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REVIEW

A restrictive transfusion policy in the paediatric intensive care unit: safe and effective

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Abstract

Background: Red blood cell transfusions are frequently used in the paediatric intensive care unit (PICU) with a primary goal of increasing oxygen delivery to the tissues. There are several disorders in which a high haemoglobin level is suggested to improve outcome, including sepsis and cardiac disease. Nevertheless, red blood cell transfusions are associated with a higher morbidity and mortality rate in critically ill children and adults. In our article, we will give a narrative review of the existing literature on a restrictive transfusion policy in the PICU.

Methods: A literature search was done using the terms "red blood cell transfusion" or "erythrocyte transfusion" and "pediatrics" or "child" in the Cochrane, Sumsearch, Trip and PubMed medical databases.

Review of literature: The TRIPICU study offers the largest number of patients in whom a restrictive transfusion policy was concluded to be as safe and effective as a liberal transfusion policy. Several sub-studies were extracted from the TRIPICU database, focusing on specific groups of patients, e.g. sepsis patients, patients with non-cyanotic heart disease who underwent cardiac surgery and patients who underwent general surgery. One additional study focused on cyanotic heart disease, using higher haemoglobin levels than the studies named before. In all sub-categories a restrictive transfusion policy was found to be safe and effective.

Conclusion: We conclude that it is safe to work with a haemoglobin threshold of 4.3 mmol/l for children admitted to the PICU with burns, sepsis or after general and cardiac surgery, and 5.6 mmol/l for patients with cyanotic heart disease.

Introduction

Up to 50% of the critically ill children admitted to the paediatric intensive care unit (PICU), receive one or more red blood cell (RBC) transfusions. After a stay of more than seven days in the PICU, this amount increases up to 75%.[1,2,3] Red blood cell transfusions can cause serious side effects.[1,4,5] Nevertheless, no international consensus exists on a haemoglobin threshold for administering RBC transfusions to critically ill children.[6] Previous research has shown that there are quite some differences between doctors' usage of RBC transfusions, and that the volume given is often not adapted to the degree of anaemia.[6,7] A clear guideline on the usage of RBC transfusions at the PICU is desirable.

Little information is known on the subject of a restrictive transfusion policy in critically ill children. In September 2011 the renewed Dutch consensus on Blood Transfusions was published.[8] This extensive guideline includes information about the patient population admitted to the PICU. The consensus concludes that a restrictive transfusion policy is safe for patients in the PICU based on literature published until the year 2008. We want to support and emphasise this statement by offering a narrative review on the subject of a restrictive transfusion policy in the PICU. We will also describe more recent literature, making a more specific usage of RBC transfusions possible.

Methods

The Cochrane, Sumsearch, Trip and PubMed medical databases were used during the literature search. We used the following terms in searching the databases "red blood cell transfusion" or "erythrocyte transfusion" and "pediatrics" or "child". We then confined the results to articles comparing a restrictive and liberal transfusion policy. We excluded literature on neonates, premature neonates and children admitted elsewhere than the PICU. We focused on randomised clinical trials for our review and used citations from associated articles.

Background

Anaemia is defined as a haemoglobin (Hb) level in the blood that is lower than two standard deviations below the median of the age-dependant reference. Anaemia is common in children admitted to a PICU. At admission, already 33% of these children

have anaemia and after 48 hours, another 18% have developed anaemia.[1] The pathogenesis of anaemia in critically ill children is multi-factorial, including poor nutritional state, changes in iron metabolism, lowered erythropoietin production and response, blood loss and frequent blood tests in the PICU.[4]

Physiological changes

Hb is of importance for the delivery of oxygen (DO2) to tissues and thereby maintaining an adequate organ function. At low serum Hb levels, less oxygen can be transported to the tissues. The tissues will extract proportionally more oxygen from the blood resulting in an increased concentration of deoxyhaemoglobin in the red blood cells. This process stimulates the production of 2,3-diphosphoglycerate (2,3-DPG). 2,3-DPG ensures a shift of the oxygen-dissociation curve, making it easier for the tissues to extract oxygen from the blood. Other compensating mechanisms to ensure an adequate DO2 are a redistribution of blood flow and an increase in cardiac output.[1]

High haemoglobin target level

Based on pathophysiological changes, it seems reasonable to strive for a high Hb level to ensure adequate tissue oxygenation in at least two categories of PICU patients. The first category consists of septic patients. During sepsis, endotoxins, tumour necrosis factor-alpha and nitrogen-oxygen molecules are released, causing mitochondrial depression and thereby an increased oxygen demand of the tissues. Yet, the oxygen supply is limited through decreased myocardial function and maldistribution of blood flow in the microcirculation results.

The second category consists of patients who have undergone cardiac surgery. A compromised respiratory and cardiac condition results in limited oxygenation of the blood. The percentage of unsaturated blood is even higher in patients with a mixed circulation. Decreased contractility of the myocardium and/or arrhythmia can contribute to a decreased cardiac output. For both categories of patients it seems that a higher Hb level is able to compensate for the restricted oxygen delivery to the tissues.

Effects of RBC transfusions

The primary goal of RBC transfusions is to preserve organ function by ensuring an adequate oxygen supply. Yet, for the individual patient, it is unknown at which haemoglobin threshold the oxygen supply to the tissues becomes critical. Also, RBC transfusions seem to have a limited effect on improvement in the oxygen supply to the tissues.[1] Three mechanisms can explain this limited effect. First, the storage of red blood cells leads to a depletion of 2,3-DPG in a couple of days. We explained earlier that 2,3-DPG is necessary for the compensatory shift of the oxygen dissociation curve. Second, adenosine triphosphate (ATP) is depleted from stored blood. A shortage of ATP can lead to deformation of the membrane and thereby destruction of red blood cells. Finally, a small amount of

free Hb in stored blood binds to endogenously produced nitric oxide (NO). NO can lead to vasoconstriction of the microcirculation, restricting the oxygen delivery to the tissues.[1,2]

Adverse effects of RBC transfusions

Different studies in adults as well as children show that RBC transfusions are associated with a longer duration of hospital stay and a higher morbidity and mortality. RBC transfusions are associated with a longer duration of ventilatory need, an increased usage of vasoactive medication and longer duration of stay in the PICU, independent of severity of illness.[1,4,5,9]

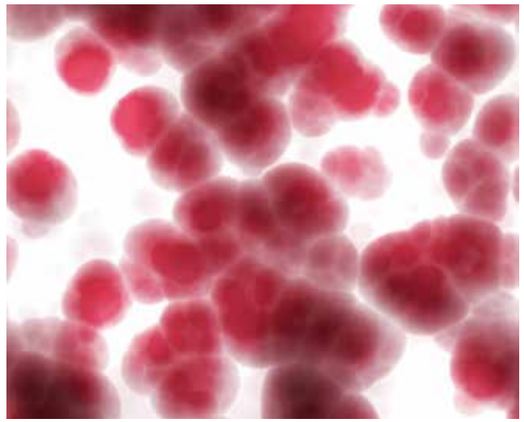
For some adverse effects of RBC transfusions, a clear causal mechanism is known. For example, cardiac decompensation can be the result of volume load in critically ill patients. Disturbances in electrolytes and/or coagulation originate from the dissimilarity in composition of stored blood products compared with fresh blood.

The mechanisms causing non-haemolytic fever and transfusion related-immunomodulation are less clear. It has been postulated that the leukocytes and cytokines that are released from the blood product cause an inflammatory cascade.[1,10] This immunomodulation is associated with an increased risk for nosocomial infections and multi-organ failure.[1,2,4] Nevertheless, two recent studies have shown that leukocyte-depleted RBC transfusions are also associated with nosocomial infections.[2,4] Because of this controversy with respect to leukocyte depletion, more research is desired. In addition, a longer storage time of blood products seems to be associated with a worse outcome, but this has not been confirmed universally.[2,10,11]

Until more research is done, it seems recommendable to use fresh leukocyte-depleted RBC transfusions when treating critically ill children. In the Netherlands this is already standard practice.

Restrictive transfusion strategy

Several articles have been published on a restrictive transfusion strategy in critically ill adults and children. In the year 1999, the TRICC study (Transfusion Requirements in Critical Care)[13] compared a traditional transfusion policy (liberal strategy: Hb threshold of 10 g/dl or 6.2 mmol/l) with a restrictive transfusion strategy (Hb threshold of 7 g/dl or 4.3 mmol/l) in adults. According to this multicentre, prospective, randomised trial, a restrictive strategy is as effective and safer than the traditional policy. The TRICC motivated different researchers to evaluate the transfusion policy in critically ill children. We will now describe the published literature on restrictive transfusion strategies in children. From each study, patient characteristics, transfusion information and outcome parameters are assembled in *table 1*, *table 2* and *table 3*, respectively.



First indications, 2007

The first study on a restrictive transfusion strategy in children concerned a population of burn patients. In a retrospective review two groups of patients were compared who were treated in a burns centre for children in the period of 2000-2006.[14] The first group (traditional group, n=146) received a RBC transfusion at a Hb threshold of 10 g/d (6.2 mmol/l). In the second group (restrictive group, n=127) this Hb threshold was lowered to 7 g/dl (4.3 mmol/l). No differences were found in outcome parameters such as duration of stay, duration of ventilation, amount of surgery needed and mortality. The restrictive transfusion strategy did lead to a great decrease in

Table 1. Patient characteristics per study*

	Group	Number of patients	Age (years)	Sex (% M)	PRISM score#	Ventilation (%)	Hb at start of the study° (mmol/l)
Palmieri[14]	Liberal	146	6.6 ± 0.4	2:1			5.9 ± 0.03
	Restrictive	127	5.9 ± 0.4	2.3:1			5.4 ± 0.04
Two historical cohorts of burn patients		P value		NS			<0.001
Lacroix[3] (TRIPICU)	Liberal	317	3.3 ± 3.4	60	7.2 ± 5.2	79	5.0 ± 0.6
	Restrictive	320	3.0 ± 3.8	59	6.5 ± 4.8	79	5.0 ± 0.6
Randomised PICU patients		P value	NS	NS	NS	NS	NS
Karam[12] (Sub-TRIPICU)	Liberal	69	2.7 ± 3.6	57	5.6 ± 4.2	85	4.8 ± 0.6
	Restrictive	68	2.5 ± 3.3	59	7.4 ± 5.4	87	4.9 ± 0.6
Randomised sepsis patients		P value	NS	NS	NS	NS	NS
Willems[15] (Sub-TRIPICU)	Liberal	62	2.2 ± 3.3	57	7.2 ± 5.4	64	5.0 ± 0.6
	Restrictive	63	2.6 ± 3.2	57	7.2 ± 4.8	60	5.2 ± 0.5
Randomised non-cyanotic heart disease		P value	NS	NS	NS	NS	NS
Cholette[16]	Liberal	30	2.7 ± 2.3	56.6			7.4 ± 0.7 (post-surgery)
	Restrictive	30	1.9 ± 2.3	56.6			7.5 ± 0.8 (post-surgery)
Randomised cyanotic heart disease patients		P value	NS	NS			NS
Roulette[17] (Sub-TRIPICU)	Liberal	64	6.1 ± 5.2		7.2 ± 5.4	48	4.9 ± 0.6
	Restrictive	60	4.5 ± 4.3	37	7.2 ± 4.8	46	4.8 ± 0.7
Randomised surgery patients		P value	NS	NS	NS	NS	NS

* Plus–minus values are means ± SD. Total percentage can differ from 100% because of rounding. # Scores of the Pediatric Risk of Mortality (PRISM) range from 0 to 76, with higher scores indicating a higher risk of death. Score taken at the moment of randomisation. ° Before randomisation. ° At the moment of randomisation. NS = not significant.

Table 2. Transfusion information per study*

	Group	Threshold Hb before transfusion (mmol/l)	Amount of patients receiving RBC transfusion (%)	Amount of units of RBCs per transfused patient	Total amount of transfused units of RBCs	Length of storage of RBCs (days)
Palmieri[14]	Liberal	6.2	95	12.3 ± 1.8	1715	13.6 ± 0.2
	Restrictive	4.3	94	7.2 ± 1.2	862	17.3 ± 0.3
P value			NS	<0.001	<0.001	<0.001
Lacroix[3] (TRIPICU)	Liberal	5.9	98	1.7 ±2.2	542	16.0 ± 10.5
	Restrictive	4.3	46	1.9 ± 3.4	301	15.7 ± 10.3
P value			<0.001	NS	<0.001	NS
Karam[12] (Sub-TRIPICU)	Liberal	5.9	99	1.2 ± 0.4	80	15.6 ± 8.6
	Restrictive	4.3	56	1.5 ± 1.2	58	14.3 ± 8.3
P value			<0.01	NS	<0.01	NS
Willems[15] (Sub-TRIPICU)	Liberal	5.9	100	1.3 ± 0.6	82	13.2 ± 10.9
	Restrictive	4.3	17	1.2 ± 0.4	13	16.7 ± 9.3
P value			<0.001	NS	<0.001	NS
Cholette[16]	Liberal	8.1	97	2.2	63	
	Restrictive	5.6	37	1.2	13	
P value			<0.01	NS	<0.01	
Rouette[17] (Sub-TRIPICU)	Liberal	5.9	97	1.8	109	16.4 ± 9.2
	Restrictive	4.3	50	1.3	39	16.0 ± 11.4
P value			<0.01	NS	<0.01	NS

* Plus–minus values are means ± SD. Total percentage can differ from 100% because of rounding. NS = not significant.

the amount of RBC transfusions resulting in cost saving. An important point of concern is the time frame of the study. The traditional group was treated in the period 2000-2003, while the restrictive group was treated in the period 2003-2006. Changes in the general treatment of burn patients could very well have influenced the outcome of this study.

TRIPICU study

After the TRICC study, a comparable research was designed for critically ill children in 2007. The TRIPICU study (Transfusion Requirements in the Pediatric Intensive Care Unit) included more than 600 stable but critically ill children who were admitted to the PICU.[3] Patients were considered stable if the mean systemic arterial pressure was not less than 2 SD below the normal mean for age and if cardiovascular treatments had not been increased for at least two hours. The patients were randomised in a liberal transfusion group (Hb threshold 9.5 g/dl or 5.9 mmol/l) and a restrictive transfusion group (Hb threshold 7.0 g/dl or 4.3 mmol/l). RBCs were transfused within 12 hours after the threshold value had been reached and were always leukocyte depleted. The results showed no differences in primary outcomes of mortality and multiple organ dysfunction syndrome (MODS). Regarding the side effects and thus safety of RBC transfusions, no differences were found between the two groups. The authors conclude that for stable critically ill children in the PICU a haemoglobin threshold of 4.3 mmol/l can be used. An important remark is that the TRIPICU study did not include children with cyanotic heart disease.

Sepsis patients

The TRIPICU study included a group of 137 critically ill children with stabilised sepsis.[12]

The patients were analysed after randomisation in a liberal and a restrictive transfusion group (*table 2*). In the restrictive group, 39 of 68 patients received a blood transfusion, compared with 68 of 69 patients in the liberal group. No differences were found in mortality, MODS and length of hospital stay (*table 3*).

Cardiac surgery patients

From the TRIPICU study, another subgroup of post-cardiac surgery patients was analysed, using the same Hb threshold as described above.[15] In the restrictive transfusion group, twice as much MODS was found than in the liberal group but because of the small number of patients this was not statistically significant. No difference was found in mortality or in the secondary outcomes of length of hospital stay and length of ventilation. As described before, an important restriction is the exclusion of patients with cyanotic heart disease.

Table 3. Outcomes per study *

	Group	New/ progressive multi-organ dysfunction syndrome (%)	Mortality (%)	Nosocomial infections (%)	Reactions to RBC transfusion (%)	Length of ventilation (days)	Length of stay at the PICU (days)
Palmieri[14]	Liberal		8.2			13.2 ± 2.3	
	Restrictive		5.7			8.4 ± 1.5	
P value			NS			NS	
Lacroix[3] (TRIPICU)	Liberal	12	4	25	2	6.0 ± 5.4	9.9 ± 7.4
	Restrictive	12	4	20	1	6.2 ± 5.9	9.5 ± 7.9
P value		NS	NS	NS	NS	NS	NS
Karam[12] (Sub-TRIPICU)	Liberal	19.1	3	34	0	7.3 ± 6.0	7.1 ± 6.2
	Restrictive	18.8	10	17	1	8.6 ± 7.2	7.5 ± 6.3
P value		NS	0.08	0.02	NS	NS	NS
Willems[15] (Sub-TRIPICU)	Liberal	6.5	3.2	19.4	1.6	4.7 ± 4.6	
	Restrictive	12.7	3.2	19.1	0	4.6 ± 3.1	
P value		NS	NS	NS	NS	NS	
Cholette[16]	Liberal		4			0.8 (0.2-9)	5.4 ± 3.3
	Restrictive		0			1.0 (0.2-26)	6.6 ± 6.4
P value			NS			NS	NS
Rouette[17] (Sub-TRIPICU)	Liberal	8	2	31		7.6 ± 6.1	11.6 ± 10.2
	Restrictive	9	2	23		6.9 ± 5.5	7.7 ± 6.6
P value		NS	NS	NS		NS	0.03

* Plus–minus values are means ± SD. Total percentage can differ from 100% because of rounding. NS = not significant.

A second, smaller study on RBC transfusions in children after cardiac surgery was published in 2011.[16] In this study, 60 patients who underwent a cavopulmonary connection were randomised in a restrictive and a liberal transfusion group, receiving leukocyte-depleted RBC transfusions. These patients all suffered from cyanotic heart disease. Therefore, higher Hb thresholds were used, 9.0 g/dl (5.6 mmol/l) and 13.0 g/dl (8.1 mmol/l) for the restrictive and the liberal group, respectively. No differences were found in the outcomes of oxygen saturation, mortality, length of stay on the PICU and length of ventilation. Side effects, for example nosocomial infections, were not described in this study.

General surgery patients

A third subcategory of the TRIPICU study includes a group of 124 children who underwent general surgery.[17] This group was also randomised in a liberal transfusion group (Hb threshold 9.5 g/d or 5.9 mmol/l) and a restrictive transfusion group (Hb threshold 7 g/dl or 4.3 mmol/l). In the restrictive group, 30 of 60 patients received an RBC transfusion, compared with 62 of 64 patients in the liberal group. No differences were found in mortality and MODS. A difference in length of hospital stay was found in favour of the restrictive transfusion policy.

Conclusion

The literature described above clearly indicates that a restrictive transfusion policy is effective in the treatment of stable critically ill children admitted to the PICU. From the number of adverse effects of RBC transfusions, including nosocomial infections, duration of ventilatory support and occurrence of MODS, it can be concluded that a restrictive policy is as safe as a liberal policy. We therefore support the CBO consensus with the addition that a restrictive transfusion policy can also be used in specified groups of patients, such as sepsis patients and general and cardiac surgery patients. It must be noted that in the subcategory of cardiac surgery patients, more MODS was found in the restrictive group. This finding was not found to be significant, yet a greater number of patients should be included to further investigate this finding. The studies described above advise to use a haemoglobin threshold of 4.3 mmol/l in PICU

patients, decreasing the exposure to RBC transfusions and their possible side effects. For patients with cyanotic heart disease, a haemoglobin threshold of 5.6 mmol/l can be used. Multicentre studies with greater numbers of patients are recommended to confirm these statements.

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