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The Relationship between Low Intraoperative Hematocrit Levels during Cardiopulmonary Bypass and Postoperative Neurological Events

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ABSTRACT

Objective: The objective of our study is to analyze whether low intraoperative hematocrit levels have an effect upon postoperative neurological events.

Methods: Our study included 140 patients who underwent isolated coronary bypass under cardiopulmonary bypass between 2009 and 2012. The main group of the study was 70 patients with intraoperative hematocrit levels lower than 22%. These patients' 30-day postoperative neurological (particularly stroke) follow up was registered as the main data of the study. Another group of 70 patients possessing the same demographic features who underwent open heart surgery with hematocrit levels remaining above 22% were registered as the control group for perioperative neurological data.

Results: The average age of the patients with hematocrit levels below and above 22% was 56.8 ± 5.8 years and 54.1 ± 7.3 years, respectively. The mean follow-up period of the patients was 37.2 ± 8.6 days. None of the patients had any neurological postoperative sequalae. No mortalities occurred. One patient who had mild paresthesia and motor weakness of the left hand had no pathological finding on computed tomography and was diagnosed with peripheral neuropathy due to intraoperative sternal retraction.

Conclusion: Because our study revealed no cerebrovascular events, coronary bypass surgery under cardiopulmonary bypass may be safely conducted even in patients with hematocrit levels lower than 22%.

INTRODUCTION

Despite rapid advances in the field of open heart surgery and cardiopulmonary bypass (CPB), stroke remains a significant problem following surgery. Even though the results of the primary operative procedure are good enough, stroke following cardiac surgery affects the survival rate and has a negative effect upon the doctor–patient relationship, the patient's relatives, and hospital's reputation. In order to avoid neurological complications, a number of different methods have been applied (intraoperative epiaortic echocardiography, bilateral carotid artery occlusion while releasing the cross-clamp) alongside trying to identify and combat risk factors.

The relationship of neurological events with CPB following open heart surgery is well known. However, the relationship between the low hematocrit (Hct) levels, hemodilution, and neurological events has not been proven. Some of the previous experimental studies revealed that low hemoglobin (Hb) levels (3-4 g/dL) are related to cerebral tissue hypoxia and neurological injury. The relationship between postoperative cerebrovascular accident (CVA) in normal human physiology and low levels of intraoperative Hct is not clear [Hare 2008]. Surgenor et al discovered that perioperative blood transfusion is associated with high mortality and morbidity. In addition, there was an increased risk of postoperative renal dysfunction, pneumonia, wound infection, and sepsis [Surgenor 1998].

In this study, we searched for the incidence of postoperative neurological event occurrence in patients with intraoperative Hct levels below 22% under CPB regardless of administration of a blood transfusion.

MATERIALS AND METHODS

One hundred forty patients under the age of 65 years who underwent isolated coronary bypass surgery (CABG) between 2009 and 2012 were included in this study. The main group of the study was 70 patients with intraoperative Hct levels lower than 22%. These patients' 30-day postoperative neurological (particularly stroke) follow-up was registered as the main outcome of the study. Another group of 70 patients possessing the same demographic features who underwent open heart surgery with Hct levels remaining above 22% were registered as the control group for perioperative neurological data. Power analysis with a value of 84% identified that the number of patients in each group was sufficient.

Data on sex, age, diabetes mellitus (DM), hyperlipidemia (HL), obesity, family history, peripheral arterial disease (PAD), smoking, chronic obstructive pulmonary disease (COPD), thyroid function test (TFT) abnormality, rise in urea-creatine,

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Table 1. The Demographic Data of the Patients

Patient Characteristics	All Patients (n = 140)	Hematocrit Value		
		≤ 22.0% (n = 70)	> 22.0% (n = 70)	*P*
Age, y ± standard deviation	55.5 ± 6.5	56.8 ± 5.8	54.1 ± 7.3	.021*
Male sex, n (%)	117 (83.6%)	54 (77.1%)	63 (90.0%)	.068†
Diabetes mellitus, n (%)	51 (36.4%)	35 (50.0%)	16 (22.9%)	.001†
Hypertension, n (%)	76 (54.3%)	40 (57.1%)	36 (51.4%)	.497†
Hyperlipidemia, n (%)	58 (41.4%)	27 (38.6%)	31 (44.3%)	.493†
Obesity, n (%)	30 (21.4%)	17 (24.3%)	13 (18.6%)	.537†
Peripheral arterial disease, n (%)	3 (2.1%)	1 (1.4%)	2 (2.9%)	.622†
Smoking, n (%)	73 (52.1%)	26 (37.1%)	47 (67.1%)	<.001†
Chronic obstructive pulmonary disease, n (%)	19 (13.6%)	9 (12.9%)	10 (14.3%)	.805†
Carotid stenosis				
Normal, n (%)	105 (75.0%)	57 (81.4%)	48 (68.6%)	.079†
Insignificant stenosis, n (%)	35 (25.0%)	13 (18.6%)	22 (31.4%)	

*Mann-Whitney U test
†Chi-square test

preoperative ejection fraction (EF), postoperative bleeding or re-exploration, duration and amount of inotropic support, postoperative awakening period, duration of intraoperative cross-clamp (X-CL) and CPB, systemic cooling degree, intraoperative mean arterial pressure, amount of transfusion, and continuous electrocardiography (ECG) monitorization were collected in both groups and cross analyzed. The demographic data of the patients are given in Table 1.

Certain risk factors detected were accepted as exclusion criteria for this study. These included age greater than 65 years, previous neurological event, severe carotid stenosis (50%), additional surgical procedures (such as valvular surgery, surgery involving the ascending aorta), calcification or plaque visible on a chest radiograph and/or transthoracic echocardiography (TTE), and intraoperative palpation of aortic calcifications or plaques of the ascending aorta.

Occurrence of neurological events during the early postoperative period was monitored using the Glasgow Coma Scale while the patients were still intubated. During the first postoperative day and on the day of discharge, a detailed neurological examination of the neurological and locomotor system (including peripheral muscle power, cranial nerve examination, and cognitive function) was performed. One month after discharge, the patients were called to the outpatient clinic for evaluation of ECG, chest radiography, TTE, and routine blood tests (total blood count, biochemistry). A systematic review and systems examination was also performed.

Non-pulsatile flow was used for all patients under CPB. Roller pump and membrane oxygenators were used for perfusion. The mean arterial pressure of the patients was kept at and above 60 mmHg. The Hct levels during CPB were followed and registered. General methods were applied for cerebral protection (no additional methods were applied). Ringer Lactate solution (1500 mL) was used for hemodilution, and normovolemic hemodilution was aimed for while initiating CPB.

This study complies with the Declaration of Helsinki, and ethical approval was granted by the local institutional review board. Informed consent was obtained from all patients.

Statistical Analysis

The data obtained were analyzed using SPSS pocket program (SPSS for Windows 15.0, Inc., Chicago, IL, USA). A *P* value below .05 was accepted as demonstrating significant difference. Normally distributed continuous variables were expressed as mean values ± standard deviation (SD). Categorical variables were expressed as numbers and percentages. Demographic characteristics and perioperative variables were compared using independent samples t-tests or Mann-Whitney U tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. Correlations were assessed using Pearson's correlation test.

RESULTS

None of the patients had any neurological postoperative sequalae. No mortalities occurred. The average age of the groups with Hct levels below and above 22% was 56.8 ± 5.8 years and 54.1 ± 7.3 years, respectively. The mean patient follow up was 37.2 ± 8.6 days.

Two patients underwent re-exploration due to postoperative bleeding. One patient underwent re-exploration for sternal infection occurring during the follow-up period. One patient who had mild paresthesia and motor weakness of the left hand on the first postoperative day was examined by a neurologist. The patient had no pathological findings on computed tomography and was diagnosed with peripheral neuropathy secondary to intraoperative sternal retraction. Full recovery was seen following physiotherapy. The rest of the patients had normal findings on physical examination and laboratory testing with no neurological deficit.

Table 2. Perioperative Data of the Patients*

Features	Hematocrit Value		
	≤ 22.0% (n = 70)	> 22.0% (n = 70)	*P*
Number of anastomoses	3.2 ± 1.2	3.1 ± 1.1	.679
Duration of cardiopulmonary bypass, min	91.2 ± 29.3	87.3 ± 30.8	.706
Duration of cross-clamp, min	58.1 ± 20.9	58.6 ± 22.6	.877
Degree of hypothermia, °C	31.6 ± 1.1	31.8 ± 1.1	.432
Postoperative awakening time, h	8.5 ± 2.7	7.3 ± 2.7	.011
Volume of erytrocyte suspension transfused, mL	2.8 ± 0.6	1.1 ± 0.8	< .001

*Data are shown as mean ± standard deviation.

The demographic data of the patients are summarized in Table 1. There was no significant difference regarding the COPD, TFT abnormality, preoperative EF, and existence of carotid plaque between the groups ($P > .05$). Age variability was found to be higher in the group with Hct ≤ 22% ($P = .021$). The presence of DM was 50% (significantly higher) and 22.9% in the groups with Hct ≤ 22% and Hct > 22%, respectively ($P = .001$). Smoking was significantly higher (67.1%) in the group with Hct > 22% ($P < .001$).

There was no significant difference in operative variables including the duration of X-CL, CPB, and systemic cooling degrees ($P > .05$) between the 2 groups. The postoperative awakening period and the amount of erythrocyte suspension (ES) transfused were significantly higher ($P = .011$ and $P < .001$, respectively) in the group with Hct ≤ 22%. These data are presented in Table 2.

No neurological events or mortalities occurred during the follow-up period. However, the postoperative awakening time was significantly higher in the group with Hct ≤ 22%. Hence, factors affecting the postoperative awakening time were further analyzed. None of the factors was found to be significant.

DISCUSSION

Neurological complications following CPB can reach up to 40% in the general population. However, most of the cases are composed of transient neuropsychiatric dysfunction (from mild cognitive and intellectual changes to delirium and organic brain syndrome), which are pathophysiologically different from stroke.

The study of Karkouti et al included patients with a history of neurological events who had undergone additional procedures alongside isolated coronary bypass in their study. TEE was used to detect calcification and plaques of the ascending aorta in patients who had been classified as high risk preoperatively. Before performing sternotomy, aprotinin was administered to the patients with increased risk of postoperative bleeding. Blood was used as a priming solution for certain cases in order to prevent hemodilutional anemia. As a result, in this study, the prevalence of neurological events was 1.5%, and bi-variable analysis of lowest Hct level and neurological event revealed that every 1% decrease in the lowest Hct level resulted in a 10% increase in cerebrovascular event [Karkouti 2005; Karkouti 2008].

The study of Habib et al included patients who underwent open heart surgery between 1994 and 2000. The patients in this study had advanced age (older than 65 years) and a past history of neurological events and surgery (valve surgery, combined surgery, etc.). This study differs from other studies in that the patients were subdivided according to the lowest Hct levels. The decrease in the lowest Hct values in this study was associated with increased perioperative mortality, postoperative bleeding, and reoperation due to tamponade, cerebrovascular event, pulmonary edema, septicemia, perioperative myocardial infarction, renal failure, and multiorgan failure [Habib 2003].

The study of DeFoe et al revealed that rates of re-exploration due to bleeding, low cardiac output, and hospital mortality increased relative to the degree of hemodilution. Contrary to the other studies, however, there was no increase in the incidence of cerebrovascular events [DeFoe 2001]. Hardy et al found that low Hct levels resulted in increased renal failure, hemodynamic instability, and mortality [Hardy 1998]. Fang et al determined that an Hct level below 14% resulted in a 2-fold increase in mortality [Fang 1997]. Pugsley et al showed an increase in the neurocognitive dysfunction resulting from a decrease in Hct levels [Pugsley 1994].

Blood transfusion is not a complication-free procedure. Hence, every single blood transfusion has to be accounted for, as does tissue and organ transplantation. Moreover, we should bear in mind that a blood transfusion could give rise to infections and immunological reactions. Hence, unnecessary blood transfusion must be avoided [Karkouti 2008].

There are some methods used to eliminate or decrease the need for homologous blood transfusions and resulting risks facing patients undergoing surgical procedures [Utley 1981; Simpson 1992; The National Blood Resource Education Program Expert Panel 1990]. These include autologous blood transfusion, controlled hypotension, pharmacological agents affecting coagulation mechanisms, epsilon aminocaproic acid, tranexamic acid and desmopressin, attentive surgical technique, and surgical hemostasis and others (acute normovolemic hemodilution, etc.) [Simpson 1992; Murkin 1994].

In 2002, Engoren et al revealed that patients who had received blood transfusions had a 2-fold increase in 5-year mortality compared to patients who did not undergo a blood transfusion (15% and 7%, respectively). Even after equalization of comorbidity and other factors, transfusion increased mortality by 70%. They also revealed that blood transfusion during and after CABG surgery had negative affects upon long-term morbidity and mortality [Engoren 2002]. Another study held at the Cleveland Clinic involving 1500 patients operated on under CPB revealed that intraoperative blood transfusions had a very strong relationship with the occurrence of postoperative infection [Banbury 2006].

In that case, what type of a strategy should we follow for blood transfusion? Which circumstances require blood transfusion? What should the threshold value of Hb be? Should we follow different strategies for patients bearing additional risk factors?

There are guidelines produced according to the results of previous multicenter studies. The guideline of perioperative blood transfusion and blood conservation in cardiac surgery [The Society of Thoracic Surgeons Blood Conservation Guideline Task Force 2007] include:

1. Blood transfusion must be given if Hb levels are below 6 g/dL while under CPB.
2. Transfusion is not indicated for stable patients with Hb levels below 7 g/dL. However, patients older than 65 years, with diabetes, or who have severe carotid stenosis with a history of previous neurological event and COPD require transfusion.
3. The benefit of transfusing blood to patients with Hb levels between 7 and 10 g/dL has not been proven.
4. Blood transfusion is indicated in patients with an acute blood loss of more than 1500 mL or 30%.

Hare et al highlight the fact that the Hb levels in patients with an increased risk of neurological event should not be kept below 7 g/dL and the Hct below 21% [Hare 2008].

Our study involved 140 patients who underwent isolated coronary bypass under CPB held between 2009 and 2012. Patients over the age of 65 years were excluded from the study because this age group of has concomitant atherosclerotic pathologies such as cerebral atherosclerosis, which may increase the incidence of cerebrovascular events during CPB. Therefore, in order to determine the correlation between cerebrovascular events and low hematocrit levels, patients over the age of 65 years were excluded from the study.

During the postoperative follow-up of these patients, there were no neurological complications or mortalities. The findings of our study, which are in contrast to those of previous large observational studies, may be due to our population lacking preoperative risk factors that were present in patients of past studies [Habib 2003; Hare 2008; Karkouti 2008;]. When previous studies were analyzed, it was observed that the study populations were heterogeneous; for example, additional cardiac procedures were carried out alongside isolated CABG, and patients with advance age and patients with previous cerebrovascular accident were included. In studies bearing high preoperative risk factors, even though a low Hct level is statistically significant for increased risk in cerebrovascular event, it has not been found to be an independent risk factor.

CONCLUSION

As a result, because no cerebrovascular events occurred in our study group, we suggest that CABG under CPB can be safely conducted in patients with Hct levels similar to those of our study population.

Limitations of the Study

Our study is a prospective, observational, cohort study looking for incidence of cerebrovascular events among patients who underwent isolated CABG between 2009 and 2012. Because intraoperative anemia is currently a potential risk factor for perioperative cerebrovascular events, there are serious ethical limitations to study this subject further. If the number of observational studies held with the selected group of patients increase, controlled clinical trials, approved by the ethical committees of the hospitals, will be possible in the future. Thanks to this, the relationship of intraoperative anemia and postoperative cerebrovascular events can be studied in further detail. Our study included 140 patients who underwent isolated coronary bypass under CPB and revealed no neurological events or mortalities during the follow-up period. In order to strengthen this hypothesis, strong randomized, controlled, clinical trials have to be performed. Besides this, more detailed experimental laboratory studies have to be performed in order to display the pathophysiology of anemia-related cerebral injury and the cellular mechanisms involved.

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