An Individualized Red Blood Cell Transfusion Strategy Using Pediatric Perioperative-Transfusion-Trigger Score Reduced Perioperative Blood Exposure for Children: A Randomized Controlled Clinical Trial

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Abstract

Background

The optimal red blood cell transfusion strategy in children remains unclear. We developed an individualized pediatric red blood cell transfusion strategy, and postulated that red blood cell transfusion guided by this strategy in children would reduce blood exposure without compromising patients' safety.

Methods

In this randomized controlled clinical trial, 99 children undergoing non-cardiac surgeries who had blood loss of more than 20% total blood volume were randomly assigned to an individualized-strategy group using Pediatric Perioperative-Transfusion-Trigger Score, or a control group. The amount of transfused red blood cells was counted, and patients were followed up for postoperative complications by day-30. This trial was registered at the Chinese Clinical Trial Registry (Registration number: ChiCTR-IRP-16007909, Date:07/02/2016).

Results

26 children (53.1%) in individualized-strategy group received transfusion perioperatively, as compared with 37 children (74%) in the control group ($p<0.05$). During surgery, children in individualized-strategy group were exposed to fewer transfusions than in the control group (0.87 ± 1.03 vs. 1.33 ± 1.20 red-blood-cell units per patient, $p<0.05$). The incidence of severe complications in individualized-strategy group had the lower trend compare to the control group (8.2% vs. 18%, $p=0.160$). No significant differences were found in the other outcomes.

Conclusion

This study proved that transfusion guided by the individualized strategy reduced perioperative blood exposure in children, without increasing the incidence of severe complications. This conclusion needs to be further confirmed by implementing multicenter, large-sample clinical trials.

Trial registration

The study was registered at <http://www.chictr.org.cn/showproj.aspx?proj=13361> (Registration number: ChiCTR-IRP-16007909, Date:07/02/2016).

Background

Allogeneic Red blood cell (RBC) transfusion is an important therapeutic way in children with great blood loss during surgery. However, allogeneic transfusion can increase risks, which has been reported associated with increased perioperative morbidity and mortality in children. [1, 2, 3] Therefore, the benefits and risks of allogeneic RBC transfusion in children should be assessed carefully.

Current studies have demonstrated significant changes in RBC transfusion practices, among which restrictive strategy has become a worldwide consensus. [4, 5, 6] However, attention must be paid to the use of restrictive strategy in children, for the concern that it might lead to the risk of oxygen deficiency. [7, 8, 9] Therefore, an individualized strategy considering patients' medical condition and age is necessary.

Evaluating oxygen supply and consumption balance, we established an individualized transfusion strategy using "Perioperative-Transfusion-Trigger Score" in adults. We conducted a clinical trial of adult patients with spinal surgery and the results suggested this individualized strategy was safe and cost-effective. [10]

Based on this score, taking account of children's age and developmental stage, we designed a Pediatric Perioperative-Transfusion-Trigger Score (Pediatric-POTTS) (Table 1) to guide transfusion in children. We designed this trial to test the hypothesis that transfusion guided by the individualized strategy could decrease exposure to blood, without increasing perioperative complications in children.

Methods

Ethics and Consent to Participate

The study protocol was registered at <http://www.chictr.org.cn/showprojen.aspx?proj=13361> (Registration number: ChiCTR-IRP-16007909, Date: 07/02/2016). The protocol was reviewed and approved by the ethics committee of West China Hospital, Sichuan University (No. 2013-101). Written informed consent was obtained from all of the children's parent or surrogate decision maker.

Study Design and Treatment Protocols

This study was designed as a single center, prospective, open-label, randomized, controlled clinical trial, assessing the safety and efficacy of the individualized strategy in pediatrics. The participants were randomly assigned to an individualized-strategy and a control group. By following the NIDCR Policy on Data and Safety Monitoring, the statistician and members of the data and safety monitoring committee were masked.

From June 2014 to June 2016, we enrolled children between 1 days and 14 years of age undergoing elective non-cardiac surgery with blood loss more than 20% total blood volume in West China Hospital of Sichuan University. Premature infants or low-birth-weight newborns (body weight <2500g), patients declined to receive transfusion, patients with cyanotic congenital heart disease, severe hematological disorders or hemoglobinopathy, metastasis of tumor or multiple tumors were excluded.

The Pediatric Perioperative-Transfusion-Trigger Score

RBC transfusion in the individualized-strategy group were guided by the Pediatric Perioperative-Transfusion-Trigger Score (Table 1), which is modified from Perioperative-Transfusion-Trigger Score for adults. It consists of 4 items: 1) Minimum inhale oxygen concentration to keep pulse oxygen saturation $\geq 95\%$, which is a clinical indicator for pulmonary function; 2) Infusing rate of adrenaline required to maintain an adequate cardiac output. Here, adrenaline could be replaced by other inotropic agents with equivalent potent infusing rates because different institution or medical group may use different drug as the first line inotropic; 3) Core body temperature, a clinical indicator of total body oxygen consumption; 4) Age of the child.

Table 1
Pediatric Perioperative-Transfusion-Trigger Score

Points added	Adrenaline infusion rate ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)	Minimum FiO_2 to keep $\text{SpO}_2 \geq 95\%$	Core body Temperature ***** ($^{\circ}\text{C}$)	Age	Maximum score
0	Not required	35%	38 $^{\circ}\text{C}$	7~14y	10
+1	$\leq 0.05 \mu\text{g/kg.min}$	36~50%	38~40 $^{\circ}\text{C}$	1~7y	11
+2	$> 0.05 \mu\text{g/kg.min}$	$\geq 51\%$	40 $^{\circ}\text{C}$	1m~1y	12
+3				Newborn	13
The final score is the sum of 6 basal points plus all added points.					

Adrenaline infusion rate: Adrenaline infusion rate required to maintain an adequate cardiac output.

$\text{FiO}_2\%$: Fraction of inspired oxygen, a clinical indicator for pulmonary function. **Core body temperature:** a clinical indicator of total body oxygen consumption. **Maximum score:** Every age group has a maximum score, the final score is no more than the maximum score.

Treatment assignment

For all the patients, hemoglobin(Hb) concentration and the Pediatric-POTTS were measured before surgery, at completion of surgery, on the day of discharge, and whenever RBC transfusion were considered.

In the individualized-strategy group, RBC transfusion triggered when the Hb concentration was below the Pediatric-POTTS. If the instant Hb concentration was equal to or lower than the Pediatric-POTTS, RBC would be transfused. (see S1 Appendix to use Pediatric-POTTS)

The amount of RBC transfusion was set according to the formula:

The volume of packed RBC (ml) = Total blood volume $\times$ (target Hb - observed Hb) / Hb of packed RBC

(Target Hb = Score +2)

In the control group, when the patient's Hb concentration was lower than 8g per deciliter (newborn lower than 10g per deciliter), RBC transfusion would be initiated. The target Hb concentration was based on the decision of the physician, which was not subject to special restrictions.

During the 30-day follow-up period, Hb concentration were measured at least once within 6 hours after each transfusion and at hospital discharge. Postoperative complications were observed and recorded daily. Follow-up after discharge were completed by telephone. Data were collected by trained research personnel and stored in West China Hospital. Statistician and members of the safety and data monitoring board were unaware of the assignments.

Outcomes

The primary outcomes were the utilization of RBC transfusion and perioperative complications by day-30. The secondary outcomes included ICU occupancy, ICU duration time, mechanical ventilation rate, hospitalization costs, postoperative to discharge cost.

Statistical analysis

We estimate that we need to enroll at least 90 children in order to detect an absolute reduction of 10 percent in RBC transfusion exposure in the individualized-strategy group compare to the control group, with an overall one-sided alpha of 5% and a power of 90%.

The statistical analysis of this study was performed using the SAS 9.1 statistical software. All statistical tests were performed on a two-sided test with an alpha of 0.05.

Preoperative demographic baseline characteristics were compared between individualized-strategy and the control group. We presented mean $\pm$ standard deviation or median [Interquartile range] for continuous variables as appropriate. Frequency (percentage) was used to summarize categorical variables.

The chi-square test was used to study transfusion rate and ICU occupancy rates between two groups. The student t-test was used for comparison of the amount of RBC transfusion, ICU time, hospitalization time and costs. A rank-sum test was used to compare the incidence of severe complications.

Results

Baseline information

242 patients were eligible for participation in this trial (June 2014 to June 2016), of whom 142 were excluded. 100 patients underwent randomization and 1 patient was withdrawn at surgeon' request. Therefore, 99 patients enrolled in the study and were included in the final analysis, of whom 49 in the individualized-strategy group, 50 in the control group (Fig. 1).

242 patients were eligible for the trial, of whom 96 had hemoglobin concentrations not dropping 20% of total blood volume, and 23 declined to sign informed consent, 11 declined by surgeon, 6 excluded because surgery was cancelled and 6 for other reasons. 100 patients underwent randomization and 1 patient was withdrawn at surgeon's request. 99 patients were included in the final analysis, 49 in the individualized-strategy group, 50 in the control group.

Patients' baseline characteristics were similar between two groups. Hemoglobin concentrations at the time of randomization were similar (Table 2).

Table 2
Baseline characteristics of the patients

Characteristic	Individualized group (n = 49)	Control group (n = 50)	p-value
Age -yr	3.40±3.40	3.36±4.11	0.809
Male sex-no.(%)	24(49.0)	16(32.0)	0.085
Body weight -kg	13.79±9.41	15.87±19.45	0.517
Height -cm	89.86±31.19	86.08±32.63	0.410
ASA-no. (%)			0.904
or	39(79.6%)	38(76%)	
	9(18.4%)	11(22%)	
	1(2%)	1(2%)	
Preoperative Hemoglobin concentration -g/dl	11.29±1.67	11.88±1.86	0.118
Type of surgery-no.(%)			0.138
General	33(67.3%)	32(64%)	
Orthopedic	11(22.4%)	17(34%)	
Thoracic	5(10.2%)	1(2%)	
Operation time -min	116.31±86.13	177.52±87.27	0.423
Tumor –no.(%)	11(24.5%)	12(24%)	0.855
Data reported as means ±SD. Percentages may not sum to 100 because of rounding.			

RBC transfusion rate

26 patients (53.1%) received RBC transfusions in the individualized-strategy group while 37 patients (74.0%) received RBC transfusions in the control group perioperatively(53.1% vs.74.0%; odds ratio, 0.40; 95% confidence interval [CI] 0.17 to 0.93; p=0.03). In addition, the hemoglobin concentrations at

discharge were 9.87 ± 2.34 g per deciliter in individualized-strategy group as compared to 11.03 ± 1.53 g per deciliter in the control group (Difference in means, -1.16; 95%CI -1.95 to -0.38; $p=0.004$). There were no significant differences in the amount of RBC transfusion per patient (162.25 ± 305.25 ml vs. 247.40 ± 263.09 ml, $p=0.140$).

During surgery, 24 patients (49.0%) received RBC transfusions, as compared with 34 patients (68.0%) in the control group ($p=0.055$). Children in the individualized-strategy group were exposed to fewer transfusions than in the control group (0.87 ± 1.03 vs. 1.33 ± 1.20 RBC units per patient; difference in means, -0.46; 95% CI -0.91 to -0.016; $p=0.043$). A smaller volume of RBC was transfused per patient in individualized group than that in the control group (123.67 ± 186.34 vs. 219.60 ± 250.00 ml per patient; difference in means, -95.93; 95% CI -184.02 to -7.83; $p=0.033$).

During the period from postoperative to discharge, the number of transfused patients in both groups was 6. There were no significant differences in the amount of RBC per patient (38.57 ± 160.08 ml vs. 27.80 ± 82.23 ml, $p=0.67$) postoperatively. (Table 3)

Table 3
Red blood cell transfusion

Variables	Individualized group (n = 49)	Control group (n = 50)	Odds Ratio or Difference in Means (95%CI)	p-value
Intraoperative				
RBC transfusion - No. of patients (%)	24 (49%)	34 (68%)	0.45(0.20 to 1.02)	0.055
Units of RBC transfused per patient -u	0.87±1.03	1.33±1.20	-0.46(-0.91 to -0.016)	0.043
RBC transfusion per patient -ml	123.67±186.34	219.60±250.00	-95.93(-184.02 to -7.83)	0.033
Volume of RBC per transfused patient -ml/kg	19.68±1.75	27.45±4.27	-7.76(-17.07 to 1.53)	0.099
Postoperative				
RBC transfusion - No. of patients (%)	6 (12.2%)	6 (12%)	1.02(0.31-3.42)	0.970
Units of RBC transfused per patient -u	0.26±0.85	0.17±0.48	0.09(-0.19 to 0.36)	0.540
RBC transfusion per patient -ml	38.57±160.08	27.8±83.23	10.77(-40.00 to 61.52)	0.674
Volume of RBC per transfused patient -ml/kg	20.71±4.98	32.67±9.02	-11.96(-34.92 to 10.99)	0.272
Total				
RBC transfusion - No. of patients (%)	26 (53.1%)	37 (74.0%)	0.40(0.17-0.93)	0.030
Units of RBC transfused per patient -u	1.12±1.59	1.50±1.24	-0.38(-0.94 to 0.19)	0.189
RBC transfusion per patient -ml	162.25±305.25	247.40±263.09	-85.16(-198.75 to 28.44)	0.140
Volume of RBCs per transfused patient -ml/kg	22.95±13.51	30.52±27.67	-7.57(-19.32 to 4.17)	0.202
Pre-discharge Hemoglobin concentration-g/dl	9.87±2.34	11.03±1.53	-1.16(-1.95 to -0.38)	0.004

Data reported as means ±SD. Percentages may not sum to 100 because of rounding. In China, one unit of red blood cell is collected from 200ml of whole blood.

Postoperative complications

20 patients developed postoperative complications. According to our complication rating system (S2 Appendix), grade 1 and 2 were defined as mild complications, grades 3, 4, and 5 were defined as severe complications. There was 1 patient with severe complication in individualized-strategy group and 3 patients in the control group. A 30-day postoperative mortality was equal in two groups. The prevalence of severe complication in the individualized-strategy group was no more than that in the control group (8.2% vs. 18%, $p=0.160$) (Table 4).

Table 4
Postoperative complications

Grade	Individualized group(n.)	Control group(n.)	p-value
1	6	1	
2	3	6	
3	0	1	
4	0	1	
5	1	1	
Rank sum test	8.2%	18%	0.160

Secondary analysis

The number of patients who were admitted to ICU after surgery was 26 (53.1%) in the individualized-strategy group and 28 (56%) in the control group ($p= 0.769$). There were no significant differences in ICU duration between two groups (55.69 ± 85.74 h vs. 54.14 ± 96.16 h, $p= 0.8$). There were no statistical differences in mechanical ventilation time after surgery

(5.43 ± 17.23 h vs. 2.70 ± 4.00 h, $p=0.802$). There were no differences between two groups in total hospitalization costs (37863.77 ± 25960.83 Chinese yuan vs. 41991.12 ± 24421.14 Chinese yuan, $p= 0.198$), ICU costs (5858.00 ± 9341.74 Chinese yuan vs. 6899.45 ± 12332.26 Chinese yuan, $p= 0.901$), and postoperative costs (12453.8 ± 14989.81 Chinese yuan vs. 11405.93 ± 11713.63 Chinese yuan, $p=0.605$) (Table 5).

Table 5
ICU occupancy and hospitalization costs

Variables	Individualized group	Control group	p-value
ICU occupancy - No. of patients (%)	26 (53.1%)	28 (56%)	0.769
ICU duration -h	55.69±85.74	54.14±96.16	0.8
Mechanical ventilation - No. of patients (%)	26 (53.1%)	28 (56%)	0.769
Mechanical ventilation time -h	5.43±17.23	2.70±4.00	0.802
Total hospitalization costs-yuan	37863.77±25960.83	41991.12±24421.14	0.198
ICU costs-yuan	5858.00±9341.74	6899.45±12332.26	0.901
Postoperative cost-yuan	12453.8±14989.81	11405.93±11713.63	0.605
Data reported as means ±SD.			

Discussion

Compared with the control group, the individualized-strategy group resulted in a 44.6% decrease in the number of patient exposure to transfusion and 35.7% reduction in the number of RBC units transfused. The study demonstrated that there were no differences in the incidence of severe postoperative complications.

Red blood cell is the main carrier of oxygen in human. The requirements to transfuse RBC depends on whether it has the capacity to prevent or reverse tissue hypoxia which caused by insufficient oxygen transport. [11,12] The balance of oxygen supply and consumption is directly proportional to hemoglobin concentration, arterial oxygen saturation, cardiac output and inversely proportional to human oxygen consumption. [13] Based on this, we used 1)infusing rate of adrenaline required to maintain an adequate cardiac output; 2) Minimum inhale oxygen concentration to keep pulse oxygen saturation $\geq 95\%$; 3) Core body temperature to establish a

Perioperative-Transfusion-Trigger Score to guide RBC transfusion in adults. We integrated age in Pediatric Perioperative-Transfusion-Trigger Score because ranges for hemoglobin concentration in children change with age. [14] This semi-quantitative score could be applied by any physician without complex measurements. [10,15]

Above all, the pediatric individual transfusion strategy was designed in order to reduce perioperative blood exposure in children. The reason why this strategy was able to reduce the amount of RBC transfusion may be multifactorial. First, this strategy was based on a restrictive transfusion strategy, setting the minimum hemoglobin threshold in the best status of children. Second, when the transfusion target was reached, RBC transfusion stopped immediately.

There are individual differences in children's tolerance to anemia. We were able to identify and treat children of insufficient oxygen supply by the transfusion strategy using Pediatric-POTTS, which guaranteed those children to get enough oxygen supply to avoid further damage.

Furthermore, the Pediatric-POTTS was a dynamic score. With the change of clinical condition of patients, repeated evaluation were carried out to determine whether RBC transfusion was needed, which provided a prompt response to patient's need.

In the control group, we chose the strategy that start RBC transfusion when Hb concentration was lower than 8g per deciliter (newborn less than 10g per deciliter), which was recommended by the guideline of RBC transfusion from the European Society of Anesthesiology. [16]

This study was a single-center study with a sample size of 99 patients, including general surgeries, orthopedic surgeries, and a small number of thoracic surgeries. It did not include cardiac surgery or neurosurgery. In addition, we were unable to detect meaningful differences in secondary clinical outcomes. Due to the low incidence of transfusion adverse reactions, [2] there were no reports of relevant transfusion reactions in the study.

Based on this study, we plan to conduct a multicenter, randomized, large-sample trial to produce stronger evidence. We are trying to observe whether this individualized RBC transfusion strategy could affect the long-term prognosis and neurodevelopment of children who have surgery.

Conclusion

This trial demonstrated that the individualized RBC transfusion strategy with Pediatric-POTTS could significantly reduce perioperative blood exposure in children, without increasing the incidence of severe complications. This conclusion needs to be confirmed by multicenter, large-sample clinical trials.

Abbreviations

Pediatric POTTs	Pediatric Peri-Operative Transfusion Trigger Score
ICU	Intensive Care Unit
Hb	Hemoglobin
SvO2	Oxygen Saturation of Mixed Venous Blood
SaO2	Oxygen Saturation of Arterial Blood
CO	Cardiac Output
SpO2	Pulse Oxygen Saturation
CRF	Case Report Form
MABL	Maximum Allowable Blood Loss
EBV	Estimated Blood Volume
EBL	Estimated Blood Loss
Hct	Hematocrit
CVP	Central Venous Pressure
PCWP	Pulmonary Capillary Wedge Pressure
FiO2	Fraction of inspiration O2
SAE	Serious Adverse Event

Declarations

Ethics approval and consent to participate

The study protocol was in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the ethics committee of West China Hospital, Sichuan University (No. 2013-101). Written informed consent was obtained from all of the children's parent or surrogate decision maker. The study protocol was registered at <http://www.chictr.org.cn/showprojen.aspx?proj=13361> (Registration number: ChiCTR-IRP-16007909, Date: 07/02/2016).

Consent for publication

All authors made an agreement for publication.

Availability of data and material

All data will be available on request.

Competing interests

The authors have no conflict of interest to declare.

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Authors' contributions

Zhen Luo participated in the study conception, proposal writing, data collection and the article writing and editing and final draft. She was a major contributor in writing the manuscript.

Yunxia Zuo has contributed in the study conception, proposal writing, manuscript revision and article draft. Yansong Li participated in study design, data analysis. Jin Liu has contributed in the study conception, proposal writing. Ren Liao has contributed in proposal preparation, data collection. The authors read and approved the final manuscript.

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Supplementary Information

Supporting Information S3-S6 are not available with this version.

Figures

Figure 1

Consort flow chart

Supplementary Files

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- [S1Appendix.docx](#)
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