

# The Neurocognitive Outcomes of Hemodilution in Adult Patients Undergoing Coronary Artery Bypass Grafting Using Cardiopulmonary Bypass

Rabie Soliman<sup>1,2</sup>, Dalia Saad<sup>1</sup>, Walid Abukhudair<sup>3</sup>, Sabry Abdeldayem<sup>4</sup>

<sup>1</sup>Department of Anesthesia, Cairo University, Egypt, Departments of <sup>2</sup>Cardiac Anesthesia and <sup>3</sup>Cardiac Surgery, King Fahd Armored Forces Hospital, Jeddah, Saudi Arabia, <sup>4</sup>Department of Neurology, Tanta University, Egypt

## ABSTRACT

**Objective:** The study aimed to evaluate the effect of mild and moderate hemodilution during CPB on the neurocognitive dysfunction in patients undergoing coronary artery bypass grafting.

**Design:** A randomized clinical study.

**Setting:** Cardiac center.

**Patients:** 186 patients scheduled for cardiac surgery with cardiopulmonary bypass.

**Intervention:** The patients were classified into 2 groups (each = 93), Mild hemodilution group: The hematocrit value was maintained >25% by transfusion of packed-red blood cells plus hemofiltration during CPB. Moderate hemodilution group: the hematocrit value was maintained within the range of 21-25%.

**Measurements:** The monitors included the hemofiltrated volume, number of transfused packed red blood cells, and the incidence of postoperative cognitive dysfunction.

**Main Results:** The hemofiltrated volume during CPB was too much higher with mild hemodilution compared to the moderate hemodilution ( $p = 0.001$ ). The number of the transfused packed red blood cells during CPB was higher with mild hemodilution compared to the moderate hemodilution ( $p = 0.001$ ), but after CPB, the number of the transfused packed red blood cells was lower with the mild hemodilution group than the moderate hemodilution ( $p = 0.001$ ). The incidence of total postoperative neurological complications was significantly lower with the mild hemodilution group than moderate hemodilution ( $p = 0.033$ ). The incidence of neurocognitive dysfunction was significantly lower with mild hemodilution group than moderate hemodilution ( $p = 0.042$ ).

**Conclusions:** The mild hemodilution was associated with a significant decrease in the incidence of neurocognitive dysfunction compared to moderate hemodilution in patients undergoing coronary artery bypass grafting. Also, the transfused packed red blood cells increased during CPB and decreased after CPB with the mild hemodilution than moderate hemodilution.

**Keywords:** Cardiopulmonary bypass, coronary artery bypasses grafting, hemodilution, neurocognitive dysfunction.

**Address for correspondence:** Dr. Rabie Soliman, Department of Anesthesia, Cairo University, Egypt.

E-mail: rabiesoliman@hotmail.com

**Submitted:** 14-Aug-2020 **Revised:** 29-Apr-2021 **Accepted:** 10-May-2021 **Published:** 11-Apr-2022

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.aca_206_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Soliman R, Saad D, Abukhudair W, Abdeldayem S. The neurocognitive outcomes of hemodilution in adult patients undergoing coronary artery bypass grafting using cardiopulmonary bypass. *Ann Card Anaesth* 2022;25:133-40.

## INTRODUCTION

Hemodilution during cardiopulmonary bypass (CPB) was used to improve the microcirculatory flow<sup>[1-4]</sup> and counteract the adverse effects of hypothermia such as increased viscosity and red cell rigidity.<sup>[5]</sup>

However, hemodilution may reduce the perfusion pressure which increases the risk of adverse neurologic outcome after CPB,<sup>[6]</sup> and also it increases the cerebral blood flow, and therefore it may increase the incidence of microemboli to the brain. Also, hemodilution reduces the oxygen-carrying capacity of blood and, in combination with the effect of the hypothermia; the hemodilution may decrease the oxygen delivery to brain tissues.<sup>[7,8]</sup>

We hypothesized that hemodilution during CPB will increase the risks of neurocognitive dysfunction after cardiac surgery.

The aim of the present study was to evaluate the effect of mild and moderate hemodilution during CPB on the neurocognitive dysfunction in patients undergoing coronary artery bypass grafting.

## PATIENTS

After obtaining informed consent and approval of local ethics and research committee in the cardiac center (45/2017, 15/01/2017), a prospective randomized study included 186 patients undergoing coronary artery bypass grafting using cardiopulmonary bypass. The inclusion criteria were patients with ischemic heart disease, hypertension, diabetes, ejection fraction  $\geq 50\%$ . Exclusion criteria included patients with valvular surgery, previous neurologic diseases, congestive heart failure, acute myocardial infarction, atrial fibrillation or obstructive cardiomyopathy, off-pump coronary artery bypass grafting (CABG), renal, hepatic impairment or patients with hematocrit (HCT) value  $< 21\%$ . The patients were randomly allocated (the concealment of allocation was done by using random numbers generated through excel) into two equal groups ( $n = 93$  each).

### Mild hemodilution group

The hematocrit value was maintained  $> 25\%$  by hemofiltration plus transfusion of packed-red blood cells during CPB.

### Moderate hemodilution group

The hematocrit value was maintained within the range of 21-25% by hemofiltration plus transfusion of packed-red blood cells during CPB.

The patients were evaluated by trained neuropsychiatrist using a battery of tests that is composed of a comprehensive assessment of the cognitive status, including the memory, attention, language, executive function, and motor speed, on the day before surgery, the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> postoperative days for the diagnosis of neurological complications. The neuropsychiatrist was blinded for the all patients of the two groups.

### Anesthetic technique

For all patients and under local anesthesia, a radial arterial cannula and central venous line were inserted guided by ultrasound before the operation to enable continuous hemodynamic monitoring. Induction was done by intravenous Fentanyl (3-5  $\mu\text{g}/\text{kg}$ ), Etomidate (0.3 mg/kg), Rocuronium (0.8 mg/kg). The anesthesia was maintained with oxygen/air (50%), Fentanyl infusion (1-3  $\mu\text{g}/\text{kg}/\text{hr}$ ), Cisatracurium (1-2  $\mu\text{g}/\text{kg}/\text{min}$ ), and Sevoflurane or Propofol according to the study medication protocol. Epiaortic ultrasound scanning using a transducer applied directly to the ascending aorta and the aortic arch after opening the chest to enable the detailed visualization of the aortic wall and to show the distribution of calcified atherosclerotic lesions and also to determine the optimal and safe location for aortic cannulation. At the end of surgical intervention, the patients were prepared for weaning from CBP. If there was difficulty to wean from CPB, pharmacological support (dopamine or epinephrine or norepinephrine, or nitroglycerine), mechanical support (IABP), or pacing were started. At the end of the surgery, the patients were transferred to the cardiac surgery ICU with full monitoring.

### Cardiopulmonary bypass

The pump (Roller pump, Stockert S5 Germany) was primed with 1000 ml of ringer lactate, 300 ml hetastarch 6%, 100 ml albumin 20%, 50 meq of sodium bicarbonate, 5000 IU of heparin and 200 ml of mannitol 20%. Cardiopulmonary bypass was established with cannulation of the ascending aorta and right atrium. The patients received cold blood cardioplegia in the standard ratio (4:1) four parts of blood from the cardiopulmonary bypass circuit, and one part potassium-rich crystalloid named Plegisol (Hospira, Inc, Lake Forest, IL, USA). The initial dose was 30 ml/kg, and subsequent doses were 20 ml/kg given every 20 min. The temperature was reduced to 28-32°C and pump flow rates 2-2.4 L/min/m<sup>2</sup> was used to maintain the perfusion pressure of 100-125 mmHg. The arterial blood gases monitoring was done using alpha-stat PH-stat strategy during cardiopulmonary bypass.

In the two groups, cardioplegia solution was given two-thirds through the antegrade and one-third through

the retrograde route, and a hot shot (warm blood) antegrade dose was given just before the myocardium reperfusion. After the initiation of CPB and stabilizing the hemodynamics according to the standardized parameters during CPB, the hemofiltration was started and continued up to 10 min before weaning from CPB. The hemofiltration and the packed red blood cells transfusion were done to maintain the hematocrit value either  $>25\%$  or  $21\text{--}25\%$  according to the study protocol.

### Monitoring of patients

Hemodynamic monitoring included the heart rate; mean arterial blood pressure (MAP), a continuous electrocardiograph with automatic ST-segment analysis (leads II and V), central venous pressure, and cerebral near-infrared spectroscopy (NIRS) to measure the regional cerebral oxygen saturation. The patients with postoperative neurological complications were assessed by a neuropsychiatrist through the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> postoperative days for the diagnosis of neurocognitive dysfunction or stroke. Postoperatively, the CT scan or MRI brain was done in patients with neurological complications.

Hemodynamic values were serially collected at the following timepoints: T0: Baseline reading; T1: 15 minute after induction; T2: before cardiopulmonary bypass; T3: 30 minutes after cardiopulmonary bypass; T4: at ICU admission; T5: 6<sup>th</sup> hour after ICU admission; T6: 12<sup>th</sup> hour after ICU admission; T7: 24<sup>th</sup> hour after ICU admission. In addition to the previous timepoints, regional cerebral oxygen saturation was assessed during CPB at the 15<sup>th</sup>, 30<sup>th</sup> minute after initiation of CPB and five minutes before weaning of CPB. The neurological functions were evaluated before surgery, the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> postoperative.

### Outcomes

The primary outcome was the effect of mild hemodilution and moderate on the incidence of neurocognitive dysfunction symptoms such as the inability to concentrate, amnesia, confusion, anxiety, the feeling of imbalance, changes in vision, and abnormal behavior of the patients. Secondary outcomes were the requirement and safety of blood product transfusion which was assessed by the occurrence of any adverse events.

### Sample size calculation

Power analysis was performed using the Chi-square test for independent samples on the frequency of patients associated with neurocognitive dysfunctions because it was the main outcome variable in the present study. A pilot study (10 patients in each group) was done before starting this study because there is no available data in

the literature for the comparison of the neurocognitive function of mild hemodilution and moderate hemodilution in patients undergoing coronary artery surgery. The results of the pilot study showed that the incidence of postoperative neurological complications was 20% in the mild hemodilution group, and 50% in the moderate hemodilution group. Taking power 0.8, alpha error 0.05, and beta 0.2, a minimum sample size of 93 patients was calculated for each group.

### Statistical analysis

Data were statistically described in terms of mean  $\pm$  standard deviation ( $\pm$  SD), or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the student t-test for independent samples. Repeated measure ANOVA was used to compare the hemodynamics and regional cerebral oxygen saturation at different follow-up intervals. For comparing categorical data, Chi-square ( $X^2$ ) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

## RESULTS

Table 1 shows no significant differences regarding the demographic data, co-morbidities, preoperative medications, hematocrit, NYHA class, Euroscore, and the ASA physical status score ( $p > 0.05$ ).

Table 2 shows the changes in the hemodynamics of patients during the procedure and through the first 24 hours in the ICU. There was no significant difference in the perioperative heart rate, mean arterial blood pressure, and central venous pressure between the patients of the two groups ( $p > 0.05$ ).

Table 3 shows the changes in regional cerebral oxygen saturation. There was no significant difference in the right or left regional cerebral oxygen saturation as measured by cerebral near-infrared spectroscopy before, during, or after the CPB between the two groups ( $p > 0.05$ ).

Table 4 shows the intraoperative data and the outcomes of patients of the two groups. There was no difference in the number of coronary artery grafts, cardiopulmonary bypass time and temperature, cross clamping time, blood loss, intraoperative fluid, urine output, blood sugar, postoperative renal complications, allergic reactions, ICU

**Table 1: Preoperative Data of Patients (Data are Presented as Mean±SD, Number, %)**

Variable	Mild Hemodilution Group (n=93)	Moderate Hemodilution Group (n=93)	P
Age (year)	59.63±14.70	57.80±13.45	0.376
Weight (Kg)	87.78±10.63	88.45±12.40	0.692
Gender Male:Female	69:24	73:20	0.604
Diabetes mellitus	74	80	0.331
Hypertension	79	72	0.260
Ischemic heart disease	93	93	1.000
Atrial fibrillation	28	23	0.510
Pulmonary hypertension	22	17	0.471
Ejection fraction (%)	55.40±3.75	54.87±3.48	0.319
Angiotensin-converting-enzyme inhibitors	62	55	0.362
Beta-blockers	77	81	0.538
Calcium channels-blockers	24	15	0.486
Aspirin	93	93	1.000
Statins	82	87	0.308
Hematocrit (%)	39.74±3.65	38.90±3.53	0.112
Carotid stenosis			
<50%	15	8	0.181
Unilateral	9	5	0.404
Bilateral	6	3	0.494
Smoking	55	60	0.546
NYHA			
II	19	21	0.858
III	67	62	0.524
IV	7	10	0.610
ASA			
III	79	85	0.256
IV	14	8	0.256
Euroscore (%)	12.82±2.97	12.34±2.10	0.204
Body surface area (m <sup>2</sup> )	1.75±0.19	1.78±0.16	0.245

NYHA: New York Heart Association; ASA: American Society of Anesthesiologists Physical Status Score

or hospital length of stay, and mortality between the two groups ( $p > 0.05$ ). There was no difference in the hematocrit before or after the CPB between the two groups ( $p > 0.05$ ), but during the CPB, the hematocrit was significantly higher in the patients of the mild hemodilution group compared to the moderate hemodilution group ( $p < 0.05$ ). The hemofiltrated volume during CPB was too much higher in the patients of the mild hemodilution group compared to the moderate hemodilution group ( $p = 0.001$ ).

The number of the transfused packed red blood cells during CPB was higher in the patients of the mild hemodilution group compared to the moderate hemodilution group ( $p = 0.001$ ), but after the CPB, the number of the transfused packed red blood cells was lower in the patients of the mild hemodilution group compared to the moderate hemodilution group ( $p = 0.001$ ).

The weaning from CPB was easier in patients of the mild hemodilution group compared to the moderate hemodilution group. Patients of the mild hemodilution group needed smaller doses of pharmacological

**Table 2: Heart Rate, Mean Arterial Blood Pressure and Central Venous Pressure of Patients (Data are Presented as Mean±SD)**

Variable	Mild Hemodilution Group (n=93)	Moderate Hemodilution Group (n=93)	P
Heart rate (bpm)			
T0	78.14±12.35	76.49±11.90	0.354
T1	75.10±10.75	74.33±10.09	0.615
T2	74.65±9.38	73.25±10.10	0.328
T3	73.90±10.44	75.30±9.66	0.343
T4	75.80±9.20	74.70±8.31	0.393
T5	79.22±10.50	78.08±11.40	0.479
T6	82.00±11.62	80.95±10.38	0.479
T7	81.27±10.30	79.83±11.90	0.378
Mean arterial blood Pressure (mmHg)			
T0	105.17±13.58	106.80±14.55	0.430
T1	106.46±14.34	104.93±12.30	0.435
T2	103.52±11.26	105.10±12.15	0.358
T3	104.50±13.63	103.70±11.95	0.670
T4	107.77±14.60	109.13±13.71	0.513
T5	110.43±13.70	112.00±14.30	0.445
T6	112.40±12.58	113.10±13.54	0.715
T7	113.65±14.42	111.89±13.73	0.395
Central venous pressure (mmHg)			
T0	10.00±1.55	10.14±1.64	0.550
T1	11.88±1.64	12.07±1.72	0.441
T2	13.13±1.23	12.83±1.45	0.129
T3	12.88±1.55	12.74±1.34	0.510
T4	13.34±1.61	13.20±1.42	0.530
T5	12.73±1.81	13.08±1.91	0.201
T6	13.27±1.47	13.10±1.47	0.431
T7	12.40±1.34	12.16±1.25	0.208

T0: Baseline reading; T1:15 minute after induction; T2: before cardiopulmonary bypass; T3: 30 minute after cardiopulmonary bypass; T4: at ICU admission; T5: 6<sup>th</sup> hour after ICU admission; T6: 12<sup>th</sup> hour after ICU admission; T7: 24<sup>th</sup> hour after ICU admission

support (Dopamine, Epinephrine, Norepinephrine, and Nitroglycerine) than the moderate hemodilution group ( $p < 0.05$ ), and the requirement for mechanical support (IABP) and the pacing was lower in patients of the mild hemodilution group compared to the moderate hemodilution group ( $p < 0.05$ ). The total number of patients who suffered from postoperative neurological complications was significantly lower in patients of the mild hemodilution group compared to the moderate hemodilution group ( $p = 0.033$ ). The incidence of neurocognitive dysfunction was significantly lower in patients of the mild hemodilution group compared to the moderate hemodilution group (18.72% vs. 32.25% respectively,  $P = 0.042$ ). The incidence of stroke was lower in the patients of the mild hemodilution group than the moderate hemodilution group, but the difference was insignificant ( $p = 0.650$ ). The number of patients who suffered from pulmonary edema and required postoperative mechanical ventilation was lower in the mild hemodilution group compared to the moderate hemodilution group, but the difference was insignificant ( $p = 0.164$ ). There was

**Table 3: Regional Cerebral Oxygen Saturation of Patients (Data are presented as %)**

Variable	Mild hemodilution group (n=93)	Moderate hemodilution group (n=93)	P
Right regional cerebral oxygen saturation (%)			
T0	68.15±4.36	67.15±3.92	0.101
T1	71.29±2.53	70.76±2.47	0.150
T2	71.90±2.80	72.11±2.94	0.618
CPB			
15 min	64.40±3.58	65.25±4.52	0.156
30 min	66.53±6.73	65.85±5.52	0.452
5 min before weaning	65.37±5.62	64.64±4.70	0.337
T3	71.20±4.82	70.77±4.25	0.519
T4	70.79±3.54	71.15±3.64	0.495
T5	72.30±3.83	71.76±3.66	0.326
T6	70.37±3.48	70.73±3.60	0.489
T7	71.50±4.30	70.75±3.74	0.206
Left regional cerebral oxygen saturation (%)			
T0	71.13±3.55	70.85±3.10	0.567
T1	70.54±3.34	70.08±3.17	0.336
T2	71.44±4.37	70.95±3.75	0.412
CPB			
15 min	66.13±3.34	65.79±2.76	0.450
30 min	65.53±3.65	65.30±3.43	0.658
5 min before weaning	66.86±3.87	66.24±4.10	0.290
T3	72.40±3.48	71.92±3.27	0.333
T4	72.74±3.72	72.55±3.64	0.725
T5	72.07±4.37	71.79±3.87	0.644
T6	70.72±2.15	71.15±3.20	0.283
T7	71.45±3.50	71.24±3.71	0.691

CPB: cardiopulmonary bypass. T0: Baseline reading; T1: Reading 15 minutes after induction; T2: before initiation cardiopulmonary bypass; CPB 15 min: 15 minutes after initiation of cardiopulmonary bypass; CPB 30 min: 30 minutes after initiation of cardiopulmonary bypass; CPB 5 min: five minutes before weaning of cardiopulmonary bypass; T3: 30 minutes after cardiopulmonary bypass T5: 30 minutes after cardiopulmonary bypass; T6: at ICU admission; T9: 6th hour after ICU admission; T10: 12th hour after ICU admission; T7: 24th hour after ICU admission

no incidence in the anaphylactic reaction, disseminated intravascular coagulopathy, postoperative graft occlusion and acute myocardial infarction, thromboembolism, neurological complications, or mortality in the two groups.

## DISCUSSION

Hemodilution during CPB results from the mixing of pump crystalloid and colloid prime solution with the blood of the patients and these two mixed volumes plus to the pre-CPB hematocrit determine the degree of hemodilution.<sup>[9]</sup> The hemodilution during CPB is classified into three groups: mild (Hct >25%), moderate (Hct 21-25%), and severe (Hct <21%).<sup>[10]</sup>

In the present study, the hematocrit value was maintained >25% in the mild hemodilution group and in the range of 21-25% in the moderate hemodilution group by hemofiltration plus transfusion of packed-red blood cells

during CPB. The incidence of neurocognitive dysfunction symptoms such as the delirium, inability to concentrate, amnesia, confusion, anxiety, the feeling of imbalance, changes in vision, and abnormal behavior of the patients was significantly lower in the mild hemodilution group compared to the moderate hemodilution group (18.72% vs. 32.25% respectively).

Progressive hemodilution is associated with a progressive decrease in the oxygen-carrying capacity and viscosity of the blood,<sup>[11,12]</sup> and it leads to a reduction in the tissue oxygen delivery and organ dysfunction.<sup>[13-15]</sup> This finding is supported by other observational studies that showed a direct relationship between the severity of hemodilution and the risk of intra- and postoperative renal, hepatic, and central nervous system dysfunction, as well as mortality.<sup>[9,16-23]</sup>

McCusker *et al.*,<sup>[24]</sup> and Vijay *et al.*<sup>[25]</sup> showed that higher intraoperative hematocrit between 25 and 30% is required to maintain an adequate regional cerebral oxygen saturation during CPB and other studies showed the association of postoperative neurological complications and the intraoperative cerebral desaturation during CPB.<sup>[26-28]</sup> Esper *et al.*,<sup>[29]</sup> reported that moderate to severe hemodilution can result in impaired oxygen-carrying capacity and tissue ischemia despite a decrease in the basal metabolic rate and affect the outcomes after cardiac surgery.

Some studies reported the association of ischemia and inflammatory tissue injury with greater hemodilution and these findings to explain the improved neurological outcomes with high hematocrit<sup>[15,30]</sup> and other studies reported the increased incidence of complications with the increased hemodilution severity.<sup>[20,31,32]</sup>

Mathew *et al.*,<sup>[33]</sup> found that extreme hemodilution was associated with severe postoperative neurocognitive impairment among older patients undergoing cardiac surgery. Karkouti *et al.*,<sup>[34]</sup> found that the odds of neurological complications increased by 10% for each 1% decrease in hematocrit during CPB.

Habib *et al.*,<sup>[9]</sup> showed that the adverse outcomes and the neurological complications after CPB were related to the degree of hemodilution severity and they are recommending to minimize on-pump hemodilutional anemia and to maintain the hematocrit value >24.5-27% to improve the outcomes after cardiac surgery.

Wypij *et al.*,<sup>[35]</sup> showed that hematocrit ≥24% was associated with higher psychomotor development index scores

**Table 4: Intraoperative Data and Outcome of Patients (Data are Presented as Mean±SD, Number, %)**

Variable	Mild hemodilution group (n=93)	Moderate hemodilution group (n=93)	P
Number of coronary artery grafts			
2	17	20	0.713
3	19	24	0.486
4	48	45	0.769
5	5	2	0.441
6	4	2	0.678
CPB time (minute)	118.30±20.57	115.69±18.40	0.363
Cross clamping time (minute)	89.13±14.50	86.79±13.90	0.262
CPB temperature (°C)	29.08±1.14	29.12±1.17	0.813
Hematocrit (%)			
10 min before CPB	36.15±3.50	36.46±3.62	0.553
15 min during CPB	27.24±1.46	23.81±1.09	0.001*
30 min during CPB	28.35±1.17	23.40±1.24	0.001*
5 min before weaning	27.30±1.22	24.02±0.65	0.001*
15 min after weaning	29.27±1.78	26.75±1.60	0.001*
End of surgery	32.10±2.30	28.18±2.14	0.001*
Hemofiltrated volume during CPB (ml)	1808.24±253.54	1294.75±210.32	0.001*
Transfused P-RBC (unit)			
During CPB	2.65±0.83	2.23±0.58	0.001*
After CPB	1.15±0.45	1.66±0.81	0.001*
Blood loss (ml)			
Intraoperative (ml)	2184.60±252.55	2250.75±268.40	0.085
Postoperative (ml/24 hr)	548.75±131.10	576.80±145.17	0.168
Intraoperative fluids			
Crystalloids (ml)	2992.54±497.43	3120.82±527.30	0.089
Hesteril 6% (ml)	625.75±135.30	652.20±143.55	0.197
Dopamine (µg/kg/min)	6.30±2.50	7.15±2.90	0.033*
Epinephrine (µg/kg/min)	0.05±0.02	0.06±0.03	0.008*
Norepinephrine (µg/kg/min)	0.04±0.01	0.07±0.02	0.001*
Nitroglycerine (µg/kg/min)	0.7±0.40	0.6±0.35	0.071
Intra-aortic balloon pump	12	27	0.011*
Pacing	17	30	0.042*
Intraoperative urine output (ml)	2142.63±181.80	2181.20±218.30	0.192
Intraoperative blood sugar levels (mmol/L)	8.19±1.30	8.02±1.23	0.360
Postoperative neurological complications			
Total	19 (20.43%)	33 (35.48%)	0.033*
Neurocognitive dysfunction	17 (18.72%)	30 (32.25%)	0.042*
Stroke	2	3	0.650
Postoperative renal impairment	6	9	0.793
Postoperative renal failure	4	3	0.700
Postoperative dialysis			
Temporarily	2	2	1.000
Permanent	2	1	0.560
Pulmonary edema	4	10	0.164
Postoperative mechanical ventilation	4	10	0.164
Allergic reaction	4	2	0.678
Hepatic complications	-	-	
Anaphylactic reaction	-	-	
Disseminated intravascular coagulopathy	-	-	
Thromboembolism	-	-	
Infection	-	-	
ICU length of stay (days)	2.78±1.17	3.02±1.24	0.176
Hospital length of stay (days)	8.15±2.53	8.32±2.41	0.639
Mortality	4	3	0.700

\*  $P < 0.05$  significant comparison between the two groups. CPB: Cardiopulmonary bypass; P-RBC: Packed- red blood cells; ICU: Intensive care unit

in infants undergoing cardiac surgery and also, it was associated with a reduction in the lactate level that indicates better tissue perfusion during CPB.

Richard A<sup>[36]</sup> showed that the hematocrit was the only CPB parameter that has an important effect on the cognitive outcome and suggested that a hematocrit of 25% be considered the lowest acceptable level with normal flow

rates for adults during CPB and the same results were reported by other studies.<sup>[34-38]</sup>

There are some recommendations to minimize the incidence of severe hemodilution during CPB:

- (1) controlling preoperative blood loss during routine preoperative phlebotomy and cardiac catheterization;

- (2) minimizing the size of CPB circuits according to patient BSA;
- (3) minimizing of the tubing size by minimizing the length and diameter of the tubes connecting the patient and pump;
- (4) returning the collected blood to the circulating volumes;
- (5) controlling the intraoperative blood loss and fluid administration;
- (6) using of retrograde autologous priming of the CPB circuit, which has been shown to reduce hemodilution and transfusion requirements<sup>[39,40]</sup>;
- (7) The acceptable hematocrit levels during CPB must be determined according to the age and co-morbidities of the patient<sup>[29]</sup>;
- (8) Transfusion of packed red blood cells is reasonable and indicated if the hemoconcentration is not possible or is ineffective to maintain the hematocrit above the required levels.<sup>[41]</sup>

There are limitations to the present study. First, the study was not a blinded study; and second, it was done in a single center.

## CONCLUSION

The mild hemodilution was associated with a significant decrease in the incidence of neurocognitive dysfunction compared to moderate hemodilution during CPB in patients undergoing coronary artery bypass grafting. Also, the transfused packed red blood cells increased during CPB and decreased after CPB with the mild hemodilution more than moderate hemodilution.

## Acknowledgments

The authors thank all staff-nurses in the operative rooms, post anesthesia care unit and intensive care unit for their efforts and performance during the study.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Intaglietta M. Hemodilution and blood substitutes. *Artif Cells Blood Substit Immobil Biotechnol* 1994;22:137-44.
2. Cooper JR, Slogoff S. Hemodilution and priming solutions for cardiopulmonary bypass. In: Gravlee GP, Davis RF, Utley JR, editors. *Cardiopulmonary Bypass Principles and Practice*. Baltimore, Md: Williams and Wilkins; 1993. p. 124-37.
3. Messmer K. Blood rheology factors and capillary blood flow. In: Gutierrez G, Vincent J-L, editors. *Tissue Oxygen Utilization*. Berlin, Heidelberg, New-York: Springer-Verlag; 1991. p. 103-13.
4. Lipowsky HH, Firrel JC. Microvascular hemodynamics during systemic hemodilution and hemoconcentration. *Am J Physiol* 1986;250:H908-22.
5. Nollert G, Sperling J, Sakamoto T, Jaeger BR, Jonas RA. Higher hematocrit improves liver blood flow and metabolism during cardiopulmonary bypass in piglets. *Thorac Cardiovasc Surg* 2001;49:226-30.
6. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, *et al.* Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg* 1995;110:1302-11.
7. Sungurtekin H, Cook DJ, Orszulak TA, Daly RC, Mullany CJ. Cerebral response to hemodilution during hypothermic cardiopulmonary bypass in adults. *Anesth Analg* 1999;89:1078-83.
8. Duebener LF, Sakamoto T, Hatsuoka S, Stamm C, Zurakowski D, Vollmar B, *et al.* Effects of hematocrit on cerebral microcirculation and tissue oxygenation during deep hypothermic bypass. *Circulation* 2001;104:260-4.
9. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? *J Thorac Cardiovasc Surg* 2003;125:1438-50.
10. Karkouti K, Beattie WS, Wijeyesundera DN, Rao V, Chan C, Dattilo KM, *et al.* Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg* 2005;129:391-400.
11. Chen Y, Berglin E, Belboul A, Roberts D. A mathematical analysis of haemorheologic factors during cardiopulmonary bypass for congenital heart disease. *Perfusion* 1995;10:431-8.
12. Chen Y, Belboul A, Berglin E, Roberts D. A mathematical analysis of hemorheological changes during heart valve replacement. *J Cardiovasc Surg* 2000;41:37-43.
13. Ereth MH, Oliver WC, Santrach PJ. Intraoperative techniques to conserve autologous blood: Red-cell salvage, platelet-rich plasma, and acute normovolemic hemodilution. In: Spiess BD, Counts RB, Gould SA, editors. *Perioperative Transfusion Medicine*. Baltimore: Williams & Wilkins; 1998. p. 325-50.
14. Niinikoski J, Lakksonon V, Meretoja O, Jalonen J, Inberg MV. Oxygen transport to tissue under normovolemic moderate and extreme hemodilution during coronary bypass operation. *Ann Thorac Surg* 1981; 31:134-43.
15. Shin'oka T, Shum-Tim D, Jonas RA, Lidov HG, Laussen PC, Miura T, *et al.* Higher hematocrit improves cerebral outcome after deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg* 1996;112:1610-20.
16. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, *et al.* Adverse cerebral outcomes after coronary bypass surgery. *N Engl J Med* 1995;335:1857-63.
17. McLean RF, Wong B. Normothermic versus hypothermic cardiopulmonary bypass: Central nervous system outcomes. *J Cardiothorac Vasc Anesth* 1996;10:45-53.
18. Croughwell ND, Newman MF, Blumenthal JA, White WD, Lewis JB, Frasco PE, *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1994;58:1702-8.
19. Kurth CD, Steven JM, Nicholson SC, Jacobs ML. Cerebral oxygenation during cardiopulmonary bypass in children. *J Thorac Cardiovasc Surg* 1997;113:71-8.
20. Fang WC, Helm RE, Krieger KH, Rosengart TK, Du Bois WJ, Sason C, *et al.* Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. *Circulation* 1997;96:II-194-9.
21. De Foe GR, Ross CS, Olmstead EM, Surgenor SD, Fillinger MP, Groom RC, *et al.* Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. *Ann Thorac Surg* 2001;71:769-76.

22. Jonas RA, Wypij D, Roth SJ, Bellinger DC, Visconti KJ, du Plessis AJ, *et al.* The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: Results of a randomized trial in infants. *J Thorac Cardiovasc Surg* 2003;126:1765-74.
23. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg* 2003;76:784-92.
24. McCusker K, Chalafant A, de Foe G, Gunaydin S, Vijay V. Influence of hematocrit and pump prime on cerebral oxygen saturation in on-pump coronary revascularization. *Perfusion* 2006;21:149-55.
25. Vijay V, McCusker K, Sarabu M. Cerebral oximetry based comparison of cerebral perfusion with standard versus condensed extra-corporeal circuits in adult cardiac surgery. *Heart Surg Forum* 2003;6:4.
26. Yao FS, Tseng CC, Ho CY, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2004;18:552-8.
27. Holmgaard F, Vedel AG, Langkilde A, Lange T, Nilsson JC, Ravn HB. Differences in regional cerebral oximetry during cardiac surgery for patients with or without postoperative cerebral ischaemic lesions evaluated by magnetic resonance imaging. *Br J Anaesth* 2018;121:1203-11.
28. Colak Z, Borojevic M, Bogovic A, Ivancan V, Biocina B, Majeric-Kogler V. Influence of intraoperative cerebral oximetry monitoring on neurocognitive function after coronary artery bypass surgery: A randomized, prospective study. *Eur J Cardiothorac Surg* 2015;47:447-54.
29. Esper SA, Subramaniam K, Tanaka KA. Pathophysiology of cardiopulmonary bypass: Current strategies for the prevention and treatment of anemia, coagulopathy, and organ dysfunction. *Semin Cardiothorac Vasc Anesth* 2014;18:161-76.
30. Shin'oka T, Shum-Tim D, Laussen PC, Zinkovskiy SM, Lidov HG, du Plessis A, *et al.* Effects of oncotic pressure and hematocrit on outcome after circulatory arrest. *Ann Thorac Surg* 1998;65:155-64.
31. DeFoe GR, Ross CS, Olmstead EM, Surgenor SD, Fillingner MP, Groom RC, *et al.* Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. *Ann Thorac Surg* 2001;71:769-76.
32. Hardy JF, Martineau R, Couturier A, Belisle S, Cartier R, Carrier M. Influence of haemoglobin concentration after extracorporeal circulation on mortality and morbidity in patients undergoing cardiac surgery. *Br J Anaesth* 1998;81:38-45.
33. Mathew JP, Mackensen GB, Phillips-Bute B, Stafford-Smith M, Podgoreanu MV, Grocott HP, *et al.* Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. *Anesthesiology* 2007;107:577-84.
34. Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijesundera D, *et al.* Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *Ann Thorac Surg* 2005;80:138-7.
35. Wypij D, Jonas RA, Bellinger DC, Del Nido PJ, Mayer JE Jr, Bacha EA, *et al.* The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: Results from the combined Boston hematocrit trials. *J Thorac Cardiovasc Surg* 2008;135:355-60.
36. Richard A. Optimal hematocrit for adult cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2001;15:672.
37. Soenarto RF, Arbi A. Effect of oxygen content on postoperative cognitive dysfunction in patients undergoing open-heart surgery. *J Nat Sc Biol Med* 2019;10:S7-10.
38. Ranucci M, Conti D, Castelvechio S, Menicanti L, Frigiola A, Andrea Ballotta, Pelissero G. Hematocrit on cardiopulmonary bypass and outcome after coronary surgery in nontransfused patients. *Ann Thorac Surg* 2010;89:11-17.
39. Rosengart TK, Debois W, O'Hara M, Hartman GS, Isom OW, Krieger KH, *et al.* Retrograde autologous priming for cardiopulmonary bypass. A safe and effective means of decreasing hemodilution and transfusion requirements. *J Thorac Cardiovasc Surg* 1998;115:426-39.
40. Subramaniam B, Cross MH, Karthikeyan S, Mulpur A, Hansbro SD, Hobson P. Retrograde autologous priming of the cardiopulmonary bypass circuit reduces blood transfusion after coronary artery surgery. *Ann Thorac Surg* 2002;73:1912-8.
41. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, *et al.* Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med* 2017;377:2133-44.