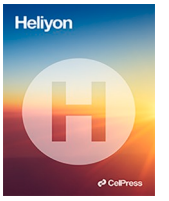
Heliyon 10 (2024) e31388

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

A modified low-priming cardiopulmonary bypass system in patients undergoing cardiac surgery with medium risk of transfusion: A randomized controlled trial

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ARTICLE INFO

Keywords:
Cardiac surgery
Cardiopulmonary bypass
Blood conservation
Red blood cell transfusion
Patient blood management

ABSTRACT

Objectives: The FUWAI-SAVE system is a modified low-priming cardiopulmonary bypass (CPB) system. The study aimed to explore whether the FUWAI-SAVE system can reduce the perioperative blood transfusion and its impact on other postoperative complications during cardiac surgery.

Metohds: This study was a single-center, single-blind, randomized controlled trial, registered at the Chinese Clinical Trial Registry (identifier: ChiCTR2100050488). Adult patients undergoing cardiac surgery with CPB and intermediate risk for transfusion risk stratification were randomly assigned to an intervention group (FUWAI-SAVE group) or a control group (conventional group). The primary endpoint of the study was the peri-CPB red blood cell transfusion (RBC) rate. The secondary endpoints included the transfusion rate of other blood products, the amount of blood products transfused, the incidence of major complications, in-hospital mortality, and others.

Results: 360 patients were randomized from December 9, 2021, to January 30, 2023. The rate of the primary endpoint was significantly lower in the FUWAI-SAVE group compared to the control group [OR (95%CI): 0.649 (0.424–0.994)]. Meanwhile, the amount of RBC transfusion during the peri-CPB period was significantly lower in the FUWAI-SAVE group compared to the control group, with a mean difference of −0.626 (−1.176 to −0.076) units. The occurrence rate of major complications did not differ significantly between the two groups.

Conclusions: Among adult patients undergoing cardiac surgery with CPB, the application of the FUWAI-SAVE system significantly reduced RBC transfusion rate and amount. The FUWAI-SAVE system can be considered an important component of comprehensive blood management strategies in cardiac surgery.

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https://doi.org/10.1016/j.heliyon.2024.e31388
Received 31 March 2024; Received in revised form 14 May 2024; Accepted 15 May 2024
Available online 18 May 2024

1. Introduction

In cardiac surgery with cardiopulmonary bypass (CPB), the perioperative red blood cell (RBC) transfusion rate is relatively high, thus increasing the risks associated with blood transfusion [1,2]. Various multidisciplinary blood conservation measures have been adopted in cardiac surgery centers to reduce perioperative blood transfusions. These interventions during CPB include retrograde autologous blood priming, reducing the priming volume, acute normovolemic hemodilution, application of minimal invasive extracorporeal circulation system (MiECC), modified ultrafiltration and other approaches [3]. Fuwai Hospital has implemented comprehensive blood management measures to reduce the potential risks of blood transfusion. The application of a low-priming modified CPB system is an important component of our center's comprehensive blood management measures [4].

Since 2010, Fuwai hospital has gradually integrated a novel low-priming modified CPB system. The system consists of **S**hort-tubing circuit, an oxygenator with an integrated **A**rterial filter, a **V**acuum-assisted venous drainage device (VAVD), and microcardiopl**E**gia. Therefore, this system is named the FUWAI-SAVE system.

Furthermore, based on our center's previous data, we established the FUWAI Transfusion Risk Stratification Score [5]. The transfusion stratification was divided into three levels: low (transfusion probability less than 30 %), medium (transfusion probability 30 %–60 %), and high (transfusion probability greater than 60 %) risk. Low-risk patients have a lower probability of transfusion, and reducing transfusion may not have significant clinical and social implications for them. Clinical interventions for high-risk patients with transfusion probabilities over 60 % may affect their prognosis. Early and proactive clinical interventions for medium-risk patients may be more effective in reducing blood transfusion and could contribute to improving patient outcomes and conserving blood.

Therefore, this study aims to explore whether the FUWAI-SAVE system can reduce the perioperative RBC transfusion rate and its impact on other postoperative complications through a prospective randomized controlled trial (RCT), to verify the effectiveness and safety of the system.

2. Materials and methods

2.1. Ethics and informed consent

The study protocol was approved by the ethics committee of Fuwai Hospital on August 11, 2021 (No. 2021-1486) and registered at Chinese Clinical Trial Registry (identifier: ChiCTR2100050488, principal investigator: Bingyang Ji, released on August 28, 2021). The study protocol was published in Chinese Journal of Extracorporeal Circulation [6]. All eligible participants gave written informed consent prior to enrolment and intervention, and consented to the publishing of all data included in the manuscript.

2.2. Trial design

This single-blinded, RCT was conducted at Fuwai Hospital between December 2021 and February 2023. The study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

2.3. Participants

Included were adult patients (≥18 years) undergoing cardiac surgery with either the FUWAI-SAVE system or conventional CPB system, who were indicated as having medium risk for blood transfusion by the FUWAI Transfusion Risk Stratification Score. We

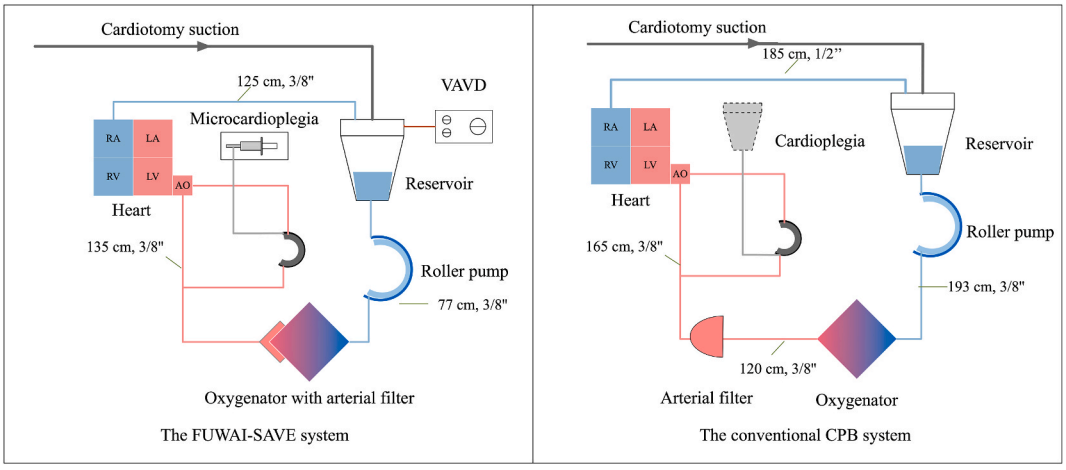

Fig. 1. The FUWAI-SAVE system and conventional CPB system. AO, aorta; CPB, cardiopulmonary bypass; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VAVD, vacuum assisted venous drainage.

excluded patients with a body weight less than 40 kg, history of allergy to CPB circuit planned open chest intervention, planned major vascular surgery, planned deep hypothermia circulatory arrest surgery, emergency surgery, history of previous cardiac surgery with CPB or other conditions deemed unsuitable for inclusion by investigators.

2.4. Interventions

Intervention was the CPB system used in cardiac surgery. The FUWAI-SAVE group underwent cardiac surgery under the FUWAI-SAVE system, while the control group underwent cardiac surgery under conventional CPB system. CPB was performed using the Stockert S5 CPB console (Stockert Instrumente, Germany) (Fig. 1).

The FUWAI-SAVE system was composed of 4 major modifications, 1) modified short-tubing, 2) an oxygenator with an integrated arterial filter (QUADROX-I 71000, Maquet, Germany or INSPIRE 6F DUAL, Sorin, Germany or Affinity Fusion, Medtronic, USA), 3) VAVD device (Xijing Medical Equipment Co., Ltd., Xi'an, China or Maquet, Germany), and 4) micro-cardioplegia (with a potassium ion concentration of 600 mmol/L and a crystal-to-blood ratio of 1:30). The arterial and venous cannulas for the FUWAI-SAVE group had an internal diameter of 3/8 inches, with an arterial line length of 135 cm and a venous line length of 125 cm. The main pump tubing had an internal diameter of 1/2 inches and a length of 77 cm. The total length of the tubing was 337 cm, and the static priming volume was 750 mL.

The conventional CPB system was composed of conventional tubing, a standard oxygenator (QUADROX-I 78000, Maquet, Germany or INSPIRE 6 DUAL, Sorin, Germany or Affinity NT, Medtronic, USA) combined with a separated arterial filter (Ningbo Fly Medical Healthcare Co., Ltd, Zhejiang, China), and conventional blood cardioplegia (with a potassium ion concentration of 100 mmol/L, and a crystal-to-blood ratio of 1:4). The arterial tubing in the control group had an inner diameter of 3/8 inches and a length of 165 cm, while the venous tubing had an inner diameter of 1/2 inches and a length of 185 cm. The main pump tubing had an inner diameter of 1/2 inches and a length of 193 cm. The tubing from the oxygenator outlet to the arterial filter had an inner diameter of 3/8 inches and a length of 120 cm. The total length of the tubing was 663 cm, with a static priming volume of 1250 mL.

2.5. Endpoints

The primary endpoint was the RBC transfusion rate during the peri-CPB period, defined as the rate of RBC transfusion from the beginning of CPB to discharge. Secondary endpoints include the rate and amount of other blood product transfusions, including platelets and fresh frozen plasma (FFP), hemoglobin level within 6 h after surgery, levels of inflammatory factors (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, IFN-α, IFN-γ) within 12–24 h after surgery, incidence of major complications during perioperative period including myocardial infarction, lung infection, acute kidney injury, and cerebrovascular events, chest drainage within 24 h after surgery, duration of mechanical ventilation, ICU stay and length of stay, in-hospital death rate, ICU costs and in-hospital costs.

2.6. Sample size

Based on our previous data, the peri-CPB RBC transfusion rate in the FUWAI-SAVE group was 13.7 %, while in the control group it was 24.2 %. With the peri-CPB RBC transfusion rate as the main outcome, a test for equivalence method was used. With a one-sided α of 0.05 and a test power (1-β) of 80 %, according to the ratio of 1:1 between the FUWAI-SAVE group and the control group, both groups will require 172 cases. Sample size calculation was performed using the PASS 15 software. In addition, considering the dropout rate, the sample size was increased to 360 cases, with 180 cases in each group.

2.7. Randomization and blinding

A block randomization with a block size of 10 was used, managed by one investigator who concealed the block size. After obtaining consent, group allocation was determined using the randomization sequence. Randomization was attempted at the start of surgery, and if a participant couldn't undergo surgery, their trial number and status were recorded. Due to the inability to blind investigators to the type of CPB system used during the procedure, the investigators were not blinded. However, participants were unaware of the group allocation.

2.8. Statistical methods

The data analysis of this study is based on the principle of intention-to-treat (ITT). For subjects who were mistakenly randomized despite not meeting the inclusion and exclusion criteria, if they have a similar treatment effect to other subjects who meet the criteria, they will not be excluded from data analysis. If the treatment effect of these subjects differs greatly from that of other subjects, they will be excluded.

For patients who were randomized into the trial prematurely but ultimately did not undergo cardiac surgery with either the FUWAI-SAVE system or the conventional CPB system, they will be excluded.

For missing or incorrect data, the data should be checked and verified before analysis, and efforts should be made to recover or correct missing or incorrect data. If missing data cannot be avoided, conservative missing data imputation methods are used. Since the primary endpoint is the peri-CPB RBC transfusion rate, effective measures can be taken to prevent its loss during data verification. For

missing data in general variables, this study adopts a complete analysis set approach, which means only non-missing data is analyzed.

For post-hoc analyses not included in the predefined statistical analysis, we defined △Hemoglobin as hemoglobin level in the last preoperative complete blood count minus hemoglobin level in the first postoperative complete blood count, and △Platelet count as platelet count in the last preoperative complete blood count minus platelet count in the first postoperative complete blood count.

Demographic and intra-operative data will be primarily presented descriptively, and the balance between the two groups after randomization will be compared. Descriptive statistics will be used to calculate means, standard deviations, medians, quartiles (Q1 and Q3), as well as the number and percentage of cases for categorical variables. Kolmogorov-Smirnov test was used to test the normality of variables. For the comparison between the two groups, appropriate methods will be used according to the type of variables. Independent sample *t*-tests or Mann-Whitney *U* tests will be used for quantitative data analysis depending on the distribution of the data. Pearson's chi-square test or exact probability method (if chi-square test is not applicable) will be used for categorical data analysis, and Wilcoxon rank-sum test will be used for ordinal data analysis.

The primary endpoint incidence and percentage in the two groups will be described, and the difference and 95 % confidence interval (CI) will be calculated. The primary endpoint estimate (odds ratio, OR) and its 95 % CI will be estimated using a univariate logistic regression analysis. The comparison between the two groups will be conducted using a Pearson's chi-square test. The secondary endpoints will be presented and compared as appropriate.

A two-sided test will be used, and $p < 0.05$ will be considered statistically significant.

3. RESULTS

3.1. Patient characteristics

The recruitment period was from December 9, 2021, to January 30, 2023, with the last follow-up on February 6, 2023. 675 patients were screened,

360 patients received randomization. Among them, 9 did not undergo cardiac surgery with either the FUWAI-SAVE system or the conventional CPB system after randomization and were not included in the primary analysis. Thus, 351 patients entered the primary analysis set, with 175 patients in the FUWAI-SAVE group and 176 patients in the control group (Fig. 2). After randomization, the baseline characteristics of the FUWAI-SAVE group and the control group were evenly distributed (Table 1).

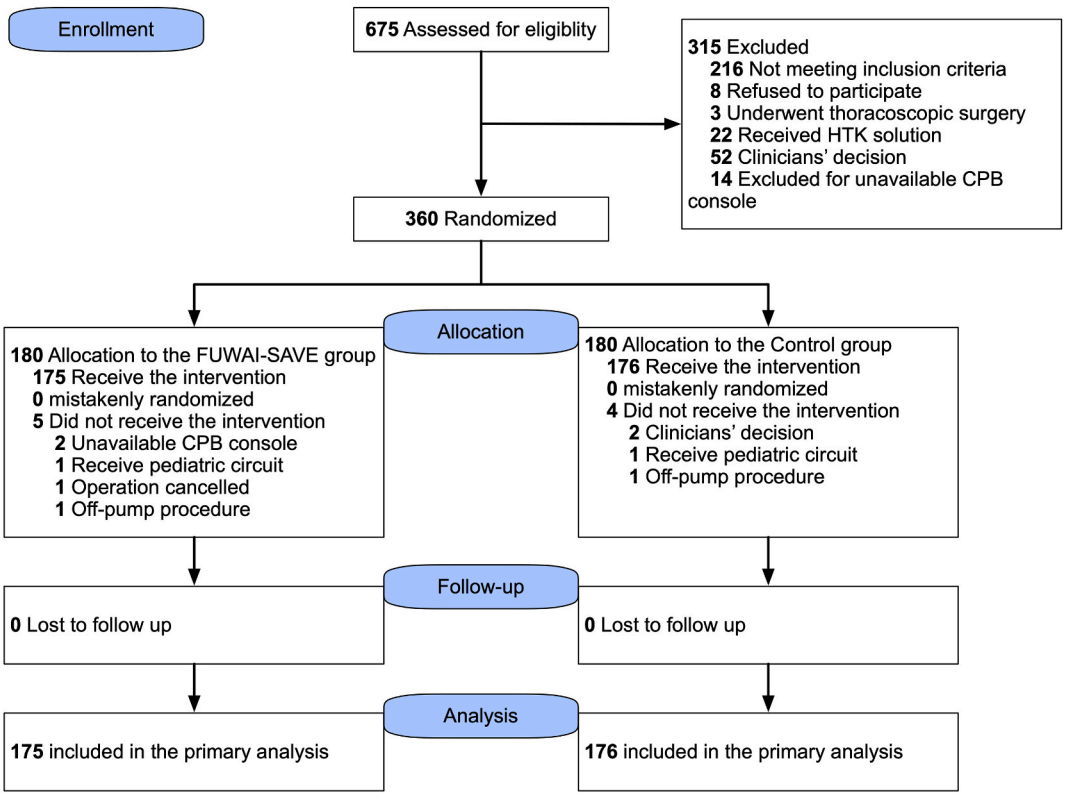

Fig. 2. CONSORT flow diagram of the study population. CPB, cardiopulmonary bypass; HTK, Histidine-Tryptophan-Ketoglutarate.

Table 1
Baseline characteristics between the FUWAI-SAVE group and the control group.

	The control group (n = 176)	The FUWAI-SAVE group (n = 175)	*P*-Value
Age (year)	66(62,70)	66(63,70)	0.696
Female	119(67.6 %)	118(67.4 %)	0.97
Height (cm)	160(158,165)	160(155,165)	0.335
Weight (kg)	61.8(56.5,68)	61(57,67)	0.719
BSA (m^2)	1.7 ± 0.1	1.7 ± 0.1	0.43
Transfusion Score[a]	16(14,17)	16(14,17)	0.716
EF (%)	60(60,65)	60(57,65)	0.955
EuroSCORE I	5(4,6)	5(4,6)	0.715
NYHA			0.551
I	5(2.8 %)	2(1.1 %)	
II	101(57.4 %)	94(53.7 %)	
III	66(37.5 %)	74(42.3 %)	
IV	4(2.3 %)	5(2.9 %)	
Comorbidities			
Diabetes Mellitus	80(45.5 %)	70(40 %)	0.302
Hypertension	110(62.5 %)	97(55.4 %)	0.178
Hyperlipidemia	96(54.5 %)	93(53.1 %)	0.792
Chronic renal dysfunction	0(0 %)	2(1.1 %)	0.248
Infective endocarditis	2(1.1 %)	0(0 %)	0.499
Cerebrovascular accidents	18(10.2 %)	25(14.3 %)	0.246
Angina	82(46.6 %)	79(45.1 %)	0.785
Lab tests			
Hemoglobin (g/L)	124 ± 13	125 ± 15	0.608
Platelets (× 10^9/L)	210(182,259)	209(168,250)	0.614
Glucose (mmol/L)	5.6(4.9,6.7)	5.6(4.9,6.9)	0.861
Urine nitrogen (mmol/L)	7.4 ± 5	7.3 ± 2.6	0.8
Serum creatinine (μmol/L)	69.2(57.8,85.2)	69.5(56.1,82.7)	0.442
Albumin (g/L)	39.7(37.9,41.6)	39.8(37.9,41.8)	0.669
Fibrinogen (g/L)	3.47(3.07,4.01)	3.36(2.93,3.93)	0.994
D-dimer (ug/mL)	0.30(0.21,0.50)	0.29(0.22,0.45)	0.777
FDP	2.5(2.5,2.5)	2.5(2.5,2.5)	0.307

BSA, body surface area; EF, ejection fraction; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FDP, fibrinogen degradation products; NYHA, New York Heart Association.

[a] FUWAI Transfusion Risk Stratification Score.

Table 2
Operative characteristics between the FUWAI-SAVE group and the control group.

	The control group (n = 176)	The FUWAI-SAVE group (n = 175)	*P*-Value
Type of procedures			0.394
Isolated CABG	119(67.6 %)	108(61.7 %)	
Isolated valve surgery[a]	20(11.4 %)	26(14.9 %)	
Other surgery	2(1.1 %)	4(2.3 %)	
Combined CABG and valve surgery	28(15.9 %)	24(13.7 %)	
Combined CABG and other surgery	7(4 %)	13(7.4 %)	
Surgeon ranking			0.421
Attending and lower ranking	10(5.7 %)	7(4 %)	
Associate Chief	86(48.9 %)	77(44 %)	
Chief	80(45.5 %)	91(52 %)	
Perfusion characteristics			
CPB time (min)	117(94,142)	117(90,139)	0.517
ACC time (min)	86(65,107)	83(63,113)	0.713
Priming volume (mL)	1600(1600,1600)	1200(1200,1299)	<0.001
Fluid intake (mL)	2430(2132.7,2933.2)	1554.4(1336.1,2019.7)	<0.001
Urine output (mL)	300(150,500)	300(120,450)	0.146
CUF (mL)	800(0,1300)	0(0,600)	<0.001
ZBUF (mL)	0(0,0)	0(0,0)	0.024
Lowest Hemoglobin (g/L)	72 ± 10	80 ± 10	<0.001
Highest Lactate (mg/dL)	0.9(0.7,1.2)	0.8(0.7,1.1)	0.292

ACC, aortic cross-clamping; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CUF, conventional ultrafiltration; ZBUF, Zero-balance ultrafiltration.

[a] isolated valve surgery includes both single valve surgery and multiple valve surgery. If valve surgery is combined with non-CABG procedures, it is categorized as other surgeries.

3.2. Operative characteristics

Both groups primarily consisted of isolated CABG procedures (Table 2). The duration of CPB and aortic cross-clamp (AAC) time were comparable between the FUWAI-SAVE group and the control group. The total priming volume was 1600 (1600, 1600) mL in the control group and 1200 (1200, 1299) mL in the FUWAI-SAVE group. The conventional ultrafiltration volume (CUF) in the FUWAI-

Table 3
Primary and secondary endpoints of the trial.

	The FUWAI-SAVE group (n = 175)	The control group (n = 176)	Difference (95%CI)	OR (95%CI)	*P*-Value
Primary endpoint					
Peri-CPB RBC transfusion rate	92(52.6 %)	111(63.1 %)	−0.105(-0.159 to −0.051)	0.649 (0.424–0.994)	0.046
Secondary endpoints					
Peri-CPB platelets transfusion rate	3(1.7 %)	7(4 %)	−0.023(-0.103 to 0.057)	0.421 (0.107–1.656)	0.337
Peri-CPB FFP transfusion rate	22(12.6 %)	22(12.5 %)	0.001(-0.075 to 0.077)	1.007 (0.535–1.893)	0.984
Peri-CPB RBC transfusion amount (u)	2(0,3)	2(0,4)	−0.626(-1.176 to −0.076)	–	0.017
Peri-CPB platelets transfusion amount (u)	0(0,0)	0(0,0)	−0.028(-0.077 to 0.02)	–	0.204
Peri-CPB FFP transfusion amount (u)	0(0,0)	0(0,0)	13.76(-29.112 to 56.632)	–	0.948
Postoperative Hemoglobin (g/L)	102 ± 12	102 ± 14	0.598(-2.235 to 3.431)	–	0.678
IL-1β (pg/mL)	1.5(1,2.1)	1.7(1.2,2.4)	−1.698(-3.137 to −0.259)	–	0.062
IL-2 (pg/mL)	1.8(1.4,2.3)	2(1.5,2.9)	−0.899(-1.672 to −0.127)	–	0.019
IL-4 (pg/mL)	1.5(0.9,2)	1.4(0.9,2)	−0.488(-1.109 to 0.132)	–	0.381
IL-5 (pg/mL)	1.4(1.1,2)	1.5(1.2,2)	−0.006(-0.569 to 0.557)	–	0.592
IL-6 (pg/mL)	163.2(103.4270.4)	172.4(109.7370)	−18.256(-93.266 to 56.753)	–	0.33
IL-8 (pg/mL)	75.2(50.7121.5)	80.6(55.3142.4)	−8.719(-30.508 to 13.071)	–	0.221
IL-10 (pg/mL)	19.3(12.2,32.5)	20(12.7,33.7)	1.009(-4.788 to 6.805)	–	0.745
IL-12p70 (pg/mL)	1.7(1.1,2.6)	2(1.1,3.1)	−3.937(-8.164 to 0.289)	–	0.109
IL-17 (pg/mL)	3.1(1.2,5.7)	3.5(0.4,7.1)	−0.865(-2.211 to 0.481)	–	0.723
TNF-α (pg/mL)	1.5(1,2.2)	1.7(1.2,2.8)	−2.036(-3.7 to −0.372)	–	0.008
IFN-α (pg/mL)	2.1(1.5,3.1)	2.3(1.7,3.4)	−3.522(-14.428 to 7.383)	–	0.248
IFN-γ (pg/mL)	1.6(1.1,2.2)	1.6(1.2,2.3)	−0.195(-0.501 to 0.111)	–	0.486
Perioperative MI	22(12.8 %)	22(12.6 %)	0.002(-0.074 to 0.078)	1.02(0.542–1.92)	0.951
Lung infection	6(3.4 %)	2(1.1 %)	0.023(-0.056 to 0.102)	3.089 (0.615–15.518)	0.174
AKI	50(25 %)	44(18.6 %)	−0.064(-0.123 to −0.005)	1.2(0.748–1.926)	0.45
Cerebrovascular events	1(0.6 %)	0(0 %)	–	–	0.499
Chest drainage within 24 h after surgery (mL)	320(230,440)	340(250,470)	−31.208(-77.65 to 15.234)	–	0.151
Duration of mechanical ventilation (h)	15(11,18)	16(12,19)	−1.279(-6.102 to 3.545)	–	0.152
ICU stay (h)	63(23,110)	60(35,92)	5.508(-10.088 to 21.105)	–	0.754
Length of stay (days)	14(12,18)	14(12,19)	−1.074(-2.369 to 0.222)	–	0.098
In-hospital death	1(0.6 %)	2(1.1 %)	−0.005(-0.088 to 0.078)	0.5(0.045–5.565)	1
ICU costs (RMB)	15914.1(9876.7,25533.3)	15716.5(10368.7,24775.9)	748.7(-3742.5 to 5239.9)	–	0.71
In-hospital costs (RMB)	121077.5 (102193.6,149372.6)	120178.8 (106967.8,146048.5)	−1351.2(-11142.9 to 8440.5)	–	0.441

AKI, acute kidney injury; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; IFN, interferon; ICU, intensive care unit; IL, interleukin; MI, myocardial infarction; OR, odds ratio; RBC, red blood cell; TNF, tumor necrosis factor.

SAVE group was less than that in the control group. During the CPB period, the lowest hemoglobin in the FUWAI-SAVE group was higher than that in the control group (80 ± 10 g/L vs. 72 ± 10 g/L, $p < 0.001$).

3.3. Outcomes

The rate of the primary endpoint was significantly lower in the FUWAI-SAVE group compared to the control group (Table 3). During the peri-CPB period, 92/175 (52.6 %) patients in the FUWAI-SAVE group received RBC transfusion, while 111/176 (63.1 %) patients in the control group received RBC transfusion. The OR (95%CI) for the primary endpoint was 0.649 (0.424–0.994). Additionally, the amount of RBC transfusion during the peri-CPB period was significantly lower in the FUWAI-SAVE group compared to the control group, with a mean difference of −0.626 (−1.176 to −0.076) units and a significant statistical difference ($p = 0.017$). There were no significant differences between the two groups in terms of platelets or FFP transfusion.

The hemoglobin level within 6 h after surgery did not differ significantly between the two groups. The levels of IL-2 and TNF-α were lower in the FUWAI-SAVE group compared to the conventional group. The occurrence rate of major complications did not differ significantly between the two groups. There were no significant differences in ICU costs and in-hospital costs between the two groups (Table 3).

Besides, the FUWAI-SAVE group had a significantly lower RBC transfusion rate and amount compared to the control group during CPB (Table 4). The postoperative total chest drainage in the FUWAI-SAVE group was significantly lower than the control group [730 (520, 1040) mL vs. 870 (600, 1200) mL, p = 0.029]. There were no significant differences between the two groups in the rate of resternotomy.

3.4. Post-hoc analysis

There was no significant difference in △Hemoglobin between the two groups. The △Platelet count in the FUWAI-SAVE group (80.8 ± 32.2 × 10^9/L) was lower than that in the control group (92.1 ± 41.6 × 10^9/L), and there was a statistically significant difference ($p = 0.005$).

4. Discussion

This single-center RCT included 351 patients undergoing cardiac surgery with medium transfusion risk. The trial compared the clinical outcomes of patients receiving a conventional CPB system to those receiving a novel modified low-priming CPB system, known as the FUWAI-SAVE system. The main results of this study are as follows: 1) Compared with conventional CPB system, the FUWAI-SAVE system significantly reduced the peri-CPB RBC transfusion rate and amount; 2) The FUWAI-SAVE system is not associate with the increasing incidence of major complications; 3) The FUWAI-SAVE system may have potential value in protecting platelets and

Table 4
Distribution of other bleeding and transfusion characteristics between the FUWAI-SAVE group and the control group.

	The control group (n = 176)	The FUWAI-SAVE group (n = 175)	*P-Value*
During CPB			
RBC transfusion rate	57(32.4 %)	14(8 %)	<0.001
RBC transfusion amount (u)	0(0,2)	0(0,0)	<0.001
Intraoperative period without CPB			
RBC transfusion rate	6(3.4 %)	4(2.3 %)	0.75
Platelets transfusion rate	1(0.6 %)	0(0 %)	1
FFP transfusion rate	9(5.1 %)	9(5.1 %)	0.99
RBC transfusion amount (u)	0(0,0)	0(0,0)	0.524
Platelets transfusion amount (u)	0(0,0)	0(0,0)	0.319
FFP transfusion amount (u)	0(0,0)	0(0,0)	0.999
Protamine (mg)	310(300,400)	300(300,400)	0.574
Hemostatic agent[a]	8(4.5 %)	5(2.9 %)	0.402
Tranexamic acid (g)	3(3,3)	3(3,3)	0.792
Postoperative period			
RBC transfusion rate	75(42.6 %)	85(48.6 %)	0.262
Platelets transfusion rate	6(3.4 %)	3(1.7 %)	0.502
FFP transfusion rate	15(8.5 %)	14(8 %)	0.859
RBC transfusion amount (u)	0(0,2)	0(0,2)	0.418
Platelets transfusion amount (u)	0(0,0)	0(0,0)	0.316
FFP transfusion amount (u)	0(0,0)	0(0,0)	0.904
Hemostatic agent[b]	14(8 %)	9(5.1 %)	0.287
Total chest drainage (mL)	870(600,1200)	730(520,1040)	0.029
Resternotomy	4(2.3 %)	6(3.4 %)	0.542

CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; RBC, red blood cell.

[a] Intraoperative hemostatic agents include human fibrinogen and human prothrombin complex concentrate.

[b] Postoperative hemostatic agents include human fibrinogen, human prothrombin complex concentrate, aminomethylbenzoic acid, phenylephrine, and freeze-dried thrombin powder.

reducing inflammatory responses.

Current guidelines for blood conservation in cardiac surgery recommend comprehensive perioperative blood management (PBM) strategy to reduce blood dilution and decrease the RBC transfusion [3]. Among them, the application of MiECC is an important component of the comprehensive PBM strategy during CPB [7]. Previous studies have shown that MiECC increased biocompatibility, reduced blood dilution, minimized gas-blood contact, and significantly reduced the use of allogeneic blood products [8,9]. However, MiECC has some inherent drawbacks and has not been widely used worldwide [10].

Therefore, centers started to design modified MiECC systems based on their own clinical demands. Since 2010, our center has been designing and applying a modified low-priming CPB system. The system was composed of four main modifications, **S**hort tubing, an oxygenator with integrated **A**rterial filters, a **V**acuum-assisted venous drainage device (VAVD), and microcardiopl**E**gia, hence the name **SAVE** system. In the past decade, our center has made multiple improvements to the FUWAI-SAVE system, gradually forming the current system with a tubing length of 337 cm and a static priming volume of 750 mL. As the components of the FUWAI-SAVE system are commercial products, other centers can assemble the FUWAI-SAVE system according to the parameters reported in the manuscript. This study showed that the FUWAI-SAVE system not only reduced the peri-CPB RBC transfusion rate but also did not increase the incidence of major complications. Also, it is worth noting that the use of the FUWAI-SAVE system does not increase hospitalization costs and has high promotional value in clinical practice.

The primary end point of this study was the peri-CPB RBC transfusion rate. During CPB, the transfusion rate and amount of RBC in the FUWAI-SAVE group were significantly lower than those in the control group, and the lowest hemoglobin in the FUWAI-SAVE group was higher than that in the control group. There was no significant difference in the first postoperative hemoglobin between the two groups. The incidence of the primary endpoint and the peri-CPB RBC transfusion amount in the FUWAI-SAVE group were significantly lower than those in the control group. This suggests that the effect of the FUWAI-SAVE system in reducing blood product transfusion is not limited to a single phase of CPB, but rather has a significant impact throughout the entire perioperative period. The risk due to blood transfusion will be reduced, and the clinical blood resource shortage can be lessened by using the FUWAI-SAVE system.

In addition, the FUWAI-SAVE system may influence the coagulation balance perioperatively. Although there was no significant difference in the 24-h chest drainage between the two groups, the total chest drainage in the FUWAI-SAVE group was significantly lower than that in the conventional group after surgery. According to the △Platelet, the FUWAI-SAVE group had a lower decrease in platelet count during the surgery compared to the control group. This may indicate that the FUWAI-SAVE system has less destructive effect on platelets compared to the conventional system. However, since there was no significant difference in the changes in fibrinogen, D-dimer, and FDP between the two groups, the specific impact of the FUWAI-SAVE system on coagulation balance cannot be further explained, and future prospective studies are needed.

The contact between blood and the extracorporeal circuit induces a systemic inflammatory response [11]. Many factors affect the inflammatory response during CPB [12]. Among these factors, the use of MiECC with a closed circuit reduces contact between blood and air, thereby alleviating the inflammatory response [13–15]. Additionally, coated tubing effectively improves biocompatibility, mitigating the systemic inflammatory response and coagulation system activation [16]. The results of this study suggest that post-operative IL-2 and TNF-α levels were reduced in patients who received the FUWAI-SAVE system compared to the control group. IL-2 and TNF-α are pro-inflammatory cytokines without anti-inflammatory effects [11,17]. Previous studies have shown that elevated levels of IL-2 and TNF-α after cardiac surgery are associated with the occurrence of complications such as acute kidney injury [18], atrial fibrillation [19], and delirium [20].

The FUWAI-SAVE system shortens the circuit, and reduces the contact area between blood and the circuit to alleviate systemic inflammatory response. However, as no fundamental intervention has been made in biocompatible materials or blood-gas contact, the effect of reducing inflammatory response by the FUWAI-SAVE system may be relatively limited.

4.1. Limitations

Firstly, it was a single-blind RCT, which may introduce potential bias related to perfusionists' expectations. Secondly, the study did not perform a correction for multiple secondary clinical endpoints in the trial design. Therefore, the results of the secondary endpoints should be interpreted as exploratory. Thirdly, since the sample size calculation did not account for post hoc analyses, the statistical power was limited, and these analyses should be considered exploratory. Fourthly, this study included patients at medium transfusion risk according to the Fuwai Transfusion Risk Stratification Score. Stratified randomization based on the risk stratification may provide more evidence for the optimal patient population for the application of the FUWAI-SAVE system. Lastly, due to the lack of baseline data of inflammatory factors, the interpretation of postoperative inflammatory factors in both groups should be cautious.

5. Conclusion

Among adult patients undergoing cardiac surgery with CPB, the application of the FUWAI-SAVE system significantly reduced RBC transfusion rate and amount. Additionally, the FUWAI-SAVE system showed potential benefits in platelet protection and attenuating inflammatory responses. The FUWAI-SAVE system can be considered an important component of comprehensive blood management strategies in cardiac surgery.

Funding

This work was supported by the National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of

Medical Sciences (Grant No. NCRC2020005).

Data availability statement

The data associated with the study has not been deposited into a publicly available repository. The complete data that support the findings of this study are available on request from the corresponding author.

CRediT authorship contribution statement

Sizhe Gao: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Gang Liu:** Project administration, Investigation, Data curation. **Jing Wang:** Investigation, Data curation. **Qiaoni Zhang:** Validation, Methodology. **Jian Wang:** Investigation. **Yuan Teng:** Software. **Qian Wang:** Investigation. **Shujie Yan:** Methodology, Formal analysis. **Luyu Bian:** Investigation. **Qiang Hu:** Validation, Supervision. **Tianlong Wang:** Visualization, Software. **Weidong Yan:** Visualization, Data curation. **Bingyang Ji:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31388.

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