Cardiopulmonary bypass without transfusions of red blood cells did not affect the recovery of uncomplicated congenital heart surgery in children with bodyweights of 8-17kg

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Abstract

Background:Most cardiac surgeries with cardiopulmonary bypass (CPB) in children need transfusions of packed red blood cells (PRBCs), but the risks and benefits of transfusions remain controversial. There are still few studies on the outcome of transfusion or not during CPB in children with bodyweights of 8-17kg undergoing cardiac surgery, so we aim to investigate the effects of PRBCs transfusions during CPB. Methods: A total of 155 children with bodyweights of 8-17kg undergoing uncomplicated congenital heart surgery with CPB were divided into the non-transfusion group (group A, n=60) and transfusion group (group B, n=95) according to whether they were transfused perioperatively. By using a propensity score matching method, 55 patients were ultimately included in each group. The perioperative hematological test results and recovery of patients were compared by the independent sample t-tests or the chi-squares tests. Postoperative follow-up information within 0.5 to 2.5 years was also collected. Results: Hb before CPB was higher in group A than in group B ($p<0.05$). There were no differences in Hb during CPB or before hospital discharge, except that the Hb on the first day after surgery was lower in group A than in group B ($p<0.05$). There were no differences in the hematological test results, postoperative recovery or follow-up outcomes between the two groups. Conclusions: Non-transfusion CPB does not affect the Hb concentrations before hospital discharge, the postoperative recovery or short-term follow-up outcomes in children with bodyweights of 8-17kg undergoing uncomplicated congenital heart surgery, indicating these children can avoid transfusions.

Introduction

The perioperative transfusion rate in cardiac surgery is high worldwide, with approximately 40% of patients requiring transfusions [1, 2], and occupies approximately 15%-20% of blood product resources [3]. In addition, transfusion rate during CPB is even higher in children due to the larger priming volume of CPB relative to the blood volume of children and obvious hemodilution that occur as a consequence [4]. A database analysis of 81 centers found that transfusion rate of packed red blood cells (PRBCs) was close to 100% in younger children with complicated congenital heart disease (CHD) surgery and that the standard deviation was low in different centers [5]. For children aged 1 to 4 years old or with a bodyweight more than 10 kg and a low surgical risk, the transfusion rate is reduced, but the standard deviation of transfusion rate is still high [5]. During the 10 years from 2005 to 2014, the PRBC transfusion rate in pediatric cardiac surgery with CPB did not change significantly [6].

At present, the effects of hemodilution on children are not fully understood, and the minimum safe hematocrit (Hct) and the general accepted transfusion threshold during CPB in children have not been standardized [7]. That is, the balance between the risks of anemia and transfusion has not been determined. On the one hand, anemia may lead to a reduced oxygen supply and hypoxia, which is associated with increased morbidity and mortality [8], on the other hand, although PRBC transfusions correct anemia, blood products

are precious and may lead to transfusion-related infections and other complications and may affect the prognosis of cardiac surgery [9, 10]. Transfusions are even associated with increased postoperative mortality [11]. Besides, the effects of transfusions in children vary with the transfusion stage. Transfusions after CPB are less complicated than transfusions during CPB [12]. However, there are no unified guidelines for transfusions during pediatric CPB, and the experience of perfusionists in different centers, and even those in the same center, varies [13]. Although age of patient and the surgical complexity of pediatric cardiac surgery are similar across different centers, transfusion strategies still vary greatly [6]. Goal-directed transfusion strategies have not yet emerged in pediatric cardiac surgery with CPB [14], and the effects of a restrictive transfusion strategy during pediatric CPB are still controversial [15,16]. Few studies investigate the effects of non-transfusion CPB in children with bodyweights of 8-17kg, and long-term results have not been published [14].

The improvements of CPB equipment are the key to reducing the priming volume of CPB and the amount of PRBC transfusions [17]. In our center, with the use of a membrane oxygenator integrated with a microembolus filter and microsized CPB tubes, the lowest priming volume of CPB can be reduced to 110 ml. In this way, some children with bodyweights[?]8 kg can achieve non-transfusion CPB. Therefore, by using the propensity score matching method, this study retrospectively analyzed the effects of non-transfusion CPB on the recovery of uncomplicated CHD surgery in children with bodyweights of 8-17 kg.

METHODS

Grouping

The clinical case data of 155 children with bodyweights of 8-17 kg who underwent uncomplicated CHD surgery with CPB in our hospital from May 2017 to August 2019 were collected. According to whether the children were transfused during CPB and postoperatively, they were divided into the non-transfusion group (group A, n=60) or transfusion group (group B, n=95). Then, patients with similar ages, body weights, CPB times and aortic cross-clamping times were selected for 1:1 matching by the propensity score matching method, and 55 patients were ultimately included in each of the two groups.

Diagnostic criteria, inclusion criteria and exclusion criteria

Diagnostic criteria: All patients were clearly diagnosed according to their clinical manifestations, echocardiography and chest radiographs. Inclusion criteria: body weight of 8-17 kg; CPB priming volume of 110 to 350 ml; Terumo RX05 or FX05 membrane oxygenators were used; children undergoing selective uncomplicated CHD surgery with CPB, and the Risk Adjustment in Congenital Heart Surgery (RACHS-1) category was 1 to 2; children with stable hemodynamics before surgery. Exclusion criteria: children with complicated CHD or in a critical illness; children receiving blood transfusions postoperatively.

Main clinical outcomes

The main clinical outcomes included the following items: the Hb concentrations before CPB, during CPB, after CPB, on the first day after surgery, on the second or third day after surgery and before hospital discharge; the change in the perioperative value of lactic acid, white blood cell (WBC) number, platelet count, C-reactive protein (CRP), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine; the volume of PRBCs used during CPB; the urine volume and the dose of furosemide 24 hours after surgery, the total volume of thoracic drainage fluid; the postoperative mechanical ventilation time, the ICU stay time; and the length of the postoperative stay in the general ward.

CPB management and transfusion strategy

A Stockert type III or V CPB machine was used. Two types of membrane oxygenators were used, Terumo FX05 and Terumo RX05. The latter oxygenator was a membrane oxygenator integrated with a microembolus filter that did not require an additional one. For children with bodyweights less than 10kg, the minimum priming volume of CPB was 110ml by using the oxygenator of FX05, the thinner and shorter CPB tubes, as well as a vacuum-assist venous drainage (VAVD) controller. However, the oxygenators used in our center

for children were all RX05 before 2019, and the lengths and diameters of CPB tubes used by different perfusionists varied, resulting in different priming volumes with a range of 110-350ml.

A shallow low temperature and high flow perfusion was adopted during CPB. The cardioplegic solution was a histidine-tryptophan-ketoglutarate solution at a dose of 40 ˜ 60 ml/kg. The mean arterial pressure, central venous pressure, pump pressure, mixed venous oxygen saturation (SvO2), blood gas analysis, activity coagulation time and nasopharyngeal temperature were continuously monitored during CPB, and all parameters were adjusted within the normal range. The conventional ultrafiltration was performed to remove excess fluid and to increase the Hb concentrations.

In group A, none of the children received transfusions of PRBCs and plasma during CPB and postoperatively. In group B, all PRBCs prepared in advance were transfused during CPB, and a moderate amount of plasma were transfused in some children during CPB. No other blood products such as platelet or cryoprecipitate were transfused. Since our study was a retrospective analysis, transfusion strategies were not completely randomised. Different perfusionists have different experiences, so whether or not to transfuse blood mainly depends on preoperative hemoglobin level and different perfusionists' experience. For children with a preoperative hemoglobin level of more than 11g/dL, they might receive PRBC transfusions during CPB or not owing to different perfusionists' experience.

Statistical methods

Statistical analysis was performed with SPSS version 25. Descriptive analysis was carried out for each variable. The measurement data are expressed as (±S), and an independent sample t -test was used to compare the measurement data between the two groups. The enumeration data are expressed as the frequency or rate, and the chi-square test was used to compare the enumeration data between the two groups. P values < 0.05 were considered to be statistically significant.

RESUITS

1. **Comparison of the preoperative clinical data between the two groups.** As shown in table 1, the Hb concentration before CPB was significantly higher in group A than in group B (p <0.05), and there were no significant differences between the two groups in terms of other preoperative data.
2. **Comparison of the intraoperative clinical data between the two groups.** As shown in table 2, there were no significant differences in Hb concentrations between the two groups during CPB, before CPB weaning or after CPB weaning. The average lowest Hb concentration and Hct in the two groups were¿9.4g/dL and 26%, respectively, and the lowest Hb concentration and Hct among the two groups were 7.2 g/dL and 20%, respectively.
3. **Comparison of the postoperative clinical data between the two groups.**

As shown in table 3, the Hb concentration on the first day after surgery was lower in group A than in group B (p <0.05), but there was no difference between the two groups in Hb concentration before hospital discharge. There were no statistically significant differences in terms of the values of total bilirubin, creatinine, ALT and AST, the volume of urine, the dose of furosemide used 24 hours after surgery or the total volume of thoracic drainage fluid. There were also no statistically significant differences between the two groups in terms of postoperative pneumonia, mechanical ventilation time, ICU stay time or length of stay in the general ward postoperatively. There were no serious liver or kidney dysfunction, neurological complications or deaths in either group postoperatively.

0.5- to 2.5-year follow-up of patients in the two groups after surgery.

Patients in the two groups were followed up by telephone from 0.5 to 2.5 years after surgery. The follow-up rates were 92.73% and 90.91% for group A and group B, respectively. The reason that some patients were lost to follow-up was because the telephone information was recorded incorrectly or the telephone number could not be connected. During the follow-up, all patients were alive, and most of them had good growth, mental states and exercise tolerance. 2 patients in each group had mild anemia after surgery, and 1 patient in

each group had a slightly worse physical condition after surgery, which manifested as being sick more easily postoperatively than preoperatively.

2.5 Line charts of changes in perioperative Hb concentrations.

Changes in Hb concentrations during hospital stay: As shown in figure 1, the Hb concentration before CPB was higher in group A than in group B (p <0.05). When CPB began, the Hb concentration dropped significantly. There were no significant differences between the two groups in Hb concentrations during CPB, before and after CPB weaning. The Hb concentration on the day after surgery was significantly lower in group A than in group B (p <0.05), but there was no difference between the two groups 2 or 3 days after surgery or before hospital discharge.

Discussion

The patients included in this study were children with a bodyweight of 8-17 kg and stable hemodynamics preoperatively; children with complicated CHD and critical illness were excluded. Complicated CHD increased the need for transfusions due to hemodynamic instability and a higher risk of bleeding, and eliminating such patients could reduce the interference factors and analyze the influence of transfusions more effectively. In addition, the propensity score matching method was adopted in our study to achieve 1:1 matching for ages, body weights, CPB times and aortic cross-clamping times between the two groups, and the RACHS-1 categories of the patients were all 1-2 to improve the preoperative baseline data and surgical homogeneity of the two groups and improve the reliability of the analysis.

In these children, the average preoperative Hb concentration was [?]12g/dL in the two groups, and it was higher in the non-transfusion group than in the transfusion group, indicating that a higher preoperative basal Hb concentration can reduce the amount of transfusions needed during CPB. The Hb concentration dropped significantly when CPB began [18]. The Hb concentration was not different between the two groups during CPB and after CPB weaning. This means that choosing an appropriate membrane oxygenator and reducing the diameter and length of the CPB tubes to reduce the priming volume of CPB and removing extra water from the body using ultrafiltration technology can decrease hemodilution, maintaining a similar Hb concentration during CPB in the non-transfusion group and transfusion group. In this study, the average lowest Hb concentration and Hct in the two groups were¿9.4g/dL and 26%, respectively, and the lowest Hb concentration and Hct among the two groups were 7.2 g/dL and 20%, respectively. The SvO2 was >65% and there was no significant difference in lactic acid, indicating an adequate oxygen supply in both groups during CPB.

The Hb concentration the day after surgery was lower in the non-transfusion group than in the transfusion group, but there was no difference between the two groups before hospital discharge. This shows that although children have a smaller reserve of Hb, diluent diuresis of the body and a proper dosage of furosemide can eliminate excess water from the body, and with the recovery of Hb regeneration, the Hb concentration can be increased to 80-90% of the preoperative value before hospital discharge. The Hb concentration in the two groups was at least 10 g/dL postoperatively, and the patients did not show an insufficient oxygen supply. There was no difference in the postoperative maximum value of lactic acid, and no adverse complications occurred. There was also no difference between the two groups in terms of postoperative mechanical ventilation time, ICU stay time or lengths of stay time in the general ward. According to the telephone follow-up interviews, most children had good growth, a good mental state and good exercise tolerance for 0.5-2.5 years. This indicates that for children weighing 8-17 kg who underwent surgery for uncomplicated CHD, an adequate oxygen supply could be provided during CPB when the Hb concentration and Hct were at least 7.2 g/dL and 20%, respectively; this can significantly reduce the amount of perioperative PRBC transfusions, saving resources and costs [19]. This approach also avoids the most serious consequence of transfusions, that is, the occurrence of transfusion-related infections such as HIV.

Currently, the minimum safe Hct during CPB is still controversial. Olshove Vincent et al. considered that the minimum acceptable Hct during CPB is usually more than 20% [19]. Budak et al. believed that an Hct[?]24% during CPB was associated with a lower level of intraoperative lactic acid and a higher

psychomotor development index score at age one [20]. There are also studies suggesting that the Hct during CPB should be maintained at more than 28-30% to alleviate acute changes during CPB and ensure that the minimum Hct is always over 23.5% [21]. However, it has also been considered that there are no great clinical benefits to increasing the Hct over 25% during CPB, and it is recommended that the Hct should be maintained at approximately 24% during CPB [22]. In our study, the average lowest Hct was¿26%, and there were no adverse complications in any of the patients postoperatively. Therefore, the minimum safe Hct during CPB still needs further study, as it determines the transfusion threshold during CPB. In addition, the higher average lowest Hct benifits from the low priming volume of CPB, so reducing the priming volume is the key to reducing the usage of blood products.

Many studies believe that there are many risks and complications associated with transfusions in children [9-11, 23]. Transfusions during CPB in neonates are associated with an increased bleeding volume 48 hours after surgery [23]. Transfusions during CPB in children are associated with a prolonged duration of postoperative mechanical ventilation, ICU stay and stay time in the general ward. Transfusions are also associated with an increased postoperative CRP peak and increased urea nitrogen/creatinine ratio [9, 10]. Transfusions in children are even an independent risk factor for postoperative mortality [11]. However, other studies have suggested that the relationship between PRBC transfusions and adverse outcomes is not causative, but indicates that patients with severe disease require PRBC transfusions [24]. In the absence of clear benefits of liberal transfusion strategies, there is growing evidence to support a restrictive transfusion strategy in adults and pediatric patients. Restrictive transfusion strategy for transfusion at 7-8g/dL in adults do not produce adverse clinical outcomes [8, 25]. A meta-analysis of randomized controlled trials and retrospective studies in pediatric patients indicate that there are no significant differences in clinical outcome between restrictive and liberal transfusion approaches [26]. There were no differences in mortality, ICU time, total hospital time, mechanical ventilation time, or mean lactic acid level between the two methods [15, 27]. The restrictive transfusion strategy significantly reduced transfusions [15]. Although the restrictive transfusion strategy has been gradually accepted for pediatric patients, children with hemodynamic instability or cyanotic heart disease may benefit more from a liberal transfusion strategy, but data are scarce. In our study, there were no obvious bad results in the transfusion group, which may be due to the small sample size, and patients in our study have relatively larger bodyweight, older age and in low surgical risks reducing the susceptibility to adverse reactions to transfusions.

The effects of transfusions on infants vary with the transfusion stage. Transfusions after CPB are less complicated than transfusions during CPB [12]. Boettcher Wolfgang et al. believes that the routine application of bloodless priming in neonatal CPB is safe, and delaying transfusions until the end of CPB is beneficial to the overall restrictive transfusion approach [10]. The reason is that transfusions during CPB make PRBCs easily form into microaggregates and the brittleness of RBCs membrane increases, which lead to microcirculation embolism easier; Blood transfusions cause an increase in the erythrocyte morphological index and a decrease in the deformation index during CPB [28]. However, to improve the accuracy of the comparison, we excluded the cases receiving blood transfusion postoperatively. Transfusions are mainly applied during CPB, but blood conservation is a team project, so in order to make significant progress in maintaining a blood reserve, perfusionists, surgeons, anesthesiologists, ICU doctors, and especially perfusionists, need to be more proactive in reducing blood product usage.

Research limitations

This study had four limitations. Firstly, this is a retrospective study, so it may have sample selection bias, and further prospective randomized controlled studies are needed to analyze the effects of PRBC transfusions on surgical prognosis. Secondly, patients with complicated CHD surgery or in a critical condition were excluded and patients had larger bodyweights and older age in our study, but the value of transfusion or not during CPB maybe more meaningful in the more complex and smaller children, so this study is limited by the excluded patients, which requires us to study further. Third, the use of near-infrared spectroscopy (NIRS) can guide clinicians to perform transfusions based on real-time data in each stage of surgery [20], helping to optimize patient management and improve brain protection during CPB. At present, NIRS in our center is

only used for patients with deep hypothermia and circulatory arrest and has not been popularized for every patient, so we aim to further expand its application to every patient. Fourth, the follow-up time of this study was 0.5-2.5 years, which is still not long enough. Further follow-up observation is needed to understand the influence of this approach on the growth and mental state of children.

Conclusion

Non-transfusion CPB does not affect the Hb concentrations before hospital discharge, the postoperative recovery or the short-term follow-up outcomes in children with bodyweights of 8-17kg undergoing uncomplicated congenital heart surgery, indicating that these children can avoid transfusions during cardiac surgery.

Abbreviations

CPB: cardiopulmonary bypass; PRBCs: packed red blood cells; Hb: hemoglobin; CHD: congenital heart disease; Hct: hematocrit; RACHS: Risk Adjustment in Congenital Heart Surgery; WBC: white blood cell; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; VAVD: vacuum-assist venous drainage; SvO2: venous oxygen saturation; ASD: atrial septal defect; PDA: patent ductus arteriosus; PAPVC: partial anomalous pulmonary venous connection; PS: pulmonary stenosis; VSD: ventricular septal defect; PECD: partial endocardial cushion defect; EF: ejection fraction; NIRS: near-infrared spectroscopy.

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Authors' contributions

LW collected the data, conceived and wrote the manuscript. YD, JZD, XCL, YQQ, XFD, LWC reviewed the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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Table 1 Comparison of the preoperative clinical data between the two groups

Items	Non-transfusion group (group A, n=55)	Transfusion group (group B, n=55)	*P* value
male/case	32	31	0.830
age/month (range)	12˜72 (29.45±14.72)	10˜72 (29.82±17.76)	0.946
body weight/kg (range)	8˜17 (12.15±2.57)	8˜17 (12.00±2.83)	0.673
surgeons/case			
A	17	14	
B	10	9	
C	7	6	
D	6	9	
E	8	9	
F	7	8	
RACHS-1 category and main diagnostic			
RACHS-1 1			
ASD (+PDA)	8	7	
PAPVC	4	4	
RACHS-1 2			
ASD+PS	4	5	
VSD	11	12	

VSD+ASD (+PDA)	8	10	
VSD+ASD+PS	4	4	
VSD+PS	7	5	
PS	5	5	
PECD	4	3	
EF/%	67.22±6.33	68.99±5.90	0.251
WBC/(10*9/L)	8.38±2.30	9.07±2.24	0.227
Hb/(g/dL)	13.80±2.15	12.72±1.90	0.036*
platelet/(10*9/L)	318.67±79.12	343.35±102.69	0.061
CRP/(mg/L)	0.32±0.32	0.78±1.45	0.129
total bilirubin (umol/L)	6.89±2.79	6.90±3.25	0.994
ALT/(IU/L)	14.47±4.17	16.97±19.20	0.504
AST/(IU/L)	33.94±7.62	31.78±8.23	0.277
creatinine/(umol/L)	28.64±6.62	30.03±7.25	0.423

Note: *p <0.05, **p <0.01. RACHS: Risk Adjustment in Congenital Heart Surgery; ASD: atrial septal defect; PDA: patent ductus arteriosus; PAPVC: partial anomalous pulmonary venous connection; PS: pulmonary stenosis; VSD: ventricular septal defect; PECD: partial endocardial cushion defect; EF: ejection fraction, WBC: white blood cell, Hb: hemoglobin, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

Table 2 Comparison of the intraoperative clinical data between the two groups

Items	Non-transfusion group (group A, n=55)	Transfusion group (group B, n=55)	P value
CPB time/min	74.45±46.77	80.12±35.83	0.517
aortic cross-clamping time/min	34.00±36.30	37.18±29.31	0.919
priming volume of CPB/ml	191.22±65.22	210.24±51.54	0.328
volume of PRBCs transfused during CPB/ml	0	218.18±81.79	0.000**
average lowest Hb during CPB/(g/dL)	9.41±1.18	9.46±1.15	0.512
average lowest Hct during CPB/(%)	26.14±3.28	26.25±3.19	0.516
lowest Hb during CPB/(g/dL)	7.2	8.3	
lowest Hct during CPB/(%)	20	23	
Hb before CPB weaning/(g/dL)	11.20±2.07	11.97±1.67	0.113
Hb after CPB weaning/(g/dL)	10.70±2.05	11.55±1.26	0.066
lactic acid before CPB/(mmol/L)	0.98±0.31	1.05±0.45	0.449
lactic acid after CPB/(mmol/L)	1.77±0.91	1.72±0.69	0.825

Note: * p <0.05, ** p <0.01. CPB: cardiopulmonary bypass; PRBCs: packed red blood cells; Hb: hemoglobin.

Table 3 Comparison of the postoperative clinical data between the two groups

Items	Non-transfusion group (group A, n=55)	Transfusion group (group B, n=55)	P value
Hb on the day after surgery/(g/dL)	11.48±1.70	12.37±1.54	0.029*
Hb on the 2 or 3 day after surgery/(g/dL)	11.62±2.36	11.87±1.65	0.754
Hb before hospital discharge/(g/dL)	11.09±1.30	11.44±1.22	0.296
lowest value of platelet count/(10*9/L)	202.59±74.14	218.15±65.87	0.374
highest value of WBCs/(10*9/L)	13.06±3.77	14.26±4.73	0.258
highest value of CRP/(mg/L)	40.10±30.13	42.64±34.58	0.779
highest value of lactic acid/(mmol/L)	2.25±0.83	2.93±2.35	0.150
highest value of temperature/	38.38±0.64	38.38±0.49	0.966
highest value of total bilirubin/(μmol/L)	13.62±7.27	14.99±12.61	0.606
highest value of ALT/(IU/L)	25.28±14.01	22.04±6.67	0.249
highest value of AST/(IU/L)	162.56±113.27	126.72±55.73	0.119
highest value of creatinine/(μmol/L)	31.27±9.06	35.79±11.85	0.110
unilateral pneumonia/case(%)	12(21.82)	9(16.36)	0.455
bilateral pneumonia/case(%)	6(10.91)	9(16.36)	0.396
urine volume 24 hours after surgery/ml	884.21±291.14	779.03±225.31	0.115
dose of furosemide 24 hours after surgery/mg	10.86±7.76	9.88±6.52	0.583
total volume of thoracic drainage fluid/ml	98.28±54.37	119.70±84.86	0.232
mechanical ventilation time/h	11.77±12.40	12.73±18.08	0.804
ICU stay time/d	1.60±1.30	1.68±1.13	0.778
postoperative stay in the general ward/d	7.28±4.36	8.82±3.72	0.131

Note: * p <0.05, ** p <0.01.