Intensive Care Med (2013) 39:2011–2019
DOI 10.1007/s00134-013-3085-7

ORIGINAL ARTICLE

**D. H. de Gast-Bakker**
**R. B. P. de Wilde**
**M. G. Hazekamp**
**V. Sojak**
**J. J. Zwaginga**
**R. Wolterbeek**
**E. de Jonge**
**B. J. Gesink-van der Veer**

# Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: a randomized controlled trial

Received: 4 April 2013
Accepted: 19 August 2013
Published online: 31 August 2013


This article is discussed in the editorial available at: doi: 10.1007/s00134-013-3082-x.

**Electronic supplementary material**
The online version of this article (doi:10.1007/s00134-013-3085-7) contains supplementary material, which is available to authorized users.

D. H. de Gast-Bakker · R. B. P. de Wilde · E. de Jonge · B. J. Gesink-van der Veer
Pediatric Intensive Care Unit, Leiden University Medical Center, Leiden, The Netherlands

M. G. Hazekamp · V. Sojak
Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands

J. J. Zwaginga
Center for Clinical Transfusion Research, Sanquin Research, Leiden, The Netherlands

J. J. Zwaginga
Department of Immuno-hematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands

R. Wolterbeek
Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

R. B. P. de Wilde (✉)
Albinusdreef 2, PO Box 9600,
2300 RC Leiden, The Netherlands
e-mail: r.b.p.de_wilde@lumc.nl
Tel.: +31-71-5262619
Fax: +31-71-5266966

**Abstract** *Objective:* To investigate the safety and effects of a restrictive red blood cell (RBC) transfusion strategy in pediatric cardiac surgery patients. *Design:* Randomized controlled trial. *Setting:* Pediatric ICU in an academic tertiary care center, Leiden University Medical Center, Leiden, The Netherlands. *Patients:* One hundred seven patients with non-cyanotic congenital heart defects between 6 weeks and 6 years of age. One hundred three patients underwent corrective surgery on cardiopulmonary bypass. *Interventions:* Prior to surgery patients were randomly assigned to one of two groups with specific RBC transfusion thresholds: Hb 10.8 g/dl (6.8 mmol/l) and Hb 8.0 g/dl (5.0 mmol/l). *Measurements:* Length of stay in hospital (primary outcome), length of stay in PICU, duration of ventilation (secondary outcome), incidence of adverse events and complications related to randomization (intention to treat analysis). *Results:* In the restrictive transfusion group, mean volume of transfused RBC was 186 (±70) ml per patient and in the liberal transfusion group 258 (±87) ml per patient, (95 % CI 40.6–104.6), $p < 0.001$. Length of hospital stay was shorter in patients with a restrictive RBC transfusion strategy: median 8 (IQR 7–11) vs. 9 (IQR 7–14) days, $p = 0.047$. All other outcome measures and incidence of adverse effects were equal in both RBC transfusion groups. Cost of blood products for the liberal transfusion group was 438.35 (±203.39) vs. 316.27 (±189.96) euros (95 % CI 46.61–197.51) per patient in the restrictive transfusion group, $p = 0.002$. *Conclusions:* For patients with a non-cyanotic congenital heart defect undergoing elective cardiac surgery, a restrictive RBC transfusion policy (threshold of Hb 8.0 g/dl) during the entire perioperative period is safe, leads to a shorter hospital stay and is less expensive.

**Keywords** Pediatrics · Cardiac surgery · Critical care · Randomized clinical trial · Erythrocyte · Transfusion

## Introduction

Blood transfusions can be lifesaving in patients with excessive bleeding or severe anemia. A retrospective survey among pediatric intensive care units in the USA showed that 54.5 % of all children with a pre-transfusion hemoglobin concentration (Hb) below 9 g/dl (5.6 mmol/l) received at least one red blood cell (RBC) transfusion [1]. Although transfusion practice has become increasingly safe over the years, numerous data published in the past decade have demonstrated various deleterious effects of blood transfusions [2–11]. Therefore, current transfusion practice has evolved to increasingly restrictive use of blood product transfusions in adults [12–14].

Up until quite recently, it has been a widely held belief that withholding blood transfusions to anemic young children, especially infants, is harmful. Children have an increased metabolic rate and thus an increased tissue oxygen demand compared to adults, while at the same time they have a limited ability to increase their cardiac output to compensate for a fall in Hb. Like in adults, pediatric studies have demonstrated not only an increase in morbidity but also an increased mortality associated with RBC transfusion [5–8, 15–17]. Most patients, also children, tolerate lower hemoglobin levels than were previously held appropriate for this age group, without any deleterious effects [9, 14, 18–26].

Since the landmark paper by Lacroix [27], which demonstrated that a restrictive RBC transfusion strategy with an Hb threshold of 7 g/dl (4.4 mmol/l) in stable, critically ill children decreases transfusion requirements without increasing adverse outcome, clinicians have questioned the need for a higher Hb in the pediatric population [15, 16, 28, 29]. However, a well-defined Hb threshold value to use for making the decision when to transfuse or not is unavailable [15, 16, 18–21, 28, 30, 31].

Perioperative management in congenital heart surgery is aimed at maximizing systemic oxygen delivery. It is generally believed that oxygen delivery can be improved by increasing Hb; therefore, treatment of anemia is the main rationale for transfusing children after cardiac surgery [9, 15–17, 20, 21, 32]. This concept, however, has never been proven [9, 28, 32].

The published experience with restrictive RBC transfusion strategies in pediatric cardiac surgery is not extensive. In this study we sought to determine the safety and effects of a restrictive RBC transfusion strategy in children undergoing corrective surgery for a non-cyanotic congenital heart defect.

## Methods and materials

### Setting

This randomized clinical trial was conducted at Leiden University Medical Center (LUMC), an academic tertiary care center. The study was approved by the institutional Ethics Committee (protocol P07.186).

### Study population

Between April 2009 and January 2012, 162 eligible patients were scheduled for elective surgery for a non-cyanotic congenital heart defect. Inclusion criteria were elective surgery for a congenital heart defect; patients between 6 weeks and 6 years of age and peripheral oxygen saturation ($SpO_2$) above 95 % on admission.

All parents/legal guardians received written information about the study protocol prior to scheduled admission to the hospital. Additional verbal information was presented to the parents/legal guardians on the day of hospital admission. Prior to anesthesia and surgery, written informed consent was obtained from all parents/legal guardians. Upon request of parents/legal guardians, patients could be withdrawn from study participation at any time.

### Study protocol

In a single-center open-labeled randomized controlled trial, the safety and effects of two RBC-transfusion policies were determined in pediatric patients with a non-cyanotic congenital heart defect that required elective cardiac surgery.

After written informed consent, sealed randomization envelopes were opened. Patients were allocated to one of two transfusion strategies. In the liberal transfusion group (group A) patients received RBC transfusion if their Hb concentration dropped below 10.8 g/dl (6.8 mmol/l). In the restrictive transfusion group (group B), patients received an RBC transfusion if their Hb concentration was 8.0 g/dl (5.0 mmol/l) or less. When a threshold was reached, each patient was to receive an RBC transfusion of 10 ml/kg. RBC units were always leukocyte-depleted. The transfusion policy was to be adhered to from induction of anesthesia until hospital discharge. All other aspects of patient care were left to the discretion of the attending physician. Hb values were measured 1 day before the operation, at induction of anesthesia, following both initiation and discontinuation of cardiopulmonary bypass (CPB) and directly on admission to the PICU. At the PICU, Hb values are checked routinely, every 6 h for the first 24 h after admission, if necessary more frequently on an individual basis and thereafter once daily. Transfusion thresholds were communicated to the attending physician and entered in the Patient Data Management System (PDMS) (Metavision, iMDsoft, Needham, MA, USA) at bedside. Nurses were asked to monitor and report blood loss and also to report all RBC transfusions by entering the RBC transfusion volume and

RBC bag ID number into the PDMS. When an RBC transfusion was either withheld or administered in contradiction to the randomization protocol, this was considered a protocol violation.

## Anesthesia and CPB

Anesthesia was performed with inhalation of sevoflurane followed by intravenous administration of pancuronium, sufentanil and propofol in all patients. All patients were intubated with a cuffed endotracheal tube (Kimvent™ Microcuff™, Kimberly-Clark Health Care, Roswell, GE, USA) and ventilated according to institutional protocol.

All patients received a peripheral venous catheter, an arterial canula and a central venous PediaSat Oximetry Catheter (Edwards Lifesciences, Irvine, CA, USA). The PediaSat catheter was preferably sited in the right jugular vein for additional monitoring of central venous oxygen saturation ($ScvO_2$). Additional monitoring in the operating theatre and PICU included bilateral cerebral oxygen saturation with a Somanetics Invos Cerebral Oximeter (Covidien, Mansfield, MA, USA) and depth of anesthesia with the Bispectral index (compact BISx Power Link™, Philips, Eindhoven, The Netherlands). The last two monitoring tools are standard care for all pediatric cardiac operations performed at our hospital.

Cardiopulmonary bypass was performed using phosphorylcholine-coated closed circuit tubing and a hollow-fiber membrane oxygenator (Sorin Group Italia, Mirandola, Modena, Italy), using standard techniques according to age and weight. The CPB circuit was primed with crystalloid and colloid solutions. Mannitol, albumin, RBCs and fresh frozen plasma (FFP) were added to the bypass circuit as needed. The amount of RBCs was individually calculated using the following variables: bodyweight, preoperative hematocrit and prime volume:

$$\mathrm{CV} = \text{weight} \times 80\ \text{ml},$$

$$\mathrm{Ek} = \mathrm{CV} \times \mathrm{Ht},$$

$$\mathrm{Tv} = \mathrm{CV} + \text{CPB volume},$$

$$\mathrm{En} = \mathrm{Tv} \times 0.25,$$

$$\mathrm{En} - \mathrm{Ek}/0.55 = \text{ml RBC needed for prime}.$$

In this calculation, CV = circulating blood volume, Ek = volume of erythrocytes, Tv = total volume, and En = the calculated amount of erythrocytes resulting in a Ht of 0.25.

Myocardial protection was achieved with cold crystalloid cardioplegia. After separation from CPB, heparin was reversed with protamine 3 mg/kg or more as necessary in order to normalize the activated clotting time to the preoperative value. On completion of CPB, performing modified ultra-filtration (MUF) is common practice in our hospital. After induction of anesthesia, dexamethasone (0.5 mg/kg) was administered to all patients. Intraoperative use of antifibrinolytic agents (tranexamic acid) and cell salvage are routine at the study site. Patients received milrinone, norepinephrine or dobutamine at the discretion of the attending anesthetist and surgical team. Perioperative antibiotic prophylaxis consisted of 24 h of cefazoline.

## Data collection

Data collection consisted of demographic data, cardiac diagnosis, RACHS-1 score [33], duration of CPB, aortic cross-clamp time, PRISM II/III and PIM 2 scores [34, 35], blood loss and blood transfusion data. Data recorded directly from PDMS included heart rate (HR), arterial blood pressure (ABP), central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), cerebral regional $O_2$ saturation of the left and right hemisphere ($rSO_2$), body temperature and ventilator settings. Additionally, we recorded protocol adherence, incidence of (serious) adverse events, complications and use of concomitant medication.

## End points

The primary outcome measure was in-hospital length of stay (LOS), calculated in days.

Secondary outcomes were PICU LOS (days), duration of mechanical ventilatory support (defined as the time between induction of anesthesia and extubation at the PICU, and expressed in hours) and incidence of all reported (serious) adverse events, complications and transfusion costs. Respiratory infections (defined as fever, leucocytosis, signs on chest X-ray and a positive sputum culture) were noted as a complication. Re-thoracotomy, hemato- or pneumothorax and resuscitation (CPR) were registered as serious adverse events and were reported to the institutional ethics committee. Costs of blood products were calculated in euros based on information from the Sanquin Blood Bank, Leiden, The Netherlands.

## Statistical analysis

Assuming a significant difference in hospital LOS from 20.1 (±21.8) (group A) to 10.1 (±10.9) (group B), we estimated that 48 patients would be needed per group for a power of 0.8 and an alpha of 0.05 (Department of Medical Statistics and Bioinformatics, Leiden University).

Statistical analysis was conducted according to an intention-to-treat approach.

Continuous variables are described as mean with (SD) or medians with interquartile range (IQR) if the data were not normally distributed. Based on distribution, continuous

variables were tested with the Mann-Whitney $U$ test or Student's $t$ test, when appropriate. Categorical variables are described as numbers ($n$) and percentages. The categorical variables were examined using a chi-square test or Fisher's exact test (if the expected number in any cell was <5). A Kaplan-Meier curve was calculated and plotted to assess hospital LOS, PICU LOS and duration of ventilatory support. The effect of a difference in gender distribution in the two groups was evaluated in a Cox regression analysis. Differences between group A and B were considered significant with two-sided $p$ values $\leq 0.05$. Data analysis was performed using SPSS 20 (Chicago, IL, USA).

## Results

Between April 2009 and January 2012, a total of 162 patients with non-cyanotic congenital heart defects were eligible for participation in the study. In 55 cases, patients were not eligible for randomization (Fig. 1).

After obtaining informed consent, we enrolled 107 patients into the study. After randomization, the study was discontinued in seven patients because of a protocol violation (Fig. 1). Of these seven patients, four (aortic coarctation) were operated on without CPB and required minimal or no RBC transfusions. For ethical considerations (the chance of randomization in the liberal group A and thereby forced RBC transfusions), patients with aortic coarctation were excluded by approved addendum to the original study protocol.

The 107 patients had a median age of 8.4 (IQR 3.2–29.5) months, with a median weight of 7.2 (IQR 5.0–12.0) kg, and 53 % were male. There were no significant differences between the groups with regard to age, weight, RACHS-1, PRISM and PIM scores. Duration of the operation, duration of CPB and cross-clamp time were similar for both groups. Characteristics of the patients according to allocation are listed in Table 1. Data inspection showed a possibly non-negligible difference in gender distribution.

All patients had comparable Hb values the day before and at the start of the operation. During CPB and surgery, an equal amount of RBC and FFP was transfused in both groups (Electronic Supplementary Material), resulting in equal Hb values directly after the CPB and MUF procedure (Table 2). After CPB, Hb concentrations began to diverge because of the implementation of the study protocol. The mean Hb concentration, prior to discharge from the PICU, was 12.2 (±1.2) g/dl (7.5 ± 0.8 mmol/l) in the liberal transfusion group after 4.5 days compared to 10.2 (±1.2) g/dl (6.4 ± 0.8 mmol/l) in the restrictive group after 3.6 days (95 % CI 1.44–2.39), $p < 0.001$. All RBC transfusions were administered in the PICU, thus none during the remainder of the hospital stay. The mean transfused RBC volumes in the liberal group (A) and restrictive group (B) were 258 (±87) vs. 186 (±70) ml per patient (95 % CI 40.6–104.6), $p < 0.001$. Average blood loss due to production from the chest tube and due to blood withdrawal was comparable between groups (Table 2).

Red blood cell units used for transfusion were up to 30 days old. The average storage time of transfused RBCs in this study was 9.8 (±7.0) days. Storage time was not different between the two study groups ($p = 0.990$) (Table 2).

### Primary outcome results

Length of stay in hospital was 9 (7–14) days for the liberal transfusion group (A), whereas for the restrictive transfusion group (B), it was 8 (7–11) days, log-rank test $p = 0.047$ (Fig. 2). Gender included in the Cox regression model with group as the main predictor changed the probability ratio (hazard ratio) of hospital discharge slightly from 1.422 to 1.434 ($p = 0.079$) in favor of the restrictive transfusion group. Gender itself was not a significant predictor ($p = 0.911$). No re-admissions to the PICU were recorded during the entire study period, and every patient was discharged home alive.

### Secondary outcome results

Duration of mechanical ventilation and LOS in PICU (days) did not differ. All (serious) adverse events and complications were recorded during the PICU stay (Table 3). Of the postoperative complications during the PICU stay, respiratory infections were most frequently observed: in five patients in group A; in six patients in group B, $p = 0.726$. After extubation one patient in group A and three patients in group B needed re-intubation, $p = 0.302$. The incidence of serious adverse events such as hemato- or pneumothorax, re-thoracotomy and resuscitation (CPR) at the PICU was equal in both groups ($n = 3$).

Postoperatively, milrinone and norepinephrine were administered in an equal number of patients in both groups. However, the average dose of norepinephrine in patients in group A of 0.09 (±0.08) μg/kg/min was slightly higher than in patients in group B with 0.07 (±0.09) μg/kg/min, $p = 0.003$. Dobutamine was infrequently used as a vasoactive drug in both study groups (in four patients in group A and seven patients in group B).

The total cost of transfused blood products calculated per patient (RBCs and FFP combined) was 438.35 (±203.39) euros in the liberal transfusion group (A) compared to 316.27 (±189.96) euros in the restrictive transfusion group (B) (95 % CI 46.61–197.51), $p = 0.002$. This resulted in a cost reduction of 28 %. The cost of blood products is presented in detail in Table 3.

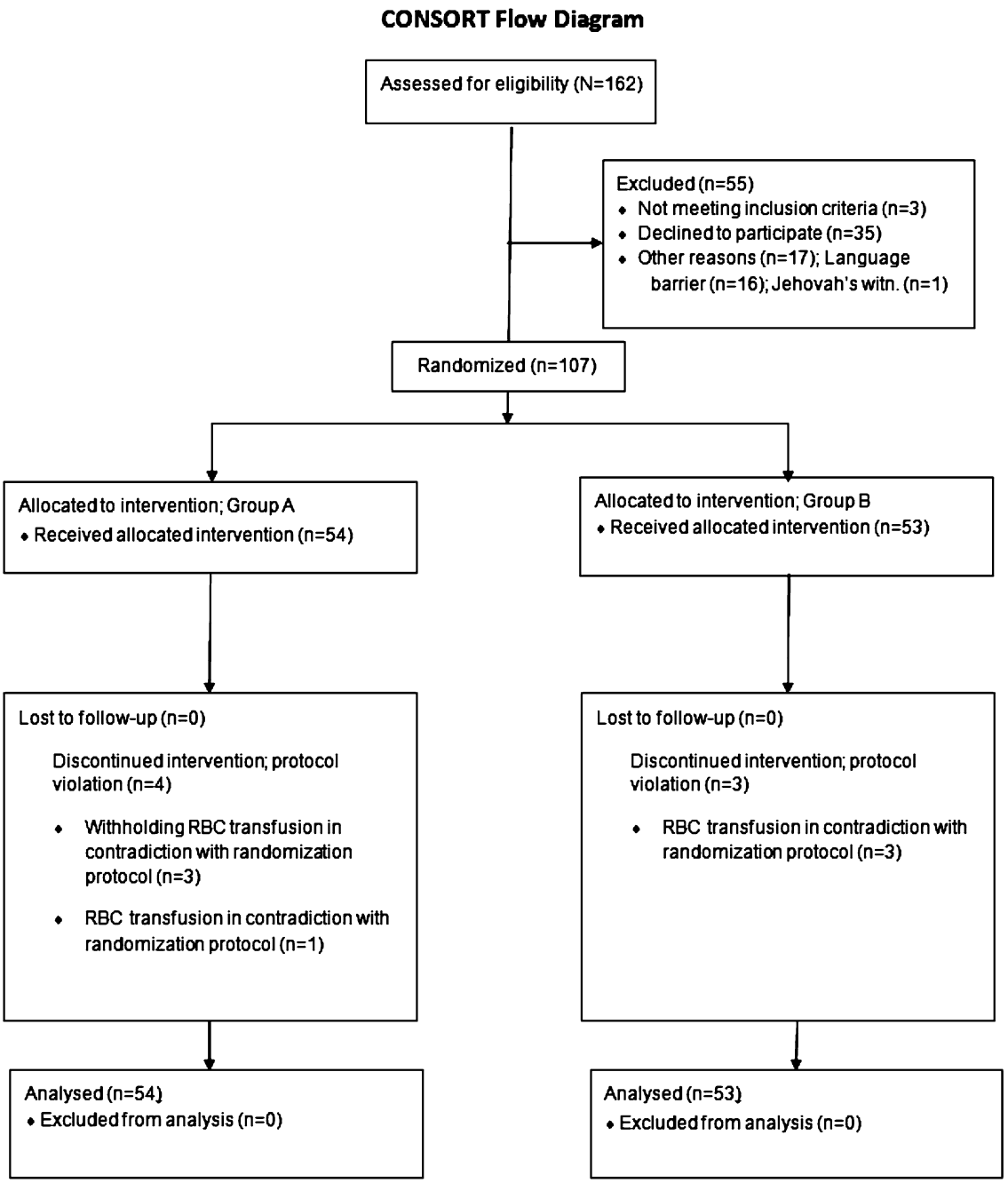


**Fig. 1** CONSORT flow chart. A randomized controlled trial evaluating two RBC transfusion strategies (group A: Hb threshold 10.8 g/dl and group B: Hb threshold 8.0 g/dl) in non-cyanotic pediatric patients with corrective operations for congenital heart defects

## Discussion

This is the first randomized controlled trial investigating a restrictive transfusion policy during the entire perioperative period (from induction of anesthesia right up to hospital discharge) in children undergoing surgery for congenital heart disease.

This randomized controlled trial demonstrated that a restrictive transfusion strategy was safe in pediatric cardiac surgery patients with a non-cyanotic congenital heart defect. We found no difference in morbidity between the groups with the exception of a significant difference in length of hospital stay in favor of the patients in the restrictive RBC transfusion group. These data are

**Table 1** Patient characteristics in 107 non-cyanotic pediatric cardiac surgery patients

| | Group A, $n = 54$ Hb 10.8 g/dl | Group B, $n = 53$ Hb 8.0 g/dl |
|---|---|---|
| Age (months) | 7.3 [3.0–29.7] | 9.5 [3.6–30.4] |
| Weight (kg) | 7.1 [4.9–12.9] | 7.9 [5.0–12.0] |
| Gender (female/male) | 31/23 | 19/34 |
| RACHS-1 score: | | |
| Score = 1 | 3 | 1 |
| Score = 2 | 37 | 34 |
| Score = 3 | 14 | 18 |
| Surgery time (min) | 191 (55) | 190 (51) |
| Bypass-time (min) | 94.8 (41) | 86.0 (35) |
| Aortic clamp-time (min) | 59.6 (32) | 56.0 (32) |
| Lowest central body temperature (°C) | 30.6 (3.5) | 31.2 (2.4) |
| $ScvO_2$ (PediaSat) (%)[ab] | 70.7 (11.8) | 69.1 (12.1) |
| $ScvO_2$ venous blood sample (%)[a] | 69.6 (12.4) | 67.5 (13.7) |
| $rSO_2$ | | |
| Left (%)[a] | 67.5 (9.2) | 70.4 (10.0) |
| Right (%)[a] | 68.3 (9.4) | 70.0 (11.1) |
| PRISM II | 6.4 (4.4) | 6.4 (3.67) |
| PRISM III | 3.23 (2.90) | 3.87 (2.76) |
| PIM 2 | −3.789 (0.404) | −3.742 (0.556) |

Comparison of two RBC transfusion strategies: group A: liberal transfusion strategy; group B: restrictive transfusion strategy

Age in months and weight in kg are presented as median and interquartile range between brackets [IQR]. All other variables are presented as mean with standard deviation between parentheses (SD)

*RACHS-1* Risk Adjustment for Congenital Heart Surgery score, *PRISM II* and *PRISM III* Pediatric Risk of Mortality scores, *PIM 2* Pediatric Index of Mortality score, *$ScvO_2$* central venous oxygen saturation, *$rSO_2$* cerebral oxygen saturation of the left and right cerebral hemisphere

[a] Measurement prior to surgical procedure

[b] $ScvO_2$ (PediaSat) measurement before calibration

**Table 2** Hb concentrations, volume of transfused red blood cells, fresh frozen plasma and blood loss in 107 pediatric cardiac surgery patients

| | Group A, $n = 54$ Hb 10.8 g/dl | Group B, $n = 53$ Hb 8.0 g/dl | $p$ value |
|---|---|---|---|
| Hb prior to surgery (g/dl) | 11.9 (1.5) | 12.2 (1.2) | 0.245 |
| RBC during surgery (ml/patient) | 158 (54) | 148 (53) | 0.336 |
| FFP during surgery (ml/patient) | 148 (50) | 146 (78) | 0.884 |
| Hb after CPB and MUF (g/dl) | 10.4 (1.1) | 10.1 (1.3) | 0.168 |
| Hb value on admittance to PICU (g/dl) | 10.3 (1.2) | 9.6 (1.1) | 0.004 |
| Blood loss chest tube (ml/patient) | 130 (101) | 139 (95) | 0.648 |
| Blood withdrawal (ml/patient) | 24 (14) | 21 (12) | 0.330 |
| RBC in PICU (ml/patient) | 120 (72) | 90 (50) | 0.087 |
| FFP in PICU (ml/patient) | 155 | | – |
| Total RBC (ml/patient) | 259 (90) | 186 (70) | <0.001 |
| Total FFP (ml/patient) | 152 (55) | 144 (77) | 0.629 |
| Number of transfused RBC units: | | | |
| RBC 280 ml | 75 | 54 | |
| RBC 65 ml | 18 | 6 | |
| Number of transfused FFP units | 32 | 25 | |
| Age of RBC (days) | 9.8 (6.8) | 9.8 (7.2) | 0.990 |

Transfusion data in 107 non-cyanotic, pediatric cardiac surgery patients. Comparison between two RBC transfusion strategies. Group A: liberal transfusion strategy; group B: restrictive transfusion strategy

All values are presented as mean with standard deviation (SD)

*RBC* red blood cells, *FFP* fresh frozen plasma, *CPB* cardiopulmonary bypass, *MUF* modified ultra-filtration, *PICU* pediatric intensive care unit

consistent with those reported in recently published comparable studies on the risks and benefits of red cell transfusions in children, including pediatric cardiac surgical patients [15, 16, 27]. The results from the TRIPICU study published by Lacroix et al. [27] demonstrated that a restrictive RBC transfusion strategy with a hemoglobin threshold of Hb < 7 g/dl (4.4 mmol/l) in stable, critically ill children decreases transfusion requirements without increasing adverse outcomes. In a subgroup analysis of pediatric cardiac surgery patients in the TRIPICU study, Willems et al. [16] demonstrated that a restrictive RBC transfusion strategy, as compared with a liberal strategy (with an Hb threshold of 9.5 g/dl; 5.9 mmol/l), was not associated with any significant difference in multiorgan dysfunction syndrome or length of PICU stay. In this substudy, however, the storage time of transfused RBCs was not similar in the two groups. Recently, Cholette et al. [15] demonstrated that children with single-ventricle physiology did not benefit from a liberal transfusion strategy after cavo-pulmonary connection. The authors concluded that a restrictive RBC transfusion strategy did decrease the number of transfusions, donor exposures and potential risks in these children.

The premise that an RBC transfusion will result in improved oxygen delivery and thus decreased tissue hypoxia no longer holds true. Recent data have suggested that RBC transfusions might, through various mechanisms, contribute to a reduction in local oxygen delivery in the tissues, which may play a role in the negative outcomes associated with transfusions in critically ill patients despite an increase in the global hemoglobin concentration and a theoretical increase in global oxygen delivery [29].

Tolerance of anemia differs over various populations. A healthy adult with normal compensatory mechanisms may be capable of dealing with lower Hb levels than an infant that has just undergone complex cardiac surgery.

The critical Hb level, at which level the body can no longer compensate for a further fall in Hb, may vary considerably, depending on many factors including age and disease. In order to apply an appropriate blood transfusion management, it is necessary to know the threshold value of Hb at which we need to transfuse blood to avoid tissue hypoxia. Unfortunately, we do not know the transfusion threshold for each individual patient.

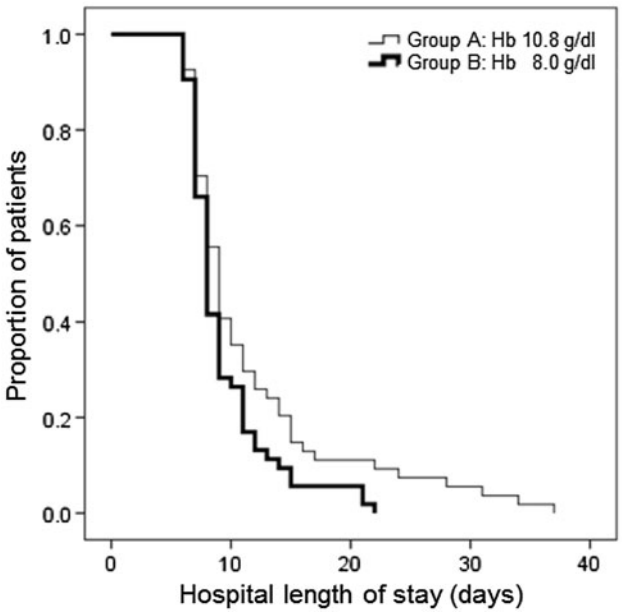


**Fig. 2** Kaplan-Meier curves presenting difference in hospital stay (in days). Comparison of length of hospital stay in 107 non-cyanotic pediatric cardiac surgery patients with two RBC transfusion strategies. For the liberal transfusion group (A), length of hospital stay is 9 (7–14) days, whereas for the restrictive transfusion group (B), it is 8 (7–11) days, log-rank test $p = 0.047$

In adult volunteers there is no evidence of impaired tissue oxygenation until Hb levels fall to 4–5 g/dl (2.4–3.1 mmol/l) [31], while the optimal Hb in critically ill adults is still unknown. However, an Hb level between 7.0 and 9.0 g/dl has been generally accepted, based on the paper by Hebert et al. in 1999 [36].

Results found in adults should not be generalized to critically ill children as they have different diseases and different adaptive responses compared with adults [30].

On average, the Hb value at which a blood transfusion is prescribed in critically ill children is 8.0 g/dl (5.0 mmol/l), which seems to be consistent with the current practice in many adult intensive care units [19]. We chose an Hb threshold of 8.0 g/dl (5.0 mmol/l) in our study for the restrictive transfusion strategy group as we felt this was a safe level in this patient group considering the close monitoring for signs of inadequate tissue oxygenation. The choice of an Hb threshold of 10.8 g/dl (6.8 mmol/l) in the liberal transfusion group in our study was based on the Hb level at which we routinely prescribe blood transfusions to children after corrective surgery for non-cyanotic cardiac lesions in our PICU.

Possible deleterious effects of "old" blood—although almost exclusively found in studies involving non-leukocyte-depleted blood products of more than 14 days storage time—did not play a role in our study as equal storage conditions were applied for the RBCs transfused in both groups. On average, the storage time was equal in both groups 9.8 (±6.8) vs. 9.8 (±7.2) days (Table 2).

Despite the fact that this is the first randomized controlled trial of a restrictive vs. liberal blood transfusion strategy in cardiac surgery patients encompassing the whole perioperative period lasting up to the day of discharge from the hospital, this study seems in line with the present findings on this issue.

A few limitations, however, have to be delineated. One limitation of our study is that it was conducted as a single-center study in a relatively homogeneous, lower risk cardiac surgical group of patients. This may limit generalization of the findings. In particular, cyanotic,

**Table 3** Outcome data and complications in a randomized controlled trial of two RBC transfusion strategies in 107 non-cyanotic pediatric cardiac surgery patients

| | Group A, $n = 54$<br>Hb 10.8 g/dl | Group B, $n = 53$<br>Hb 8.0 g/dl | $p$ value |
|---|---|---|---|
| Hb value at discharge PICU (g/dl) | 12.2 (1.2) | 10.2 (1.2) | <0.001 |
| Mechanical ventilation time (h) | 16 [9–27] | 20 [9–52] | 0.930 |
| LOS PICU (days) | 2 [1–5] | 2 [1–4] | 0.358 |
| LOS Hospital (days) | 9 [7–14] | 8 [7–11] | 0.047 |
| Complications PICU (*n*) | 11 | 15 | 0.339 |
| Rethoracotomy/resuscitation (*n*) | 1 | 2 | |
| JET (*n*) | 1 | – | |
| Pneumothorax/hematothorax (*n*) | 2 | 1 | |
| Respiratory tract infection (*n*) | 5 | 6 | 0.726 |
| Pleural effusion (*n*) | 1 | 2 | |
| Bronchospasm(*n*) | – | 1 | |
| Re-intubation (*n*) | 1 | 3 | 0.302 |
| Costs RBC/FFP per patient (€) | 328.96/109.39 | 229.20/87.08 | |
| Total costs per patient (€) | 438.35 (203.39) | 316.27 (189.96) | 0.002 |

Primary and secondary outcome data and reported (serious) adverse events in 107 non-cyanotic pediatric cardiac surgery patients. Hb values are presented as mean and (SD) between parentheses. Mechanical ventilation time and LOS are presented as median with [IQR] between brackets

*LOS* length of stay, *JET* junctional ectopic tachycardia

single-ventricle patients, in whom the hemoglobin level is a more critical factor in oxygen delivery, were excluded. Furthermore, our liberal transfusion trigger is based on local guidelines.

Another limitation of the study is that we did not include a third arm based on individual patient status. In such an individualized study arm, instead of acting on a preset transfusion threshold, a blood transfusion would additionally be triggered by signs of inadequate tissue oxygenation, such as increases in lactate concentrations and decreased $ScvO_2$, thereby providing information on the critical hemoglobin level.

Based on the results of this study, the restrictive blood transfusion policy, with a transfusion threshold of Hb 8.0 g/dl (5.0 mmol/l), has now been implemented in our pediatric intensive care unit.

## Conclusions

For patients with a non-cyanotic congenital heart defect, a restrictive RBC transfusion policy with a transfusion threshold of Hb 8.0 g/dl (5.0 mmol/l) during the entire perioperative period is safe. Furthermore, restriction in blood transfusion leads to a shorter duration of hospital stay and is less expensive compared to a liberal transfusion strategy.

**Conflicts of interest** The authors declare no potential conflicts of interest.

## References


1. Goodman AM, Pollack MM, Patel KM, Luban NL (2003) Pediatric red blood cell transfusions increase resource use. J Pediatr 142:123–127
2. Hendrickson JE, Hillyer CD (2009) Noninfectious serious hazards of transfusion. Anesth Analg 108:759–769
3. Chapman CE, Stainsby D, Jones H, Love E, Massey E, Win N, Navarrete C, Lucas G, Soni N, Morgan C, Choo L, Cohen H, Williamson LM (2009) Ten years of haemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion 49:440–452
4. Baumgartner JM, Silliman CC, Moore EE, Banerjee A, McCarter MD (2009) Stored red blood cell transfusion induces regulatory T cells. J Am Coll Surg 208:110–119
5. Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellke FW, Likosky DS, Marrin CA, Helm RE Jr, Leavitt BJ, Morton JR, Charlesworth DC, Clough RA, Hernandez F, Frumiento C, Benak A, DioData C, O'Connor GT (2009) The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg 108:1741–1746
6. Kneyber MC, Hersi MI, Twisk JW, Markhorst DG, Plotz FB (2007) Red blood cell transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med 33:1414–1422
7. Kipps AK, Wypij D, Thiagarajan RR, Bacha EA, Newburger JW (2011) Blood transfusion is associated with prolonged duration of mechanical ventilation in infants undergoing reparative cardiac surgery. Pediatr Crit Care Med 12:52–56
8. Salvin JW, Scheurer MA, Laussen PC, Wypij D, Polito A, Bacha EA, Pigula FA, McGowan FX, Costello JM, Thiagarajan RR (2011) Blood transfusion after pediatric cardiac surgery is associated with prolonged hospital stay. Ann Thorac Surg 91:204–210
9. Kuduvalli M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, Fabri BM, Rashid A (2005) Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. Eur J Cardiothorac Surg 27:592–598
10. Mohnle P, Snyder-Ramos SA, Miao Y, Kulier A, Bottiger BW, Levin J, Mangano DT (2011) Postoperative red blood cell transfusion and morbid outcome in uncomplicated cardiac surgery patients. Intensive Care Med 37:97–109
11. Oliver E, Carrio ML, Rodriguez-Castro D, Javierre C, Farrero E, Torrado H, Castells E, Ventura JL (2009) Relationships among haemoglobin level, packed red cell transfusion and clinical outcomes in patients after cardiac surgery. Intensive Care Med 35:1548–1555
12. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil FR, Sierra DB, Lopes NH, Mauad T, Roquim AC, Sundin MR, Leao WC, Almeida JP, Pomerantzeff PM, Dallan LO, Jatene FB, Stolf NA, Auler JO Jr (2010) Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 304:1559–1567
13. Vincent JL, Hajjar LA (2013) What's new in transfusion policies? Intensive Care Med 39:1002–1004
14. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
15. Cholette JM, Rubenstein JS, Alfieris GM, Powers KS, Eaton M, Lerner NB (2011) Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. Pediatr Crit Care Med 12:39–45
16. Willems A, Harrington K, Lacroix J, Biarent D, Joffe AR, Wensley D, Ducruet T, Hebert PC, Tucci M (2010) Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a subgroup analysis. Crit Care Med 38:649–656

17. Szekely A, Cserep Z, Sapi E, Breuer T, Nagy CA, Vargha P, Hartyanszky I, Szatmari A, Treszl A (2009) Risks and predictors of blood transfusion in pediatric patients undergoing open heart operations. Ann Thorac Surg 87:187–197
18. Roseff SD, Luban NL, Manno CS (2002) Guidelines for assessing appropriateness of pediatric transfusion. Transfusion 42:1398–1413
19. Armano R, Gauvin F, Ducruet T, Lacroix J (2005) Determinants of red blood cell transfusions in a pediatric critical care unit: a prospective, descriptive epidemiological study. Crit Care Med 33:2637–2644
20. Mhanna MJ, Super DM (2005) What hemoglobin value should one use in transfusing a critically ill child? Crit Care Med 33:2710–2711
21. Nahum E, Ben Ari J, Schonfeld T (2004) Blood transfusion policy among European pediatric intensive care physicians. J Intensive Care Med 19:38–43
22. Tweddell JS, Hoffman GM, Fedderly RT, Ghanayem NS, Kampine JM, Berger S, Mussatto KA, Litwin SB (2000) Patients at risk for low systemic oxygen delivery after the Norwood procedure. Ann Thorac Surg 69:1893–1899
23. Tweddell JS, Hoffman GM (2002) Postoperative management in patients with complex congenital heart disease. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 5:187–205
24. Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RD, Ghanayem NS, Frisbee SJ, Litwin SB (2002) Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. Circulation 106:I82–I89
25. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED (2005) Changes in central venous saturation after major surgery, and association with outcome. Crit Care 9:R694–R699
26. Hoffman GM, Mussatto KA, Brosig CL, Ghanayem NS, Musa N, Fedderly RT, Jaquiss RD, Tweddell JS (2005) Systemic venous oxygen saturation after the Norwood procedure and childhood neurodevelopmental outcome. J Thorac Cardiovasc Surg 130:1094–1100
27. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, Joffe A, Biarent D, Meert K, Peters MJ (2007) Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 356:1609–1619
28. Rouette J, Trottier H, Ducruet T, Beaunoyer M, Lacroix J, Tucci M (2010) Red blood cell transfusion threshold in postsurgical pediatric intensive care patients: a randomized clinical trial. Ann Surg 251:421–427
29. Marik PE, Corwin HL (2008) Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 36:2667–2674
30. Desmet L, Lacroix J (2004) Transfusion in pediatrics. Crit Care Clin 20:299–311
31. Weiskopf RB (1998) Do we know when to transfuse red cells to treat acute anemia? Transfusion 38:517–521
32. Palmieri TL, Lee T, O'Mara MS, Greenhalgh DG (2007) Effects of a restrictive blood transfusion policy on outcomes in children with burn injury. J Burn Care Res 28:65–70
33. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI (2002) Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 123:110–118
34. Pollack MM, Patel KM, Ruttimann UE (1996) PRISM III: an updated pediatric risk of mortality score. Crit Care Med 24:743–752
35. Slater A, Shann F, Pearson G (2003) PIM2: a revised version of the paediatric index of mortality. Intensive Care Med 29:278–285
36. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E (1999) A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian critical care trials group. N Engl J Med 340:409–417