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Original Article / Özgün Makale

The effect of acute normovolemic hemodilution on plasma fibrinogen level in coronary artery bypass grafting

Koroner arter baypas greftlemede akut normovolemik hemodilüsyonun fibrinojen düzeyine etkisi

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ABSTRACT

Background: This study aims to investigate the effect of acute normovolemic hemodilution on reduced plasma levels of fibrinogen.

Methods: We retrospectively evaluated data of a total of 101 adult patients (68 males, 33 females; mean age 61±8 years; range 46 to 84 years) who underwent elective coronary artery bypass grafting surgery between January 2014 and December 2015. A comparison was made between patients who received acute normovolemic hemodilution (ANH group, n=49) and patients who did not (control group, n=52) matched by predictors of mortality and postoperative bleeding.

Results: The mean decline in fibrinogen in ANH group (27.4±13.8%) was significantly lower, compared to the control group (43.7±9.5%, 95% CI: -21.4 to -11.3, p<0.0001). The mean decline in platelet count in ANH group (33.1±10.1) was similar to control group (35.6±8.9) (p=0.21). The whole blood was not re-transfused to 10 patients (20.4%) in ANH group at the end of surgery and preserved to be used in the intensive care unit. During intensive care unit stay, only eight patients (16.3%) in ANH group received allogeneic red blood cell, while 41 patients (78.8%) in the control group (p<0.0001). Only 14 patients (28.6%) in ANH group received allogeneic fresh frozen plasma, while all patients in the control group received (p<0.0001). No mortality was seen in either group.

Conclusion: Acute normovolemic hemodilution may preserve plasma levels of fibrinogen and reduce the need for allogeneic transfusion of blood products in patients with adequate preoperative fibrinogen level.

Keywords: Acute normovolemic hemodilution; blood transfusion; coronary artery bypass; fibrinogen.

ÖZ

Amaç: Bu çalışmada, akut normovolemik hemodilüsyonun, fibrinojen düzeylerindeki düşüşe etkisi araştırıldı.

Çalışma planı: Ocak 2014 - Aralık 2015 tarihleri arasında elektif koroner arter baypas greftleme yapılan toplam 101 erişkin hastanın (68 erkek, 33 kadın; ort. yaş 61±8 yıl; dağılım 46-84 yıl) verileri retrospektif olarak incelendi. Akut normovolemik hemodilüsyon uygulanan hastalar (ANH grubu, n=49) ile uygulanmayan hastalar (kontrol grubu, n=52), mortalite ve ameliyat sonrası kanama belirteçlerine göre eşleştirilerek karşılaştırıldı.

Bulgular: Fibrinojen düzeyinde ortalama düşüş ANH grubunda (27.4±13.8%), kontrol grubuna kıyasla (43.7±9.5%) anlamlı düzeyde düşüktü (%95 GA: -21.4 ve -11.3, p<0.0001). Trombosit sayısında ortalama düşüş ANH grubunda (33.1±10.1), kontrol grubu ile (35.6±8.9) benzerdi (p=0.21). Cerrahi sonunda ANH grubunda 10 hastaya (%20.4) tam kan yeniden transfüze edilmedi ve yoğun bakım ünitesinde kullanılmak üzere saklandı. Yoğun bakım ünitesinde yatış sırasında, ANH grubunda sadece sekiz hastaya (%16.3) allojenik kırmızı kan hücre verilirken, kontrol grubunda 41 hastaya (%78.8) verildi (p<0.0001). ANH grubunda yalnızca 14 hastaya (%28.6) allojenik taze donmuş plazma verilirken, kontrol grubunda tüm hastalara verildi (p<0.0001). İki grupta da mortalite izlenmedi.

Sonuç: Akut normovolemik hemodilüsyon, yeterli ameliyat öncesi fibrinojen düzeyine sahip hastalarda, plazma fibrinojen düzeylerini koruyabilir ve allojenik kan ürünü transfüzyonuna olan ihtiyacı azaltabilir.

Anahtar sözcükler: Akut normovolemik hemodilüsyon; kan transfüzyonu; koroner arter baypas; fibrinojen.

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Allogeneic blood transfusion is used in 45 to 80% of coronary artery bypass grafting (CABG) to replace coagulation factors lost due to contact of blood with the extracorporeal circuit.[1] Transfusion of allogeneic blood is associated with frequent postoperative complications, if blood older than 14 days are used,[2] and increased incidence of postoperative infections and organ insufficiencies.[3,4] Acute normovolemic hemodilution (ANH) is used to reduce the need for allogeneic blood products, collecting a certain amount of the whole blood of the patient before initiating the bypass.[5] The whole blood is preserved throughout bypass, and transfused back to the patient following the bypass period. A similar benefit may be the preservation of coagulation factors which may become activated or be consumed during bypass.[6] There are controversial results in the literature on beneficial and harmful effects of ANH.[7] A clinical trial of 2004 reported an increased total bleeding with ANH, compared to other blood conservation methods.[8] However, a recent clinical trial reported a reduced need for transfusion in parallel with the amount of the collected whole blood.[9]

Low levels of fibrinogen may increase the need for red blood cell (RBC) transfusion.[10] In this study, we hypothesized that ANH may preserve postoperative plasma levels of fibrinogen and reduce the need for allogeneic blood cell transfusion. To test our hypothesis, we aimed to analyze the effect of ANH on the decline in level of fibrinogen, need for allogeneic blood, and 30-day outcomes in the setting of elective, isolated, on-pump CABG.

PATIENTS AND METHODS

Following approval of Recep Tayyip Erdogan University Local Ethics Committee (No. 2015/57), surgical, anesthetic, perfusion, intensive care unit (ICU), and ward records of a total of 101 adult patients (68 males, 33 females; mean age 61±8 years; range 46 to 84 years) who underwent CABG between January 2014 and December 2015 were retrospectively analyzed. The study was conducted in accordance with the principles of the Declaration of Helsinki. Exclusion criteria were as follows: emergency, off-pump surgery, deep hypothermic or normothermic cardiopulmonary bypass (CPB), concomitant surgery (valve replacement, carotid endarterectomy, or aortic root replacement), use of cell saver or anti-fibrinolytic treatment. All patients who received ANH (ANH group, n=49) were included in the study. An equal number of patients who did not receive ANH (control group, n=52) were matched by predicted mortality according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II,[11] predictors of blood use in CABG,[12] gender, age, body mass index, preoperative hematocrit levels, renal function, and diuretic and inotropic support during the operation.

Antiplatelet medications were discontinued five days before surgery, and all patients received low-molecular-weight heparin until the day of surgery. All patients were monitorized with a five-lead electrocardiogram, peripheral and cerebral pulse oximetry, and arterial line before the induction of anesthesia. Anesthesia was induced with 0.1 mg/kg of midazolam, 3 μg/kg of fentanyl, 1 mg/kg of lidocaine, and maintained with bispectral index-guided bolus doses of midazolam and fentanyl, and sevoflurane, if applicable. Neuromuscular block was obtained with 1 mg/kg of rocuronium bromide, and maintained with train-of-four monitoring guided bolus doses. In ANH group, whole blood was collected from the brachial vein before heparinization, and replaced by an equal volume of 6% hydroxyethyl starch to reduce the hematocrit levels to 35.2±0.6% to achieve a hematocrit level of 28% after mixing with the circuit prime. In addition, CPB was performed with moderate hypothermia (28 °C), a coated membrane oxygenator and closed reservoir, uncoated tubing, cold hyperkalemic cardioplegia, and alpha-stat acid-base management. Blood aspirated via cardiotomy suction before sufficient heparinization (activated coagulation time >450 s) was discarded. Indication for allogeneic packed RBC transfusion was a hematocrit level of <20% during CPB. In ANH group, after reversal with protamine at 1:1 ratio and termination of CPB, whole blood was re-transfused, if hematocrit level was <24%. During weaning from CPB, inotropic support was initiated in case of reduced cardiac contractility or heart rate <100/bpm. In case of volume overload >7 mL/kg due to low urine output despite adequate warming, 0.5 mg/kg of furosemide was administered. Allogeneic packed fresh frozen plasma (FFP) was transfused, if inadequate clot formation was observed after reversal of heparin.

Upon arrival to the ICU, patients were placed on mechanical ventilation and ordered to receive 30 mL/kg/day of crystalloids. All patients routinely received one pack of FFP within the first postoperative hour. Additional FFPs were transfused, if INR >1.5 or chest tube drainage >200 mL/h for two consecutive hours. Patients with a hematocrit level of <24% received RBC. Also, inotropic support was initiated or continued, if signs of low cardiac output syndrome (elevated lactate or decreased urine output) were observed, despite optimization of the fluid status,

oxygenation, and acid-base status. The patients with volume overload due to low urine output received diuretics, until the body weight of the patient is restored to preoperative level. No patient received hemodialysis.

Primary outcome measure was the decline in the level of fibrinogen (calculation based on the level of fibrinogen obtained on the morning of operation and at the end of surgery). Secondary outcome measures included number of patients requiring transfusion of allogeneic blood products during the operation, operative mortality, and operative morbidity (duration of mechanical ventilation, ICU stay, inotropic drugs, diuretics, and renal impairment). Finally, information about new-onset atrial fibrillation, thromboembolism, and anticoagulant-related hemorrhage within 30 days of the procedure were evaluated.

Statistical analysis

Statistical power analyzed after collection of the data was 95% at a type I error rate of 5% for the primary outcome. Data were analyzed with SPSS version 12 (SPSS Inc., Chicago, IL, USA). Distribution of the data was tested with the Shapiro-Wilk test. Quantitative data were expressed in mean ± standard deviation and compared using the Student's t-test, if normally distributed or in median (IQR [range]) and compared using the Wilcoxon signed-rank test, if abnormally distributed (number of intraoperative transfusion of allogeneic packed RBC, duration of inotropic support in the ICU). Categorical data were presented in number and percent (%) and compared using the chi-square test. Independent risk factors for transfusion (age >70 years, fluid balance at 24th postoperative hour, and total fluid balance >500 mL at the end of operation) were analyzed with multiple linear regression analysis. A p value of 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of all patients are shown in Table 1. Consort flow diagram of the study is given in Figure 1.

Intraoperative variables are shown in Table 2. The median volume of whole blood collected from patients in ANH group was 460 mL (430-530 [400-1050]). The mean decline in fibrinogen in ANH group (27.4±13.8%) was significantly lower, compared to the control group (43.7±9.5%, 95% CI: -21.4 to -11.3, p<0.0001) (Figure 2). No patient received blood before the termination of CPB. The mean decline in platelet count in ANH group (33.1±10.1) was similar to the control group (35.6±8.9) (p=0.21). The median number of intraoperative transfusion of RBC in ANH group (median: 0, IQR: 0-0, range: 0 to 3) was significantly lower, compared to the control group (median: 2, IQR: 2 to 3, range: 0 to 8, non-parametric 95% CI: -2 to -1, p<0.0001). Only eight patients (16.3%) in ANH group received RBC, compared to 41 patients (78.8%) in the control group (p<0.0001, χ^2=37). The whole blood was not re-transfused to 10 patients (20.4%) in ANH group at the end of surgery, and preserved to be used in the refrigerator. Only 14 patients (28.6%) in ANH group received FFP, compared to all patients in the control group (p<0.0001, χ^2=53.7).

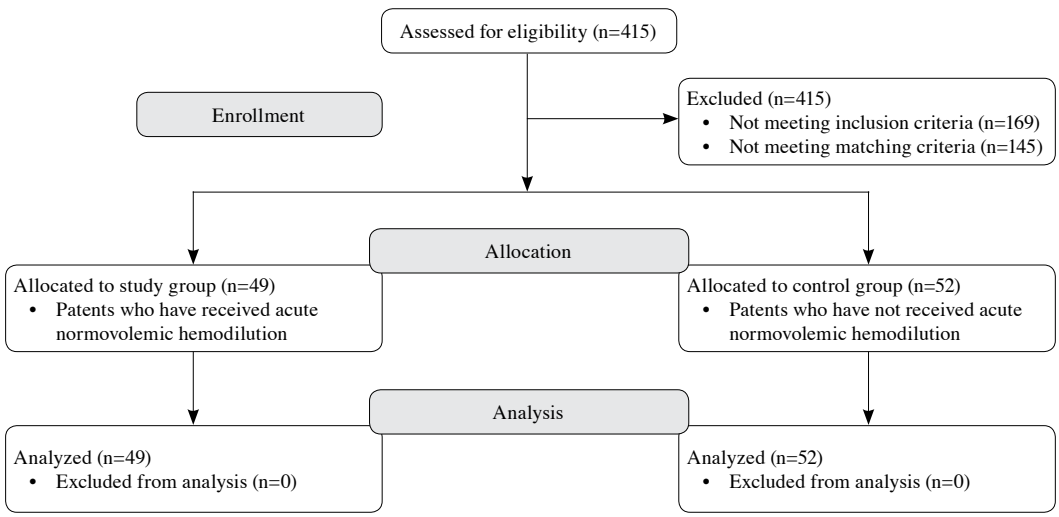

Figure 1. Consort flow diagram of the study.

Table 1. Preoperative clinical characteristics of the patients

Variables	Patients who have received ANH (n=49)			Patients who have not received ANH (n=52)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			61.5±8.8			60.9±7.6	0.7
Gender							0.83
Female	15	30.6		18	34.6		
Male	34	69.4		34	65.4		
Body mass index			27.9±1.6			28.0±1.7	0.86
Body surface area			1.9±0.2			1.8±0.2	0.09
EuroSCORE II			1.4±0.6			1.5±0.7	0.66
NYHA class							0.98
II	10	20.4		11	21.2		
III	26	53.1		28	53.8		
IV	13	26.5		13	25		
Ejection fraction (%)			51.7±10.6			55.2±9.4	0.39
Plasma level of creatinine							
>1.5 mg/dL	6	12.2		6	11.5		1
Mean			1.1±0.3			0.9±0.3	0.1
Hypertension	40	81.6		39	75		0.57
Diabetes mellitus	16	32.7		20	38.5		0.69
Current smoker	22	44.9		21	40.4		0.79
Hematocrit (g/dL)			40.5±2.4			40.8±2.4	0.22
Platelet count (1000/mm^3)			264±74			280±7	0.29
Plasma level of fibrinogen (mg/dL)			473±105			463±112	0.66

ANH: Acute normovolemic hemodilution; SD: Standard deviation; EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association.

Clinical outcomes related to ICU and hospital stay are shown in Table 3. Half of the patients in both groups required short-term inotropic support (median: 0, IQR: 0 to 2, range: 0 to 2 days) (frequencies shown in Table 3). Significantly fewer patients in ANH group had positive fluid balance during the first 24 hours of surgery. In addition, the patients in ANH group had significantly less positive fluid balance (median: 340, IQR: 155 to 380, range: 60 to 860 mL), compared to the control group (median: 395, IQR: 222 to 639, range: 60 to 990 mL) (p=0.017). Blood loss measured via chest tube drainage, occurrence

Table 2. Intraoperative variables

Variables	Patients who have received ANH (n=49)			Patients who have not received ANH (n=52)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Number of grafts			2.9±0.7			3±0.7	0.27
Cardiopulmonary bypass time (min)			83.1±21.1			89±23.9	0.19
Cross clamp time (min)			53.7±28.3			57.8±22.7	0.69
Urine output during CPB (mL/BSA)			3.8±1.7			2.3±1.1	0.053
Fluid balance during CPB (mL/BSA)			4.1±2.5			10.3±4.5	0.0003
Patients requiring inotropic support	6	12.2		7	13.5		1
Patients requiring diuretics	3	6.1		3	5.8		1
Plasma level of fibrinogen at the end of operation							
<200 mg/dL	4	8.2		17	32.7		0.005
Low (100-149 mg/dL)	1	2		5	9.6		0.48
Critical (<100 mg/dL)	0	0		1	1.9		1

ANH: Acute normovolemic hemodilution; SD: Standard deviation; CPB: Cardiopulmonary bypass; BSA: Body surface area.

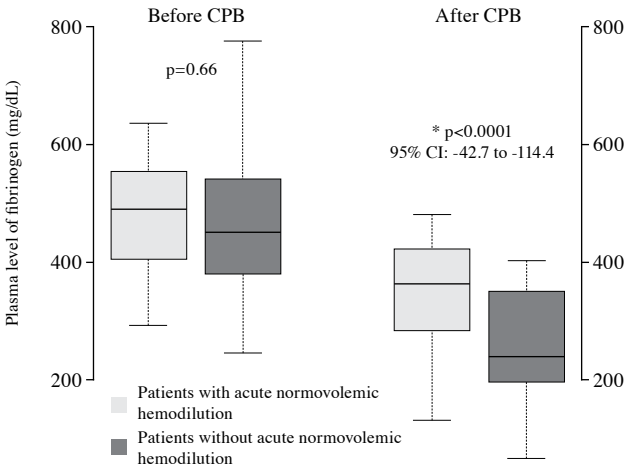

Figure 2. Changes in plasma levels of fibrinogen before and after cardiopulmonary bypass. The drop in the plasma levels is significantly lower in the patients, who received acute normovolemic hemodilution.

CPB: Cardiopulmonary bypass; * Student's t-test.

of new atrial fibrillation, duration of mechanical ventilation, ICU stay, and hospital stay were similar in both groups. The number of transfused RBC and postoperative hematocrit levels were the only significantly different variables. The number of transfused RBC were not related to age >70 years, fluid balance, or positive fluid balance >500 mL at the end of surgery (p=0.79, 0.37, 0.35, respectively). No patient had an allergic reaction, postoperative myocardial infarction, thromboembolism, stroke, or anticoagulant-related hemorrhage, persistent low cardiac output syndrome requiring revascularization or intra-aortic balloon pump, tamponade, or required revision surgery for bleeding within 30 days of the procedure. Thirty-day mortality was zero.

DISCUSSION

The present study showed that ANH attenuated the loss of plasma fibrinogen and the need for allogeneic transfusion in isolated CABG with no apparent difference in bleeding and thrombotic complications within 30 days of the procedure.

Initiation of CPB, reperfusion, and administration of protamin increase the formation of non-hemostatic forms of thrombin and fibrin.[13] Due to an increased plasmin generation, most of this soluble fibrin is degraded, and is not available for coagulation following heparin reversal.[14] If this hyperfibrinolytic state is prevented with the use of anti-fibrinolytic drugs, hemodilution appears to be the main cause of reduced fibrinogen levels.[15] However, fibrinogen also binds to the circuit, forming a binding site for platelets, only to be activated by the leucocytes.[16,17] Recent studies have demonstrated an association between the level of fibrinogen and postoperative blood loss,[18,19] and even suggested prophylactic supplementation of fibrinogen.[20] Similarly, in our study, the patients had critical or low fibrinogen levels; however, this study was not adequately powered to detect a difference between such low percentage change. Recent guidelines have suggested that fibrinogen levels should be >200 mg/dL for sufficient clot strength.[9] In the present study, we found that ANH significantly attenuated the decline in fibrinogen, and significantly more patients in ANH group had a fibrinogen level of >200 mg/dL; however, the mean volume of chest tube drainage during the first 24 hours were similar between the groups. This

Table 3. Postoperative outcomes

	Patients who have received ANH (n=49)			Patients who have not received ANH (n=52)				
Outcome	n	%	Mean±SD	n	%	Mean±SD	95% CI	*p*
Patients requiring inotropic support in ICU	21	42.9		26	50			0.6
Patients with positive fluid balance on first 24 h	8	16.3		22	42.3			0.008
Bleeding from chest tubes on first 24 h (mL)			870±363			877±346		0.96
RBC/patient transfused in ICU			1±0.9			3.1±1.7	-3.1 to -0.8	0.0016
FFP/patient transfused in ICU			2.2±1			4.2±2	-3 to -1.1	0.0002
Hematocrit at 24th h (g/dL)			29.1±1.9			27.2±1.5	1.5 to 2.8	<0.0001
Platelet count at 24th h (1000/mm^3)			264±74			280±72		0.29
New onset atrial fibrillation	5	10.2		11	21.2			0.22

ANH: Acute normovolemic hemodilution; SD: Standard deviation; ICU: Intensive care unit; CI: Confidence interval; RBC: Red blood cell; FFP: Fresh frozen plasma.

may indicate that both groups had similar amount of bleeding. However, it should be noted that hematocrit levels were significantly higher in ANH group, despite the use of significantly less allogeneic blood products. This suggests a lower hematocrit level of chest tube drainage in these patients.

On the other hand, our study design did not include the measurements of hematocrit from the chest tube drains. Another limitation of this study complicating the discussion is the hemodilution of several coagulation factors during CPB. Although all patients in this study were managed to receive normothermia, normocalcemia, and normal pH for adequate hemostasis, hemodilution of many factors such as Factor XIII was not measured due to the limitations of the study design. Furthermore, it is surprising that postoperative platelet counts were similar in both groups. A possible explanation may be the physiological sequestration of platelets within the spleen.[21] Our study outcomes are consistent with previous studies,[22] reporting less need for inotropes, or a lower incidence of new-onset atrial fibrillation. The low percentage of morbidity and mortality may be primarily related to the low number of patients in this study. The similar rate of occurrence of morbidities suggests a satisfactory paired comparison method, and also implies that ANH may have no direct effect on morbidity, but only affects the use of blood products.

Although our study findings support the benefits of ANH, increased hemodilution may harm the patient in several ways, including diluting the level of protein C, thereby, activating thrombin and causing hypercoagulation.[17] Although previous studies have shown that ANH does not depress and may even preserve cardiac functions,[22] and a hematocrit level of 17 to 21% can be well-tolerated in isolated CABG,[23] bias due to the indication of ANH is possible due to the retrospective design of this study. Since the use of ANH in cardiothoracic surgery is recommended only to reduce postoperative bleeding in selected patients with adequate preoperative hemoglobin, platelet, and coagulation factors,[24] it is possible that only patients fulfilling the aforementioned criteria may have received ANH. It should be noted that neither level of fibrinogen, nor speed and strength of clot formation were measured intraoperatively,[25] and coagulation defects during the post-CPB period were crudely managed with the measurements of activated coagulation time, and empirical transfusion of FFP.

In conclusion, our study results suggest that acute normovolemic hemodilution may preserve plasma levels of fibrinogen and reduce the need for allogeneic transfusion of blood products.

Declaration of conflicting interests

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