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Efficacy of Hemoperfusion Cartridge Procedure on Patients Undergoing Cardiac Valve Replacement Surgery with Cardiopulmonary Bypass

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ABSTRACT

Objectives: Cardiopulmonary bypass (CPB) induces inflammatory homeostasis dysregulation, closely related to many postoperative adverse effects. Minimizing the systemic inflammatory response to CPB is imperative to improving cardiac surgery safety. This study aimed to retrospectively evaluate the efficacy of the hemoperfusion cartridge, a device recently designed for extracorporeal blood purification to remove cytokines from the blood for patients undergoing cardiac valve replacement surgery using CPB.

Methods: The hemoperfusion (HP) group consisted of 138 patients, who underwent a hemoperfusion cartridge procedure during CPB. The control group included 149 patients, who received standard CPB management. The evaluated indices included inflammatory cytokines, blood biochemical indices, and postoperative outcome indices.

Results: Patients in the HP group had relatively lower interleukin (IL)-6 levels (days one and two post-CPB) and IL-8 (day one post-CPB) compared with the control group. Some relatively decreased biochemical blood indices also were observed in the HP group, including a significantly lower lactic acid level (days one, two, and three post-CPB), platelet counts (days one, two, and three post-CPB), and aspartate aminotransferase (days one and three post-CPB). Regarding the postoperative outcomes, no severe complications occurred in the patients; however, the HP group required less ventilation time than the control group.

Conclusions: The hemoperfusion cartridge seems promising in limiting the inflammatory reactions during CPB, with noteworthy potential for application in cardiac surgery.

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INTRODUCTION

Cardiopulmonary bypass (CPB) is an indispensable cardiac surgery technique that temporarily replaces the patient's heart and lung function during an open-heart surgery with bloodless vision. Despite the rapid development of biocompatible materials in CPB equipment, this technique inevitably possesses inherent risks, such as severe inflammation reactions. Blood contact with the artificial CPB circuit material damages blood cells and activates monocytes/macrophages [Bojan 2019]. The cross-clamping trauma, cardioplegic arrest, and heartbeat recovery also lead to ischemia-reperfusion injury [Evora 2016]. These factors trigger inflammatory cytokines and induce inflammatory homeostasis dysregulation. Significantly increased inflammatory mediators are observed during CPB, including complement, histamine, interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) [Evora 2016; Bronicki 2016; Jenke 2021]. The resulting systemic inflammation is closely related to many postoperative adverse effects, including arrhythmias, hemodynamic instability, pulmonary infections, and acute organ failure. The incidence of systemic inflammatory response syndrome in patients undergoing CPB can reach 40% without effective treatment [Delannoy 2009]. Therefore, minimizing the systemic inflammatory response to CPB is imperative to improving cardiac surgery safety.

Several strategies have been developed to limit CPB-induced inflammatory reactions, including perioperative management [Saračević 2020; Missault 2020], pharmaceutical interventions [Cardoso 2021; Lomivorotov 2020], and CPB equipment modification [Gorjipour 2017; Bauer 2018]. However, none of these methods is sufficient, due to the relatively narrow indication, adverse drug reaction, or cost. Filtration techniques, such as hemoperfusion cartridges (CytosorbTM cartridges and the JafronTM HA cartridges series), recently have been applied to curb inflammation. These devices are appealing because of their effective blood purification capabilities. Notably, the hemoperfusion cartridge contains biocompatible sorbent beads made from a porous resin polymer that adsorbs and captures inflammatory cytokines as blood flows through the device [Landis 2014]. This removes the cytokines and minimizes the systemic inflammatory response, as observed in several severe diseases, including multiple organ dysfunction syndromes [De Rosa 2020], sepsis [Houschyar

2017], and 2019 coronavirus disease [Ronco 2021; Iannaccone 2020]. Hemoperfusion cartridge not only corrected the imbalance of inflammatory mediators but also improved hemodynamics [Bonavia 2018], reduced vasopressor use [He 2022], and shortened the length of hospital stay [Houschyar 2017; He 2022]. Compared with perioperative management or pharmaceutical interventions, a hemoperfusion cartridge offers additional advantages of a direct and technically easier implementation without adverse drug reactions [Ronco 2022].

The hemoperfusion cartridge easily can be integrated with other therapies, such as dialysis [Ronco 2022] and continuous renal replacement therapy (CRRT) [Bonavia 2018]; however, research efforts focusing on combining this technique with CPB remain at the initial stage and induce some conflicting perspectives. Some studies suggest that hemoperfusion cartridge might absorb IL-6, IL-8, and IL-10 released during CPB and induce a long-lasting anti-inflammatory effect [He 2022; Bernardi 2016], indicating a novel approach to improve cardiac surgery prognosis. However, some studies described that hemoperfusion failed to demonstrate a reduction in postoperative organ dysfunction in patients undergoing cardiac surgery [Diab 2022] or in ECMO for treatment of COVID-19 [Stockmann 2022; Supady 2021]. Therefore, this study aimed to evaluate hemoperfusion cartridge efficacy in patients undergoing cardiac valve replacement surgery using CPB.

MATERIALS AND METHODS

Study design: Data retrospectively were collected from 287 adult patients, who underwent cardiac valve replacement surgery between January 2020 and January 2022 at the General Hospital of Western Theater Command. The inclusion criteria were: (1) age > 18 years, (2) patients with valvular heart disease diagnosed using cardiac color Doppler ultrasound, and (3) patients undergoing cardiac valve replacement surgery. The exclusion criteria were: (1) patients who underwent emergency or redo cardiac surgery, (2) preoperative platelet count < 100 × 109/L, (3) patients requiring preoperative blood transfusion, and (4) patients requiring concurrent coronary artery bypass grafting or vascular surgery.

Finally, the hemoperfusion group (HP) included 138 patients. The control group comprised 149 patients who met the same inclusion and exclusion criteria. The patients in the control group were matched, in terms of sex, age, weight, height, body mass index (BMI), preoperative ejection fraction (EF), preoperative left ventricular end-diastolic diameter (LVEDD), diagnosis, surgical procedures, total surgery time, CPB time, and cross-clamp time for comparisons with the HP group.

This research was conducted in compliance with the Declaration of Helsinki, and the Institutional Ethical Review Board of the General Hospital of Western Theater Command approved the study (2020ky013). Each recruited patient provided written informed consent.

Hemoperfusion cartridge procedure: The hemoperfusion cartridges (HA380, JafronTM HA cartridges series, Zhuhai, China) were used in the HP group. Heparin (100 mg) was injected into the hemoperfusion cartridge, and then it was turned over and thoroughly shaken for 30 s. After incubating for 30 min, the hemoperfusion cartridge was washed using 1000 mL lactated Ringer's solution. Subsequently, the hemoperfusion cartridge was connected to the CPB circuit. During hemoperfusion, the blood flow rate through the HA380 cartridge was set at 200–300 mL/min, and the perfusion and CPB time were the same. Hemoperfusion cartridges were not used in the control group.

Anesthesia induction, surgical procedures, and CPB management strategies: The HP and control groups received the same anesthesia induction, surgical procedures, and CPB management strategies. Midazolam (0.2–0.3 mg/kg), propofol (1–2 mg/kg), etomidate (0.3 mg/kg), fentanyl (20–30 μg/kg), and vecuronium (induction dose 0.1 mg/kg), were used to induce and maintain anesthesia. The SORIN Stockert SC heart-lung machine (Freiburg, Germany) and Terumo RX25 oxygenator (Tokyo, Japan) were applied for CPB. When the CPB procedure began, the whole body was cooled down. After the nasopharyngeal temperature reached 32°C, the ascending aorta was blocked. Cardiac arrest was induced using anterograde perfusion of histidine-tryptophan-ketoglutarate cardioplegia solution (CUSTODIOLTM, Bensheim, Germany) through the root of the aorta. During the CPB procedure, circulatory support was maintained using a 2.0–2.4 L/m2/min perfusion flow rate, 60–80 mmHg average arterial pressure, 75 ± 10% mixed venous oxygen saturation, 25–30 % of target hematocrit, and 28–32°C of nasopharyngeal temperature.

Outcome measures – inflammatory cytokines: Inflammatory cytokines (IL-6, IL-8, and TNF-α) were measured at the following time points: V0 (pre-CPB), V1 (CPB 30 min), V2 (1 d post-CPB), V3 (2 d post-CPB), and V4 (3 d post-CPB). The Department of Laboratory Medicine collected and detected blood samples.

Blood biochemical indices: Blood samples for lactic acid (Lac), international normalized ratio (INR), platelet counts (PLT), brain natriuretic peptide (BNP), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cre), carbamide (Urea), creatinine clearance rate (Ccr), troponin (Tn), creatine kinase MB form (CK-MB), and myoglobin (Mb) were determined at the following time points: T0 (pre-CPB), T1 (post-CPB 1 d), T2 (post-CPB 2 d), and T3 (post-CPB 3 d). The Department of Laboratory Medicine collected the blood samples and detected the levels of each index.

Postoperative outcome indices: The complications, blood transfusion, and intensive care unit (ICU) results were recorded, including incidence of pneumonia, renal failure, cerebrovascular events and reoperation for postoperative bleeding, usage of specific blood products, usage of intra-aortic balloon pump (IABP), CRRT, and extracorporeal membrane oxygenation (ECMO), ventilation time, ICU stay time, and hospital stay time.

Statistical analysis: The Kolmogorov–Smirnov method was used to test the normality of the continuous variables. Normally distributed continuous variables were expressed as mean and standard deviation, and the t-test was used to compare the groups. Non-normally distributed continuous

Table 1. Baseline demographic and clinical characteristics of patients

Parameters	HP (*N* = 138)	Control (*N* = 149)	*P*-value
Sex, n (%)			
Male	63 (45.65)	76 (51.00)	0.502
Female	75 (54.35)	73 (49.00)	0.496
Age, years	54 (50, 57.75)	53.5 (50, 60.5)	0.698
Weight, kg	60 (53.25, 70.00)	63.5 (59, 67)	0.675
Height, cm	160 (156, 167.75)	162 (158, 166.5)	0.586
BMI, kg/m2	22.72 (20.60, 25.91)	23.94 (21.77, 25.67)	0.958
Preoperative EF, %	45 (42, 55)	42 (40, 52)	0.149
Preoperative LVEDD, mm	40 (35, 46)	38 (36, 45)	0.225
Diagnosis, n (%)			
Rheumatic heart disease	94 (68.12)	97 (65.10)	0.513
Congenital valvular disease	31 (22.46)	37 (24.83)	0.283
Degenerative valvular disease	13 (9.42)	15 (10.07)	0.364
Surgical procedures, n (%)			
Double valve replacement	93 (67.39)	105 (70.47)	0.642
Aortic valve replacement	25 (18.11)	21 (14.09)	0.611
Mitral valve replacement	20 (14.50)	23 (15.44)	0.732
Concomitant surgeries, n (%)			
Tricuspid valve repair	18 (13.04)	20 (13.42)	0.654
Atrial fibrillation radiofrequency ablation	8 (5.80)	12 (8.05)	0.302
Left atrial plication	7 (5.07)	10 (6.71)	0.412
Total surgery time, min	230 (220, 255)	225 (215, 250)	0.169
CPB operation time, min	145 (128, 164)	150 (126, 171)	0.152
Cross-clamp time, min	96 (85, 110)	95 (80, 105)	0.114

variables were expressed as median (interquartile range), and the nonparametric test was used to compare the groups. Generalized Estimating Equations (GEE) were used to compare different times points in both groups. Categorical variables were expressed as frequencies and percentages. The χ^2test or Fisher's exact probability method was used for intergroup comparison. Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics software (version 26.0). All statistical tests were two-sided, and a two-tailed *P* value of < 0.05 was significant.

RESULTS

Baseline demographic and clinical characteristics: The baseline demographic and clinical characteristics of the patients are listed in Table 1. (Table 1) No significant difference was observed between both groups, regarding baseline demographic characteristics, including sex, age, weight, height, BMI, preoperative EF, and preoperative LVEDD. Most patients were diagnosed with rheumatic heart disease, whereas some suffered from congenital or degenerative valvular disease. All the patients received cardiac valve replacement surgeries, such as aortic valve, mitral valve, or double valve replacement. Some patients underwent concomitant surgeries, including tricuspid valve repair, atrial fibrillation radiofrequency ablation, or left atrial plication. Both groups did not differ in diagnosis, surgical procedures, total surgery time, CPB procedure time, and cross-clamp time.

Inflammatory cytokines: The inflammatory cytokines (IL-6, IL-8, and TNF-α) at different time points between both groups are presented in Figure 1. (Figure 1) Both groups had relatively low inflammatory cytokines before CPB and 30 min into the procedure. High IL-6, IL-8, and TNF-α levels were observed in both groups, increasing after CPB (V2 to V4), with a peak value one day post-CPB (V2). GEE linear regression models were used to compare different time points between the groups. As presented in Table 2, a significant difference was observed in IL-6 and IL-8. (Table 2) However, there were no significant differences in TNF-α between both groups. Regarding the comparison at different time points, no significant differences were observed between both groups at V0, V1, and V4 (all $P > 0.05$). At V2, the HP group had relatively lower IL-6 (HP: 174.68 vs. control: 356.36 pg/mL, $P < 0.05$) and

Table 2. Inflammatory cytokines levels between HP and control groups

Parameters	Treatment	V0 (pre-CPB)	V1 (CPB 30 min)	V2 (1 d post-CPB)	V3 (2 d post-CPB)	V4 (3 d post-CPB)	GEE Regression	
							B (95%)	*P*-value
IL-6, pg/mL	HP	5.54 (4.39, 7.79)	39.56 (36.93, 42.51)	174.68 (131.74, 191.33)	136.45 (108.63, 163.65)	24.69 (20.87, 27.06)	-23.312 (-26.018, -20.605)	0.000
	Control	6.82 (4.02, 7.91)	40.68 (36.74, 44.44)	356.36 (338.58, 380.98)	172.52 (163.52, 209.00)	25.52 (21.61, 27.68)		
	P-value	0.891	0.473	0.000	0.000	0.416		
IL-8, pg/mL	HP	3.32 (2.44, 4.56)	13.07 (11.73, 14.52)	109.57 (93.47, 127.96)	127.27 (122.59, 130.14)	14.31 (11.22, 16.44)	-9.705 (-10.612, -8.797)	0.000
	Control	3.72 (2.85, 4.70)	12.68 (10.88, 14.33)	209.12 (194.94, 222.88)	127.58 (125.31, 130.67)	14.21 (11.90, 16.02)		
	P-value	0.387	0.947	0.000	0.151	0.933		
TNF-α, pg/mL	HP	1.08 (0.74, 1.49)	2.52 (2.04, 3.58)	10.37 (9.87, 10.75)	5.73 (5.43, 6.06)	0.67 (0.39, 1.13)	0.017 (-0.05, 0.083)	0.620
	Control	1.04 (0.72, 1.34)	2.90 (2.00, 3.66)	10.34 (10.00, 11.15)	5.60 (5.31, 5.86)	0.62 (0.52, 0.86)		
	P-value	0.837	0.820	0.157	0.071	0.186		

IL-8 (HP: 109.57 vs. control: 209.12 pg/mL, $P< 0.05$) compared with the control group. At V3, the groups differed in only IL-6 (HP: 136.45 vs. control: 172.52 pg/mL, $P < 0.05$).

Blood biochemical indices: Regarding blood biochemical indices, Table 3 compares the GEE model estimation of both groups. (Table 3) There were no differences in INR, BNP, TBIL, ALT, Cre, Urea, Ccr, Tn, CK-MB, and Mb among all time points between both groups. However, the estimation differences of Lac, PLT, and AST differed significantly in the GEE results. Notably, the HP group had lower Lac and PLT than the control group at T1, T2, and T3 ($P < 0.05$). At T1 and T3, the HP group had lower AST than the control group ($P < 0.05$).

Postoperative outcome indices: The incidence of complications, blood transfusion, and ICU results also were compared. As presented in Table 4, some patients in both groups developed pneumonia, cerebrovascular events or underwent a reoperation for postoperative bleeding; however, there were no significant differences in their incidence. (Table 4) No renal failure occurred in either group. With respect to the use of specific blood products, there were no significant differences in infusion volume of packed red blood cells, fresh frozen plasma, and platelets between the groups. In the HP group, a patient received IABP treatment (2.50%). In the control group, one patient received CRRT (2.50%), and two received IABP treatment (5.00%). ECMO was not required in either group. The differences between the groups were not significant regarding CRRT ($P = 1.000$), IABP treatment ($P = 1.000$), and ECMO treatment ($P = 1.000$). Regarding the ICU outcomes, the HP group required less ventilation time than the control group (HP: 16 h vs. control: 22 h, $P < 0.05$); however, no significant difference in ICU length of stay and hospital length of stay were observed between the groups.

DISCUSSION

Hemoperfusion has been developed for blood purification by adsorption of plasma solutes on resin beads contained in cartridges, due to the advent of biocompatible production and coating technology in recent years. Over the last decade, the hemoperfusion devices most commonly used for treatment have been commercial Cytosorb ® cartridges or the HA Jafron Biomedical series [Ronco 2022], with the clinical application in intoxication, liver disease, renal disease, sepsis, and 2019 coronavirus disease. In addition, hemoperfusion in combination with other treatment approaches, such as dialysis, CRRT, CPB, and ECMO, also was recommended. This study evaluated hemoperfusion cartridge efficacy in patients undergoing cardiac valve replacement surgery using CPB. We observed that the patients in the HP group had relatively lower IL-6 (V2 and V3) and IL-8 (V2) than those in the control group, indicating that the hemoperfusion cartridge significantly influenced the absorption of inflammatory mediators. In addition, some relatively better blood biochemical indices and clinical outcomes also were observed in the HP group, including significantly lower Lac (T1, T2, and T3), AST (T1 and T3), and ventilation time. Similar attempts using hemoperfusion cartridges perioperatively during cardiac surgeries also previously have been reported. He et al. [He 2022] reported a randomized pilot trial with 60 patients undergoing surgical valve replacement. This trial observed lower inflammatory mediators (IL-6, IL-8, and IL-10), Cr, AST, and TBil. In another study of 16 patients suffering from post-CPB inflammatory response syndrome, Träger et al. [Träger 2016] reported that hemoperfusion cartridges adsorbed inflammatory mediators (IL-6 and IL-8) and improved clinical outcomes. Our results were consistent with

Table 3. Blood biochemical indices between HP and control groups

Parameters	HP T0 (pre-CPB)	HP T1 (CPB 30 min)	HP T2 (1 d post-CPB)	HP T3 (2 d post-CPB)	Control T0 (pre-CPB)	Control T1 (CPB 30 min)	Control T2 (1 d post-CPB)	Control T3 (2 d post-CPB)	GEE Regression B (95%)	*P*-value
Lac, mmol/L	1.40 (1.20, 1.80)	1.35 (1.13, 2.43)*	2.70 (2.23, 3.33)*	2.10 (1.63, 2.58)*	1.50 (1.10, 1.80)	3.00 (2.60, 4.18)	5.00 (2.33, 6.30)	3.50 (2.50, 4.08)	-1.227 (-1.463, -0.992)	0.000
INR	0.98 (1.94, 1.04)	0.95 (0.89, 1.00)	1.01 (0.95, 1.10)	1.25 (0.98, 1.55)	1.01 (0.94, 1.04)	0.98 (0.95, 1.04)	1.00 (0.95, 1.09)	1.31 (1.01, 1.54)	-0.060 (0.121, 0.001)	0.055
PLT, 109/L	160 .00(113.00, 200.00)	104.50 (81.50, 130.50)*	89.00 (68.25, 112.50)*	94.00 (64.00, 118.50)*	164.5 (137.50, 207.50)	142.50 (118.00, 172.00)	122.50 (101.50, 164.75) 109.00 (91.00, 159.00)	-31.877 (-53.106, -10.647)	0.003	
BNP, pg/ml	165.33 (86.53, 289.59)	213.83 (123.43, 351.73)	198.13 (153.41, 336.71)	220.74 (120.03, 422.89)	149.00 (113.27, 217.73)	157.48 (127.22, 281.58)	178.80 (98.00, 243.66)	166.15 (116.85, 246.74)	95.765 (-75.980, 267.511)	0.274
TBIL, μmol/L	18.20 (14.33, 23.48)	42.20 (26.88, 52.72)	35.00 (25.95, 47.58)	33.00 (21.05, 52.53)	21.10 (13.25, 27.81)	24.60 (17.90, 40.23)	27.60 (15.01, 31.81)	22.65 (14.06, 27.87)	2.998 (-11.684, 17.680)	0.689
ALT, U/L	23.25 (19.30, 36.58)	41.70 (19.20, 60.35)	23.85 (18.20, 27.54)	19.54 (15.20, 26.70)	27.95 (17.25, 42.00)	40.10 (25.43, 59.63)	29.55 (18.24, 48.23)	28.30 (17.27, 41.75)	-15.951 (-61.489, 29.587)	0.492
AST, U/L	22.90 (20.60, 32.88)	68.73 (59.55, 68.73)*	47.98 (36.72, 84.05)	33.92 (22.41, 50.44)*	31.05 (22.28, 36.39)	93.85 (76.23, 135.70)	61.00 (45.20, 89.55)	40.25 (30.73, 65.90)	-15.328 (-26.760, -3.896)	0.009
Cre, μmol/L	77.00 (59.00, 93.00)	85.50 (72.00, 100.00)	81.00 (69.25, 99.00)	74.00 (61.75, 88.25)	67 (60.25, 84.25)	92.00 (75.75, 104.75)	90.00 (74.00, 112.00)	77.00 (65.25, 92.75)	1.851 (-9.005, 12.707)	0.738
Urea, mmol/L	5.62 (4.29, 7.69)	11.04 (9.18, 12.95)	11.78 (8.94, 14.68)	10.36 (6.82, 13.64)	5.76 (4.44, 6.58)	9.96 (8.50, 12.06)	11.33 (8.77, 14.98)	9.21 (8.05, 12.94)	-0146 (-1.658, 0.036)	0.849
Ccr, mL/min	82.12 (70.44, 96.24)	73.73 (63.07, 88.53)	67.32 (55.01, 81.90)	67.55 (54.80, 86.15)	89.00 (78.78, 98.94)	74.55 (61.62, 92.90)	74.60 (65.50, 81.35)	70.04 (61.87, 74.57)	1.851 (-9.005, 12.707)	0.738
Tn, ng/mL	0.01 (0.00, 0.07)	11.65 (9.01, 16.21)	6.71 (4.82, 10.43)	4.02 (1.65, 6.19)	0.01 (0.01, 0.01)	12.13 (7.20, 20.92)	6.46 (4.00, 11.81)	3.23 (2.12, 5.30)	3.376 (-3.374, 10.126)	0.327
CK-MB, μmol/L	1.39 (1.05, 3.42)	43.19 (25.55, 58.21)	8.30 (5.36, 14.42)	4.26 (2.16, 5.96)	1.02 (0.26, 1.27)	43.74 (24.73, 59.44)	8.82 (5.45, 18.26)	1.23 (0.98, 2.51)	-0.258 (-4.410, 3.894)	0.903
Mb, μg/L	49.45 (37.66, 89.82)	309.79 (239.88, 441.82)	187.06 (123.61, 227.39)	90.43 (65.54, 154.33)	46.31 (38.06, 49.43)	327.26 (224.02, 489.61)	166.72 (102.27, 239.66)	49.56 (39.64, 86.99)	4.611 (-47.488, 56.710)	0.862

*$P < 0.05$ compared with the control group

Table 4. Postoperative outcome indices between the HP and control groups

Parameters	HP	Control	*P*-value
Pneumonia, n (%)	1 (2.50)	1 (2.50)	1.000
Renal failure, n (%)	0 (0.00)	0 (0.00)	1.000
Cerebrovascular events, n (%)	0 (0.000)	2 (5.00)	1.000
Reoperation for postoperative bleeding, n (%)	1 (2.50)	1 (2.50)	1.000
Infusion volume of packed red blood cells (mL)	250 (200, 375)	275 (150, 300)	0.832
Infusion volume of fresh frozen plasma (mL)	600 (400, 800)	575 (400, 800)	0.741
Infusion volume of platelets (mL)	300 (300, 600)	300 (300, 600)	0.675
CRRT, n (%)	0 (0.000)	1 (2.50)	1.000
IABP, n (%)	1 (2.50)	2 (5.00)	1.000
ECMO, n (%)	0 (0.000)	0 (0.000)	1.000
Ventilation time, h	16 (12, 21)	22 (20, 29)	<0.05
ICU stay time, h	75 (64, 86)	76 (62, 90)	0.231
Hospital stay time, d	12.5 (9.0, 16.0)	12.0 (7.0, 17.0)	0.741

their findings, suggesting that hemoperfusion cartridge limits CPB-induced inflammation.

Notably, two recent pilot randomized controlled trials reported conflicting results. Bernardi et al. [Bernardi 2016] evaluated the efficacy of hemoperfusion during CPB in 16 patients undergoing elective cardiac surgery. The authors observed no significant difference in perioperative levels of inflammatory mediators (IL-6, IL-10, IL-18, IL-1β, and TNF-α) or clinical outcomes. In another study with 15 patients undergoing elective cardiac surgery, Poli et al. [Poli 2019] reported that hemoperfusion during CPB was not associated with decreased pro- or anti-inflammatory cytokines or improved clinical outcomes. These conflicting results may be attributed to the low inflammatory responses observed in patients included in the above trials. For example, the peak level of IL-6 was approximately 120 pg/mL, which is lower than that observed in the study of He et al. (approximately 450 pg/mL) and our trial (approximately 350 pg/mL). The observed decreased perioperative cytokine levels or improvement in clinical outcomes in previous studies seems to be significantly associated with severe complications, such as post-CPB systemic inflammatory response syndrome [Träger 2016], acute infective endocarditis [Träger 2017], and acute kidney injury [Träger 2016].

There were some limitations to this study. The safety of the hemoperfusion cartridge procedure during CPB is of concern. Our results revealed that the HP group had lesser PLTs than the control group post-CPB; however, no severe complications occurred in the groups. The trend of transient thrombocytopenia was reported in previous studies [Schädler 2017; Sun 2015], which seems to be associated with prolonged hemoperfusion time. This study did not conduct statistical analysis on more hematological indicators, due to insufficient data. However, the safety of hemoperfusion cartridges has been confirmed by many studies. A pilot randomized controlled trial suggested that the hemoperfusion cartridge procedure during CPB resulted in insignificant coagulation factors adsorption and few signs of coagulation activation [Poli 2019]. An in vitro test also demonstrated that no adverse effect or cytotoxicity was associated with hemoperfusion cartridge [Montin 2018]. Therefore, a large prospective trial should be conducted to further confirm the efficacy and safety of the hemoperfusion cartridge procedure during CPB in cardiac surgery.

CONCLUSIONS

In patients undergoing cardiac valve replacement surgery with cardiopulmonary bypass, a hemoperfusion cartridge effectively reduced intraoperative IL-6 and IL- 8 levels. It also resulted in decreased post-CPB Lac, AST, and ventilation time. Hemoperfusion-induced PLT decreased postoperatively, and no severe complications occurred in all patients. These findings demonstrate that the hemoperfusion cartridge limits the inflammatory reactions, with potential for application in cardiac surgery.

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