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Original Article

The effect of desmopressin and tranexamic acid on blood product use and postoperative bleeding after emergent isolated coronary artery bypass grafting (CABG) surgery

Desmopresin ve traneksamik asitin acil izole koroner arter bypass greftleme (KABG) ameliyatında kan ürünü kullanımına ve postoperatif kanama üzerine etkisi

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Abstract

Aim: Bleeding is a major problem in cardiac surgery, and results in a high risk of allogeneic blood transfusion associated with increased morbidity and mortality. In recent years, studies in the literature reported that desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) reduces the blood loss after surgical interventions. The aim of the present study is to analyze the effect of desmopressin and tranexamic acid on blood product use and postoperative bleeding in patients that were pretreated with P2Y12 inhibitors by cardiologists and undergone emergent coronary artery bypass grafting (CABG) surgery.

Material and Methods: The prospectively collected data of 62 adult patients who underwent emergent isolated CABG surgery and pretreated with P2Y12 inhibitors by cardiologists were retrospectively reviewed. The perioperative data of the patients included their demographic data, laboratory findings, the amount of blood loss from chest tubes, the amount of blood product use, need of re-thoracotomy, morbidity and mortality. The patient population was divided into two groups: **Group I:** Patients that received tranexamic acid and DDAVP perioperatively (n=26); and Group II: Patients that received only tranexamic acid perioperatively (n=36).

Results: The two groups of patients had similar characteristics at baseline. There was a statistically significant difference between Group I and II regarding postoperative blood loss from the chest tubes, re-thoracotomy, red blood cell and thrombocyte transfusions ($p<0.05$). No statistically significant differences were observed between the two groups in terms of fresh frozen plasma transfusion, inotropic support and mortality.

Conclusion: We suggest that desmopressin in addition to tranexamic acid reduces bleeding and the amount of blood product use in patients undergoing emergent isolated CABG surgery.

Keywords: CABG; desmopressin; tranexamic acid; blood management

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Öz

Amaç: Kanama kalp cerrahisinde önemli bir sorundur ve artan morbidite ve mortalite ile ilişkili yüksek allojenik kan transfüzyonu riskine yol açar. Son yıllarda, literatürdeki çalışmalar desmopresinin (1-deamino-8-D-arginin vazopressin, DDAVP) cerrahi müdahalelerden sonra kan kaybını azalttığını bildirmişlerdir. Bu çalışmanın amacı, kardiyologlar tarafından P2Y12 inhibitörleri ile tedavi edilen ve acil koroner arter baypas greftleme (KABG) ameliyatı geçiren hastalarda desmopressin ve traneksamik asidin kan ürünü kullanımı ve postoperatif kanama üzerindeki etkisini analiz etmektir.

Gereç ve Yöntemler: Acil izole KABG ameliyatı geçiren ve öncesinde P2Y12 inhibitörleri ile tedavi edilmiş 62 erişkin hastanın prospektif olarak toplanan verileri retrospektif olarak incelendi. Hastaların perioperatif verileri birlikte demografik verileri, laboratuvar bulguları, göğüs tüplerinden kan kaybı miktarı, kan ürünü kullanım miktarı, yeniden torakotomi ihtiyacı, morbidite ve mortalite sonuçları değerlendirildi. Hasta popülasyonu iki gruba ayrıldı: Grup I: Perioperatif traneksamik asit ve DDAVP alan hastalar (n=26); ve Grup II: Perioperatif olarak sadece traneksamik asit alan hastalar (n=36).

Bulgular: İki hasta grubu başlangıçta benzer özelliklere sahipti. Grup I ve II arasında göğüs tüplerinden postoperatif kan kaybı, yeniden torakotomi, alyuvar ve trombosit transfüzyonları açısından istatistiksel olarak anlamlı fark vardı ($p < 0.05$). İki grup arasında taze donmuş plazma transfüzyonu, inotropik destek ve mortalite açısından istatistiksel olarak anlamlı bir fark gözlenmemiştir.

Sonuç: Acil izole KABG ameliyatı geçirenlerde traneksamik asitle birlikte desmopresin kullanımının perioperatif/postoperatif kanamayı ve kan ürünü kullanımını azalttığını düşünüyoruz.

Anahtar kelimeler: KABG; desmopressin; traneksamik asit; kan yönetimi

Introduction

Perioperative bleeding is a major problem in cardiac surgery. The underlying mechanism of bleeding is multifactorial and can be due to surgical or nonsurgical factors in general.[1] Non-surgical factors include acidosis, hypothermia, effect of heparin and mainly hemostatic abnormalities.[1,2] Perioperative bleeding results in a high risk of allogeneic blood transfusions and consequent increase in morbidity, mortality and costs.[3] Although a common issue in cardiac surgery, perioperative bleeding had no standardized definition until Dyke et al.[4] made a universal definition (Universal Definition of Perioperative Bleeding, UDPB in adult cardiac surgery). They classified perioperative bleeding into five groups as Class 0 being insignificant bleeding, and Class 4 being massive bleeding based on postoperative chest tube output, transfusion of packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, use of factor concentrates, use of recombinant activated factor, surgical re-exploration and delayed sternal closure (Table 1). The authors suggest that UDPB would standardize the nomenclature of perioperative bleeding in adult cardiac surgery. They also stated that moderate and above bleeding classes (Class 2-4) were significantly related with increased mortality.[4] It is well known that emergent status of cardiac surgery is associated with increased risk of perioperative bleeding and also with increased re-exploration risk.[5] Emergent cardiac surgical patients are mostly premedicated with a second-generation P2Y12 antagonist (ticagrelor/prasugrel) by cardiologists as these drugs are reported to decrease the risk of thrombotic complications in acute coronary syndrome. However, the risk of bleeding complications increases with these new second-generation antithrombotic agents.[6] Many pharmacological agents are studied to overcome non-surgical causes of perioperative bleeding in cardiac surgery. One of them is tranexamic acid (TA), it is a synthetic lysine analogue that interferes with the binding of plasminogen to fibrin. It is the most commonly used anti-fibrinolytic agent in cardiac surgery and its use is recommended both by STS/SCA and European blood conservation guidelines as Class IA.[6,7] It is reported that TA use in cardiac surgery resulted in a reduced transfusion of blood components and a lower incidence of postoperative mortality or morbidity.[8,9]

Table 1. Bleeding categories according to the UDPB in adult cardiac surgery (4)

Bleeding Definition	Postoperativechesttube-bloodlosswithin 12 hours (mL)	PRBC (units)	FFP (units)	PLT (units)	Cryoprecipitate	PCCs	rFVIIa	Reexploration/tamponade	Delayedsternalclosure
Class 0 (insignificant)	<600	0*	0	0	No	No	No	No	No
Class 1 (mild)	601-800	1	0	0	No	No	No	No	No
Class 2 (moderate)	801-1000	2-4	2-4	Yes	Yes	Yes	No	No	No
Class 3 (severe)	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes	Yes
Class 4 (massive)	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A	N/A

UDPB, Universal definition for perioperative bleeding; PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet concentrates; PCCs, prothrombin complex concentrates; rFVIIa, recombinant activated factor VII; N/A, not applicable. *Correction of preoperative anemia or hemodilution only; the number of PRBCs used should only beconsidered in the UDPB when accompanied by other signs of perioperative bleeding.

Desmopressin (DDAVP) is a vasopressin used in the management of von Willebrand factor (vWF) deficiency or hemophilia. It is suggested that in addition to up-regulation of plasma vWF and factor VIII, it has direct effects on platelet reactivity.

The aim of the present study is to analyze the effect of desmopressin and tranexamic acid on blood product use and postoperative bleeding in patients that were pretreated with P2Y12 inhibitors by cardiologists and undergone emergent coronary artery bypass grafting (CABG) surgery.

Material and Methods

Patients

After the institutional review board approval was obtained and Informed consent was obtained from all the patients participating in the study, and all the researchers signed the Declaration of Helsinki we retrospectively reviewed the data of 62 adult patients who underwent emergent isolated CABG surgery and pretreated with P2Y12- adenosine diphosphate (ADP) receptor blocker inhibitors, namely, ticagrelor by cardiologists from January 2017 to November 2018. The perioperative data of the patients included demographic data, laboratory findings, the amount of blood loss from chest tubes, the amount of blood product use, need of re-exploration, morbidity and mortality. The patient population was divided into two groups: Group I: Patients that received tranexamic acid and DDAVP perioperatively (n=26); and Group II: Patients that received only tranexamic acid perioperatively (n=36). The first primary outcome was postoperative blood loss from the chest tubes that is classified according to UDPB in adult cardiac surgery4. The second is the amount of blood product use defined as transfusion of packed red blood cells, fresh frozen plasma and platelets. The secondary outcomes were respiratory failure, prolonged inotropic support or renal failure during hospital stay and mortality. Patients with a history of hematologic disorders, hepatic and renal insufficiency, chronic renal failure requiring renal replacement therapy and also patients undergoing operations other than or in conjunction with CABG were excluded from the study.

CABG Procedure

All operations were performed in a standardized approach by a Terumo roller pump (Terumo Advanced Perfusion System 1, USA), membrane oxygenators (Inspire 8, LivaNova Sorin Group, Italy). Mild-to-moderate (28-32°C) hypothermia and pulsatile flow of 2.2-2.4 L/m2 were used. Myocardial protection was achieved with tepid antegrade blood cardioplegia, and a "hot shot" (250ml- 500ml) was delivered just before the removal of the aortic cross-clamp. The perfusion pressure was kept over 70mmHg at all times. Induction and maintenance of general anesthesia with endotracheal intubation were standardized in all the patients (fentanyl, midazolam, and isoflurane in oxygen with air). The same surgical team performed all of the operations.

Postoperative management

Postoperatively, patients were followed in the Intensive Care Unit (ICU), according to the protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, and hourly urine output were monitored. Drainage from chest tubes were measured at 6, 12 and 24 hours after surgery. Hemoglobin and hematocrit levels before the surgery, and at hours 6, 12 and 24 after surgery were measured. Hematocrit values <25% were corrected with erythrocyte suspension administration. The amount of transfused packed red blood cells, Fresh Frozen Plasma (FFP), platelets and cryoprecipitate within the first 24 hr were recorded. Laboratory tests including PT, INR, PTT, ACT and platelets before the surgery, and at hours 12 and 24 after surgery were investigated. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances immediately were corrected with appropriate management. Reoperation due to bleeding during the first 48 hr of the surgery was also investigated.

Statistical analysis

All statistics were performed using SPSS version 17.0 for Windows (IBM Corporation, New York, USA). Continuous variables were expressed as mean ± SD and were compared by unpaired Student's T-test or Chi-Square test. Mann-WhitneyU-test was used for multiple comparisons and the Kruskal-Wallis test was used in non-normally distributed variables. Comparisons of rates were performed using the Fisher's Exact Method. Correlation between a predictor variable and a response variable was studied with regression analysis, and the results were expressed as Odds Ratio (OR) with a 95% Confidence Interval (CI). A P-value <0.05 was considered statistically significant.

Results

There were 30 women patients, 14 in Group I and 16 in Group II. Patient demographics and perioperative data are shown in Table 2. Preoperative patient characteristics and intraoperative data did not assure statistical significance between the groups. Mean age was 61.1±10.5 for Group I and 61.4±10.5 for Group

II. BMI, hypertension, diabetes, hyperlipidemia, and smoking habits were very similar in both groups. Also, Hgb, platelet and serum creatinine levels were similar. EF was 54.4±9.4 in Group I and 55.6±10.3 in Group II.

Table 2: Demographic Data

Clinical characteristics	Group I (Tranexamic acid+DDAVP) (n=26)	Group II (Tranexamic acid) (n=36)	p[a]
Age, years	61.1±10.5	61.4±10.5	0.835
Female, %	14	16	0.164
Body mass index, kg/m2	28.9±4.9	29.5±5.6	0.152
Hypertension, n	18	24	0.390
Diabetes mellitus, n	16	22	0.445
Hyperlipidemia, n	18	25	0.359
Smoking, n	20	29	0.433
Hemoglobin, g/dl	13.3 ± 1.85	13.4± 1.89	0.425
LV function, %	54.4±9.4	55.6±10.3	0.408
Serum creatinine, mg/dl	0.9±0.24	0.9±0.20	0.139
Platelet count preoperative, x103/mm3	204 ± 73.4	204± 60.5	0.647

Perioperative findings are shown in Table 3. CPB time, Cross-clamp time, Prolonged inotrope use, FFP transfusion at first 24 hours, and mortality showed no statistical significance. ICU stay time was lower in Group I, 56.6±27.3 hours and 65.9±40.6 hours, respectively. (p=0.042) Also, in-hospital stay was lower in Group I (6.4±2.0 days and 7.2±2.8 days, p=0.024) Ventilator support time was 6.7±3.5 hours in Group I and 12.5±16.2 hours in Group II (p<0.001).

Table 3: Perioperative Data

Perioperative characteristics	Group I (Tranexamic acid+DDAVP) (n=26)	Group II (Tranexamic acid) (n=36)	p[a]
CPB time, minutes	109.2±38.9	104.1±40.3	0.290
Cross-clamp time, minutes	63.5±24.4	60.2±23.8	0.256
ICU stay time, hours	56.6±27.3	65.9±40.6	0.042
In-hospital stay time, days	6.4±2.0	7.2±2.8	0.024
Ventilatory support times, hours	6.7±3.5	12.5±16.2	<0.001
Prolonged inotrope use, n	6	12	0.116
Chest tube drainage 24 hr. after surgery	425 ± 50	500 ± 75	0.029
Packed red blood cells transfusion at first 24 h, U	2±0.8	4.4±0.7	0.006
FFP transfusion at first 24 hr., U	1.2 ± 0.15	1.3 ± 0.21	0.386
Platelet transfusion at first 24 hr. U	0.8 ± 0.4	1.85 ± 0.2	0.022
Re-thoracotomy, n	0	6	0.032
Mortality, %	0	3.2	0.096

The main parameters we tried to identify in the study like chest tube drainage after surgery, transfusion amount, platelet transfusion and re-thoracotomy requirement showed statistically significant differences between the two groups. Chest tube drainage was significantly lower in Group I (425 ± 50 ml and 500 ± 75 ml, p=0.029). According to this, the red blood cells transfused to the patients were also lower in Group I, 2±0.8 U and 4.4±0.7 U, respectively. (p=0.006). Platelet transfusion in Group I was 0.8 ± 0.4 U and 1.85 ± 0.2 U in Group II, (p=0.022). Only 6 patients needed re-thoracotomy, all of whom were patients of Group II(p=0.032). Mortality was only seen in Group II (3.2%, p=0.096).

Discussion

Cardiac surgery involves bleeding and clotting complications separately or together. Due to the characteristics of cardiac surgery patients, antiplatelet agents are given in the preoperative period, especially in coronary artery patients. For this purpose, acetylsalicylic acid and P2Y12 receptor inhibitors (ticlopidine, clopidogrel, prasugrel, and ticagrelor) are used (RANUCCI). These drugs act over P2Y12 adenosine diphosphate (ADP)-dependent receptors, and present a risk of serious bleeding during and after the operation. These bleedings often require reoperation. For this reason, these drugs often are terminated before the operation.[10,11]

Fibrinolysisis triggered due to the use of CPB during cardiac surgery, which poses another risk for bleeding. These two causes increase the risk of bleeding by creating platelet dysfunction. In the Plato study it wasargued that ticagrelor reduces mortality caused by myocardial infarction, stroke and vascular.[12] The ticagrelor examined in the study reversibly attaches to the P2Y12 receptors, and has immediate effect. Ticagrelor blocks almost all of the platelet aggregation that is stimulated by ADP.[13,14]

The incidence of postoperative bleeding is between 2-6% in patients undergoing cardiac surgery.[5] Reoperation and bleeding also cause problems like increased ICU stays, kidney failure, sepsis, and increased mortality rates.[15]

Desmopressin, like TA used against bleeding, can also be used in bleeding disorders. Desmopressin (A.K.A. DDAVP or 1-deamino-8-D-arginine vasopressin) acts by increasing plasma levels in vWF and Factor 8.[16,17] Intracellular platelet calcium/sodium ion concentrations are increased by desmopressin by increasing the procoagulant platelet formation and platelet adhesion to collagen under flow.[17-19] It also increases the platelet functions[20], and used especially in von Willebrand insufficiency and hemophilia patients.[6]

Platelet dysfunction because of antiplatelet drugs increases the risk of bleeding. Data on bleeding control of patients with platelet dysfunction is not clear.[21] As the dysfunction is higher, the bleeding occurs at higher rates; however, when the drugs are terminated, cardiovascular morbidity increases as a rebound effect.[21] Platelet dysfunction is also increasing due to CPB, which increases the risk of intraoperative bleeding.[21,22]

Many studies were conducted on bleeding control and bleeding-reducing treatments. In a study, patients at high risk of bleeding were compared with placebo group, and it was found that 24-hour bleeding was 39% less in patients who received desmopressin.[2]

In a meta-analysis study conducted in 2008, Crescenzi et al.[23] examined 38 studies, analyzing the data of 2.488 cardiac or non-cardiac surgical patients, and showed that desmopressin reduced the use of blood products.

Similar results were shown in the study conducted by Desborough et al.[21] it was reported that the risk of red blood transfusion, blood loss, and reoperations decreased. When compared with the Control Group, the use of red blood products was 25% lower, blood loss was lower at a rate of 23%, and the risk of reoperation was also lower. In the subgroups, which received antiplatelet treatment, differences were detected, even if at statistically low levels. No differences were detected in terms of overall mortality and thrombotic events.

In the study conducted bySteinlechner[24] on aortic valve replacement, desmopressin increased vWF, normalized platelet function, and reduced postoperative blood loss.

Salzman et al.[25] reported that desmopressin decreased blood loss from 2210ml to 1317ml compared to the placebo group; however, he also noted that the patients with the most blood loss were those with low vWF in the preoperative period. Similarly, Despotis et al.[26] also reported that the blood loss decreased to 624ml from 1028ml.

In the present study, a statistically significant decrease was detected in chest tube drainage, red blood transfusion, and platelet transfusion in the first 24 hours (0.029, 0.006, and 0.022, respectively). The need for reoperation decreased significantly for patients included in the study (p=0.032). However, although there was a decrease in fresh frozen plasma transfusion, it was not at a significant level. Our results are broadly consistent with the previous data on desmopressin.

In the literature, there are studies that indicate positive effects of desmopressin on bleeding, as well as studies reporting that it has no effect on bleeding. In the study conducted by Teng et al.[20] it was found that there was a decrease in the amount of bleeding with desmopressin, but it was not clinically significant. It was suggested that desmopressin does not affect ticagrelor pharmacokinetics. It was also reported that desmopressin does not prevent platelet aggregation caused by ticagrelor, but increases hemostatic activity.

In the study conducted by Carles et al.[27], it was reported that desmopressin reduces postoperative and total blood loss, but has no effects on red blood transfusion. Also, no effects of it were detected on mortality.Again, in the study of Bignami2, its effect on postoperative blood loss and RBC transfusion could not be demonstrated. Wademan[28] conducted a study and did not recommend routine use of desmopressin, but also argued that desmopressin could reduce postoperative bleeding in patients used aspirin, in patients whose CBP time exceeded 140 minutes, and in patients with platelet dysfunction.

The present study also showed a significant decrease in the intensive care stay, hospitalization time, ventilator support time, chest tube drainage, RBC transfusion quantity, platelet transfusion and reoperations; however, no statistically significant differences were detected in the amount of TDP, CPB time, Cross clamp time and mortality.

These differences in the literature are also seen in the guidelines. Desmopressin is not recommended to reduce the bleeding in 2017 EACTS/EACTA Guideline.[6] However, it was stated that it could be used to reduce bleeding and blood transfusion in patients with acquired or congenital platelet dysfunction.[2,6,28]

In a systematic study of Cochrane[27], and in a meta-analysis[23,28], it was argued that desmopressin did not reduce bleeding and the need for blood transfusion in cardiac surgeries. In a recent meta-analysis, it was reported that desmopressin had low effects on blood loss and transfusion.

The bleeding management of patients with platelet dysfunction has not yet been clearly defined. Routine use of desmopressin was not recommended, and it was stated that it could be used in patients with congenital or acquired platelet dysfunction.[6,7,21,29-32]

Although there are improvements in surgical ability and strategies, bleeding still remains as a serious problem. The amount of bleeding can be reduced by using various drugs in the control of bleeding, and efforts are spent to reduce the need for blood transfusion. The results of our study show parallelism

to the literature. In this study, it was found that desmopressin especially reduced the RBC need and total blood loss. Hypotension hyponatremia, flushing, and thrombotic event risks, which were the reported side effects of desmopressin in the literature, were not detected in our study. We believe that desmopressin can be used as an anti-bleeding medication, especially in cardiac surgery patients with platelet dysfunction.

Study Limitations

The present study has some limitations as it had a retrospective design, and not using TEG or ROTEM. Another limitation is that we did not compare other anticoagulant drugs as our patients in the study were using only ticagrelor preoperatively.

Conclusion

Desmopressin is an easy-to-apply and cheap drug. In this respect, it was frequently evaluated as an attractive option in bleeding prevention studies. Although its effect on bleeding is not clear in the literature, it was shown in many studies that it reduces total blood loss. However, further studies are required to reach an absolute consensus.

Declaration of conflict of interest

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