patient population; through additional studies involving a greater number of cases, accurate and definitive results may be produced. Second, this is an observational study and randomizing patients to the technique used was not possible because of different time periods of the patient population.

CONCLUSION

In conclusion, based on our study results, the suggested heparin titration protocol appears to be beneficial for reducing postoperative bleeding and blood product usage. We consider that blood utilization protocols like ours should be established to reduce the need for blood transfusion in cardiac surgery. This may lead to better postoperative outcomes for the patients. However, further large-scale prospective studies are needed to confirm our study results.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Funding sources: The authors declare that this study has received no financial support

Ethics Committee Approval: Türkiye Yüksek İhtisas Training and Research Hospital Clinical Ethics Committee, 31.10.2016 / 70

Peer-review: Externally and internally peer reviewed.

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