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Cerebral effects of different prime solutions used during cardiopulmonary bypass

Kardiyopulmoner baypas sırasında kullanılan farklı prime solüsyonlarının serebral etkileri

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ABSTRACT

Background: This study aims to compare the cerebral, hemodynamic, and metabolic effects of different prime solutions used in patients undergoing coronary artery bypass grafting.

Methods: Between May 2013 and May 2014, a total of 30 patients (25 males, 5 females; mean age: 59.5±9 years; range, 42 to 78 years) who were schedule for elective isolated coronary artery bypass grafting were included in this prospective study. The patients were randomized into three groups: Group 1 (n=10) (ringer's lactate [RL]), Group 2 (n=10) (6% hydroxyethyl starch [HES] 130/0.4), and Group 3 (n=10) (RL + 6% HES 130/0.4). Hemodynamic parameters, arterial blood gas analyses, hemoglobin, hematocrit, cerebral regional oxygen saturation, urine output and fluid balance were recorded preoperatively, before and after anesthesia, 10 min after the transition to extracorporeal circulation, while weaning from extracorporeal circulation, and at the end of surgery. Preoperatively and on postoperative Day 5, neuron-specific enolase enzyme and S-100 β protein were assessed. On Day 5 and Week 3 postoperatively, the Standardized Mini-Mental Test was administered to the patients.

Results: The serum neuron-specific enolase enzyme and S-100 β protein levels of the patients were within physiological limits, and there were no clinical findings suggestive of cerebral damage, or changes in the Standardized Mini-Mental Test scores in any of the patients. There was a decrease of more than 20% of the baseline value of cerebral regional oxygen saturation in a total of four patients, one in Group 1 and three in Group 3. No significant difference was observed among the groups in terms of the other parameters.

Conclusion: The prime solution content has no effect on the development of cerebral damage after cardiopulmonary bypass, and the main factor in preventing the development of cerebral damage was the preservation of cerebral perfusion, which can be achieved by monitoring cerebral perfusion in these patients.

Keywords: Cardiopulmonary bypass, cerebral damage, neuron-specific enolase enzyme, prime solution, S-100 β protein, standardized mini-mental state examination.

ÖZ

Amaç: Bu çalışmada koroner arter baypas greftleme yapılan hastalarda prime solüsyonlarının serebral, hemodinamik ve metabolik etkileri karşılaştırıldı.

Çalışma planı: Bu prospektif çalışmaya Mayıs 2013-Mayıs 2014 tarihleri arasında elektif izole koroner arter baypas greftleme yapılacak toplam 30 hasta (25 erkek, 5 kadın; ort. yaş: 59.5±9 yıl; dağılım, 42-78 yıl) alındı. Hastalar üç gruba randomize edildi: Grup 1 (n=10) (Ringer laktat [RL]), Grup 2 (n=10) (%6 hidroksietil nişasta [HES] 130/0.4) ve Grup 3 (n=10) (RL + %6 HES 130/0.4). Hastaların ameliyat öncesi, anestezi öncesi ve sonrası, ekstrakorporeal dolaşıma geçişinden 10 dk. sonra, ekstrakorporeal dolaşımdan çıkıldığında ve ameliyat sonunda hemodinamik parametreleri, arteriyel kan gazı analizleri, hemoglobin, hematokrit, serebral rejyonel oksijen satürasyonu, idrar çıkışı ve sıvı dengesi kaydedildi. Nöron spesifik enolaz enzimi ve S-100 β proteini ameliyat öncesi ve ameliyat sonrası beşinci günde ölçüldü. Hastalara ameliyat sonrası beşinci gün ve üçüncü haftada Standardize Mini Mental Test uygulandı.

Bulgular: Hastaların serum Nöron spesifik enolaz enzimi ve S-100 β protein düzeyleri fizyolojik sınırlar içinde olup, hiçbir hastada serebral hasarı düşündürecek klinik bulguya ve Standardize Mini Mental Test skor değişikliğine rastlanmadı. Biri Grup 1 ve üçü Grup 3 olmak üzere toplam dört hastada serebral rejyonel oksijen satürasyonunda başlangıca kıyasla %20'den fazla düşüş izlendi. Diğer parametreler açısından gruplar arasında anlamlı bir fark saptanmadı.

Sonuç: Kardiyopulmoner baypas sonrası serebral hasar gelişiminde prime solüsyon içeriğinin herhangi bir etkisi olmamakla birlikte, serebral hasar gelişiminin önlenmesinde en önemli nokta serebral perfüzyonun korunmasıdır; bu da hastaların serebral perfüzyonları takip edilerek sağlanabilir.

Anahtar sözcükler: Kardiyopulmoner baypas, serebral hasar, nöron spesifik enolaz enzimi, prime solüsyonu, S-100 β proteini, standardize mini mental test.

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Cardiopulmonary bypass (CPB) is a procedure in which the heart and lungs are excluded from circulation, and gas exchange occurs outside the body through the heart-lung pump; extracorporeal circulation (ECC).[1] The incidence of postoperative cognitive dysfunction after open heart surgery is 70%, and that of clinically significant neurological damage is 2 to 5%.[2]

The ECC circuit lines, oxygenator, and venous reservoir to must be filled with fluid, and air must be removed from the system. The fluid used for this purpose is called the 'prime solution', and the process is called 'priming'.[1] With the introduction of ECC into open heart surgery, blood and different crystalloid and colloid solutions have been used as the prime solution.[3] Non-pulsatile blood flow, hypothermia, and contact of blood with a foreign surface during ECC can lead to metabolic, hemodynamic, and organ function changes when combined with other factors, such as hemodilution and electrolyte changes.[4,5]

Several studies have demonstrated that high neuron-specific enolase (NSE) enzyme and S-100 β protein levels in blood samples taken at the postoperative 24th h show a significant correlation with the development of cerebral damage.[6,7]

The primary objective of our study was to investigate the effect of different prime solutions used during CPB on the cerebral damage. For this purpose, biomarkers and neurocognitive functions of patients by evaluating cerebral regional oxygen saturation (rSO_2), preoperative and postoperative NSE and S-100 β protein levels, and Standardized Mini-Mental State Examination (SMMSE) scores, as well as standard monitorization parameters were recorded. Our secondary objective was to evaluate the hemodynamic and metabolic effects of these solutions.

PATIENTS AND METHODS

This prospective study was conducted at Acıbadem Kadıköy Hospital, Department of Cardiovascular Surgery Operating Room between May 2013 and May 2014. A total of 30 patients (25 males, 5 females; mean age: 59.5±9 years; range, 42 to 78 years) who were scheduled to undergo elective isolated coronary artery bypass grafting (CABG) with ECC were included. Exclusion criteria were as follows: ejection fraction (EF) <50%, emergency surgery, presence of previous cardiac surgery, presence of additional systemic disease other than coronary artery disease and hypertension, acute myocardial infarction, detection of carotid artery stenosis, hematocrit (Hct) value <30%, application of blood product therapy (since the destruction of erythrocytes, particularly increased NSE enzyme would impair the sensitivity of cerebral damage markers), and preoperative SMMSE scores <25.

The patients were randomly assigned to three groups according to the prime solution to be used.

Group 1: Ringer's lactate (RL) solution constituting the whole prime solution (1,100 mL)

Group 2: 6% hydroxyethyl starch (HES) 130/0.4 constituting the whole prime solution (1,100 mL)

Group 3: RL solution constituting half (550 mL) and 6% HES 130/0.4 constituting the other half (550 mL) of the prime solution.

In addition, 150 mL of mannitol, 60 mL of sodium bicarbonate, and 2 mL (5,000 IU) of heparin were added to the prime solution in each group.

Standard electrocardiography and pulse oximetry monitoring were undertaken, arterial catheterization and arterial blood gas parameters were recorded. Anesthesia was induced with 10 μg/kg of fentanyl and 2 mg/kg of propofol, and neuromuscular blockade with 0.1 mg/kg of vecuronium bromide. Anesthesia was maintained with the target-controlled infusion technique, providing a serum propofol level of 3 μg/mL, fentanyl level of 5 ng/dL, and vecuronium by infusion at a rate of 0.1 mg/kg/h.

During CPB, the mean arterial pressure (MAP) was kept at 50 to 80 mmHg, and the body temperature in the range of 32 to 34°C under moderate hypothermia.

In the monitoring of the adequacy of cerebral perfusion, a decrease of more than 20% from the baseline value measured using the INVOS™ (Covidien, Somnetics, Troy, MI, USA) monitor based on the near-infrared spectroscopy (NIRS) technique was considered clinically significant.[8]

When there was a decrease in the regional oxygen saturation (rSO_2) value, the hemodynamic parameters, blood gas parameters, and Hct levels were evaluated, and interventions were made to increase the pump flow, inspired oxygen fraction (FiO_2), or MAP, according to the individual requirements. In addition, tissue oxygenation was evaluated using the InSpectra™ tissue oxygenation saturation (StO_2) (Hutchinson Technology Inc., Hutchinson, MN, USA) monitor equipped with a probe attached to the thenar region of the hand. Accepting the clinical lower limit value indicating tissue perfusion disorder as 70 to 75%, the peripheral

StO_2 monitoring of all patients was undertaken, and the data were recorded.

Cerebral damage markers were identified using the electrochemiluminescence immune assay technique using the serum samples obtained from the blood taken before the induction of preoperative anesthesia and at the postoperative 24th h. Data were recorded using the Cobas e 601® analyzer (Roche Diagnostics, Mannheim, Germany) and the sandwich test principle. A value above 17 ng/mL for the NSE enzyme and above 0.10 μg/mL for S-100 β protein were considered abnormal.

The patients' SMMSE scores were recorded one day before the operation, on the fifth postoperative day, and at the third postoperative week to evaluate their neurocognitive status before and after the operation.

Other parameters that were evaluated were as follows: hemodynamic parameters, arterial blood gas parameters, right and left rSO_2 and StO_2 values before and after anesthesia, at 10 min and end of ECC, and after the operation; pump flow, pump line pressure, FiO_2, and body temperature during ECC; hemodynamic parameters, arterial blood gas parameters, hemoglobin (Hb), Hct, urine output, and fluid balance at the postoperative 1, 2, 4, 8, and 20 h; amounts of vasoconstrictor and vasodilator drugs used during the operation and stay in the intensive care unit (ICU); complete blood count, biochemistry, C-reactive protein, prothrombin time, activated partial thromboplastin time, and thrombin time preoperatively and on postoperative Days 1, 2, and 4; CPB time; postoperative intubation time; length of stay in ICU and hospital; amount of drainage at the end of the postoperative 24 h; and complications.

Statistical analysis

Statistical analysis was performed using the Graphad Prism version 5.0 software (GraphPad Software, San Diego, CA, USA). In the analysis performed with G*Power version 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), the sample size for each group was found to be 10, when the power was 80%, the type I alpha error was 0.05, the effect size was 67% according to the postoperative neurocognitive changes as the primary outcome.[9]

Descriptive data were expressed in mean ± standard deviation (SD), median and interquartile range (IQR) or number and frequency, where applicable. The data obtained were statistically compared between and within the three groups according to the different time points. The data were compared with the Tukey post-hoc test, following the one-way analysis of variance (ANOVA) for three groups at the same time point, after investigating their compliance with a normal distribution according to the Kolmogorov-Smirnov test. The paired-samples t-test was used to compare postoperative NSE enzyme and S-100 β protein values with preoperative values, accepting $p<0.05$ as the level of significance, $p<0.01$ as a high level of significance, and $p<0.001$ as a very high level of significance.

Table 1. Patients' demographic characteristics

	Group 1			Group 2			Group 3			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			63.2±3.5			56.1±2.9			59.3±1.7	>0.05
Female patients	2	20		2	20		1	10		>0.05
Male patients	8	80		8	80		9	90		>0.05
Body surface area (m^2)			1.9±0.1			1.9±0.1			1.9±0.0	>0.05
Preoperative EF (%)			59.4±1.5			63.3±2.8			60.0±2.2	>0.05
Number of arteries			2.8±0.3			2.9±0.2			2.9±0.2	>0.05
Cross-clamp time (min)			36.1±4.8			39.8±3.3			34.4±3.0	>0.05
CPB time (min)			59.9±6.7			67.7±3.3			63.9±4.0	>0.05
Length of ICU stay (hour)			21.5±0.5			21.2±0.9			23.1±0.7	>0.05
Length of hospital stay (day)			6.3±0.4			6.9±0.8			6.0±0.3	>0.05

SD: Standard deviation; EF: Ejection fraction; CPB: Cardiopulmonary bypass; ICU: Intensive care unit; Group 1: Ringer; Group 2: HES 6%; Group 3: Ringer + HES 6%.

TABLE 2. S-100β protein and NSE enzyme levels of the patients

	S-100β preoperative	S-100β postoperative 24th h	*p*	NSE preoperative	NSE postoperative 24th h	*p*
Group 1	0.05 µg/mL	0.09 µg/mL	>0.05	1.89 ng/mL	4.37 ng/mL	>0.05
Group 2	0.07 µg/mL	0.08 µg/mL	>0.05	3.05 ng/mL	3.93 ng/mL	>0.05
Group 3	0.08 µg/mL	0.07 µg/mL	>0.05	1.63 ng/mL	3.95 ng/mL	<0.01

NSE: Neuron-specific enolase; Group 1: Ringer; Group 2: HES 6%; Group 3: Ringer + HES 6%.

RESULTS

The demographic data of the patients are given in Table 1. There was no significant difference among the groups in terms of demographic data (p>0.05) (Table 1).

The pre- and postoperative 24-h serum S-100 β protein and NSE enzyme levels of the patients were within clinically normal limits, and when the changes in the S-100 β protein values were statistically analyzed, no significant difference was observed among the three groups (Table 2). When the

Table 3. Patients' hemodynamic parameters

	Group 1	Group 2	Group 3	
	Mean±SD	Mean±SD	Mean±SD	*p*
Heart rate (beats/min)				
Before anesthesia induction	69.3±4.2	74.6±3.1	72.2±3.9	>0.05
After anesthesia induction	57.6±3.5	61.3±3.7	58.7±3.4	>0.05
End of ECC	67.0±4.0	73.4±3.1	70.8±6.5	>0.05
End of operation	68.4±4.0	74.3±4.4	76.2±4.8	>0.05
Postoperative hour 1	78.4±6.2	84.7±3.9	84.1±5.3	>0.05
Postoperative hour 20	85.7±4.7	87.4±2.6	93.3±3.6	>0.05
Mean arterial pressure (mmHg)				
Before anesthesia induction	91.4±5.2	99.4±5.0	91.9±3.2	>0.05
After anesthesia induction	80.4±2.9	82.5±4.5	79.1±5.6	>0.05
10th min of ECC	56.2±5.7	59.7±2.9	67.4±3.6	>0.05
End of ECC	60.9±4.5	59.7±2.6	61.3±3.2	>0.05
End of operation	72.6±4.5	73.7±4.7	69.4±2.3	>0.05
Postoperative hour 1	88.9±4.7	84.7±4.4	93.4±5.3	>0.05
Postoperative hour 20	81.6±3.2	77.6±2.9	79.7±2.9	>0.05
Hemoglobin values (g/dL)				
Preoperative	13.5±0.4	14.1±0.5	14.4±0.5	>0.05
Before anesthesia induction	13.2±0.5	14.2±0.5	14.1±0.4	>0.05
After anesthesia induction	12.2±0.4	13.2±0.5	12.9±0.5	>0.05
10th min of ECC	8.3±8.3	8.3±0.3	8.6±0.3	<0.01
End of ECC	8.9±0.6	8.7±0.4	9.4±0.3	>0.05
End of operation	9.7±0.5	9.2±0.5	9.9±0.3	>0.05
Hematocrit values (%)				
Preoperative	41.6±1.0	43.0±1.5	43.7±1.1	>0.05
Before anesthesia induction	40.5±1.4	43.6±1.4	43.2±1.3	>0.05
After anesthesia induction	37.6±1.3	40.6±1.4	39.6±1.4	>0.05
10th min of ECC	25.9±1.6	26.0±1.0	26.7±0.8	<0.01
End of ECC	27.5±1.8	27.0±1.1	29.1±0.9	>0.05
End of operation	30.2±1.6	28.6±1.3	30.5±0.8	>0.05

SD: Standard deviation; ECC: Extracorporeal circulation; Group 1: Ringer; Group 2: HES 6%; Group 3: Ringer + HES 6%.

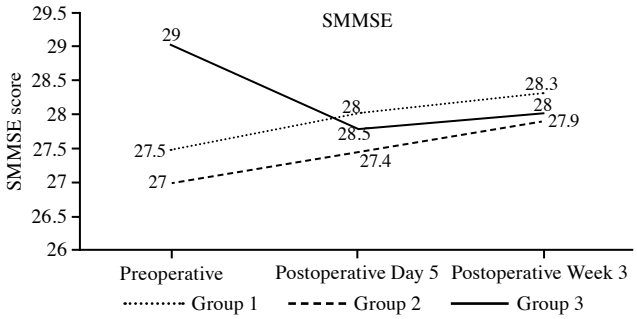

Figure 1. Comparison of the preoperative, postoperative 5th-day and postoperative 3rd-week SMMSE scores of the groups.
SMMSE: Standardized mini-mental state examination.

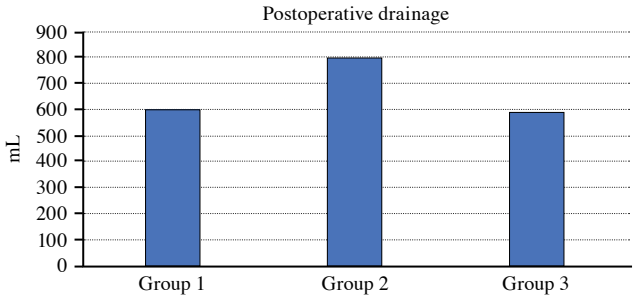

Figure 2. Postoperative drainage amounts of the groups.

changes in the values of the NSE enzyme from the preoperative period to the postoperative 24 h were statistically analyzed, no significant difference was found in Groups 1 and 2, although the increase was statistically significant in Group 3, but not clinically significant ($p<0.01$).

We evaluated SMMSE scores, and no patient scored below 25 at any measurement period and no significant difference was found among the groups ($p>0.05$) (Figure 1).

Furthermore, there was no statistically significant difference among the groups in terms of heart rate and MAP ($p>0.05$). According to the intra-group comparisons, there was a significant decrease in Hb and Hct at 10-min of ECC compared to baseline in all three groups ($p<0.001$) (Table 3).

Concerning rSO_2 and StO_2 values of the patients, there was no statistically significant decrease in any evaluation period, and in the comparison performed between the groups ($p>0.05$) (Table 4).

A clinically significant (>20%) decrease was observed in the intraoperative rSO_2 value of one patient in Group 2 and three patients in Group 3, and interventions were performed with an increase in the FiO_2 level. In one case where a decrease in rSO_2 was accompanied by reduced MAP, a positive inotropic agent was administered.

The postoperative drainage amount was higher in Group 2 than in Groups 1 and 3; however, there was no statistically significant difference between the groups ($p>0.05$) (Figure 2).

Table 4. Right and left rSO_2, and StO_2 values of the patients

	Group 1	Group 2	Group 3	*p*
	Mean±SD	Mean±SD	Mean±SD	
Right rSO_2				
Before anesthesia induction	62.6±2.1	66.4±2.9	65.4±2.2	>0.05
After anesthesia induction	63.6±2.2	66.1±3.5	62.5±2.1	>0.05
10th min of ECC	64.1±1.5	59.7±2.8	60.1±2.7	>0.05
End of ECC	62.5±2.4	57.9±2.9	55.0±2.4	>0.05
End of operation	59.4±1.8	58.4±2.5	54.9±2.0	>0.05
Left rSO_2				
Before anesthesia induction	64.8±2.4	63.8±1.6	66.8±2.2	>0.05
After anesthesia induction	66.2±1.9	65.6±2.4	65.2±2.8	>0.05
10th min of ECC	65.4±1.9	58.4±1.2	61.6±2.3	>0.05
End of ECC	62.6±2.4	55.9±1.5	60.9±2.7	>0.05
End of operation	59.9±2.5	58.5±1.8	58.6±2.4	>0.05

SD: Standard deviation; rSO_2: Cerebral regional oxygen saturation; ECC: Extracorporeal circulation; Group 1: Ringer; Group 2: HES 6%; Group 3: Ringer + HES 6%.

DISCUSSION

Cerebral complications are one of the major causes of morbidity associated with CPB. Hemodilution and electrolyte changes occur, which are the most important causes of CPB-related complications; interstitial edema as a result of decreased plasma colloid oncotic pressure, and may adversely affect oxygen distribution to tissues and functions of many organs, particularly the brain.[10-12]

In our study, we compared the hemodynamic and metabolic effects of the use of three different prime solutions on the development of cerebral damage. It is well known that the NSE enzyme is also present in the cell membrane of erythrocytes and platelets and increases in blood with hemolysis.[13,14] We considered that the differences in cross-clamp (CC) and CPB times among the groups could affect the NSE enzyme level. However, when we examined the CC and CPB times of our patients, there was no significant difference among the groups. In a study, comparing the effects of HES and RL prime solutions on the preservation of cerebral tissue in CPB, there was no significant difference between the groups in terms of the S-100 β protein levels, and the authors found the HES prime solution to produce more significant positive results in informative cognitive tests.[15]

The SMMSE is a testing technique commonly used to assess cognitive abilities in Alzheimer's disease, dementia, and pre- and postoperative periods.[16,17] It enhances inter-rater reliability by incorporating specific administration and scoring instructions. Our population has never had a SMMSE score of under 25, indicating normal results. Also, no statistically significant difference was found among the groups in terms of the SMMSE scores ($p<0.05$).

With the beginning of ECC, the prime solution enters the circulation and, as a result, hemodilution develops.[4,10,11] In our study, according to the literature there was a significant dilutional decrease in the Hb and Hct values compared to the preoperative levels.[4,10,11,18] The lowest values in all the groups were determined at 10-min of ECC, and the content of the prime solution did not cause any changes in the Hb and Hct values due to hemodilution.

There are conflicting reports concerning the effects of HES solution on the kidney. While some studies histologically showed that the infusion of HES solution caused osmotic nephrosis-like swelling in renal tubular cells, resulting in tubular obstruction and medullary ischemia, leading to acute renal failure,[19,20] the others reported that the positive fluid balance decreased and renal function was not adversely affected in pediatric and adult cases in which HES was used as the prime solution.[10,11,18] According to the data we obtained from our study, renal function was not adversely affected by the use of HES solution. In the postoperative period, no patient developed a clinical picture consistent with renal damage.

Similar to their effects on renal function, colloid solutions have also been reported to have different effects on hemostasis. In a study undergoing CABG with RL or RL + HES as the prime solution, Damar et al.[21] found no significant difference between the groups in terms of the amount of postoperative bleeding, prothrombin time, international normalized ratio (INR), sodium (Na), potassium (K), urea, creatinine, and pH values, which is in agreement with our findings. In contrast, in another study, the use of HES as the prime solution increased the amount of bleeding, need for transfusion, and rate of re-operation due to bleeding.[22] In a study where two different molecular-weight HES solutions were compared with albumin, although there was no significant difference in platelet count and function, the thrombin was not stable in patients using high-molecular-weight HES, causing more bleeding, and the use of low-molecular-weight HES did not reduce these risks.[22] Russel et al.,[23] comparing the effects of albumin and crystalloid solutions on hemostasis, reported that platelet count was better preserved in cases where albumin was used. In another study, Ünlü et al.[24] used albumin, HES, and isotonic prime solutions and showed that postoperative drainage was less with the use of albumin and HES. Also, in a study comparing the use of dextran-based colloid prime and crystalloid prime during surgery found no significant difference about neurological or neurocognitive symptoms.[7]

On the other hand, there are some new priming solutions as dextran 40 which has an electrolyte composition that mimics extracellular fluid. In a study comparing dextran 40 and standard crystalloid based prime during surgery found that dextran 40 preserved colloid oncotic pressure better than crystalloid based prime.[25] In our study, we observed that similar results were obtained in all parameters related to hemostasis, and platelet counts and postoperative drainage amounts did not significantly differ according to the prime solution content.

It is known that colloid solutions have a high molecular weight and oncotic pressure, thus, more effective in maintaining plasma colloid pressure and remain in the intravascular space longer than

crystalloid solutions.[9] In our study, the additional fluid requirement taken into the heart-lung pump during CPB; i.e., the CPB balance was found to be significantly reduced in Groups 2 and 3 compared to Group 1, supporting the results of previous studies.

Nonetheless, our study has some limitations. First, it would be advantageous to obtain additional information regarding the patient's prior medical history. Therefore, we could analyze the patient's neuroprognosis more accurately. Future research may include information on the duration of the surgery, the amount of blood lost during the procedure, and variations in surgical techniques. Second, patients may be compared more fairly using comorbidity indexes, such as the Charlson Comorbidity Index.

In conclusion, based on the clinical and laboratory data, the content of the prime solution has no effect on the development of cerebral damage, or metabolic and hemodynamic changes after cardiopulmonary bypass. The main factor in preventing the development of cerebral damage seems to be the preservation of cerebral perfusion, and this can be achieved by preventing cerebral desaturation by closely monitoring cerebral perfusion in these patients.

Ethics Committee Approval: The study protocol was approved by the Acıbadem University Medical Research Evaluation Commission (date: 26.05.2013, no: 213-475). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea: F.T., J.S.K.; Design, references and fundings: F.T., J.S.K.; Control/supervision: F.T.; Data collection and/or processing, literature review: J.S.K.; Writing article: J.S.K.; Critical review: F.T.; Materials: J.S.K.; Other: J.S.K.

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