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Red Blood Cell Storage Duration Is Associated with Various Clinical Outcomes in Pediatric Cardiac Surgery

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Red blood cell storage · Erythrocytes · Blood · Transfusion · Pediatric cardiac surgery · Clinical outcome · Inflammation

Summary

Background: Recommendations on the use of fresh red blood cells (RBCs) in pediatric patients undergoing cardiac surgery are based on limited information. Furthermore, the RBC storage time cut-off of fresh units remains unknown. **Methods:** Data from 139 pediatric patients who underwent cardiac surgery and received RBCs from a single unit within 14 days of storage were analyzed. To identify the optimal cut-off storage time of RBCs for transfusion, multiple multivariate analyses aimed at different outcome parameters were performed. **Results:** 26 patients received RBC units stored for ≤3 days, while 126 patients received RBCs that were stored for 4–14 days. The latter group required more RBC transfusions and fresh frozen plasma (FFP) than the former group (19 vs. 25 ml/kg, p = 0.003 and 73% vs. 35%, p = 0.0006, respectively). In addition, the odds for the administration of FFP increased with the transfusion of RBCs stored for more than 4 days. The optimal cut-off for post-operative morbidity was observed with a storage time of ≤6 days for length of ventilation (p = 0.02) and peak of C-reactive protein (CRP; p = 0.008). **Conclusions:** The obtained results indicate that the hazard of blood transfusion increased with increasing storage time of RBCs. The results of this study suggest that transfusion of fresh RBCs with a storage time of ≤2 or 4 days (concerning transfusion requirements) or ≤6 days (concerning postoperative morbidity) may be beneficial in pediatric patients undergoing cardiac surgery. However, further prospective randomized studies are required in order to draw any final conclusions.

Introduction

The storage age of red blood cells (RBCs) transfused often exceeds 5 days. Under storage, RBCs undergo alterations that affect their function, viability, and quality, and which are termed storage lesions [1]. The clinical relevance of these changes is controversial, with no consensus regarding a cut-off for fresh or old RBCs. An increase in infection rates and morbidity following transfusion of old blood has been described [2–11]. Other groups did not find a correlation between the storage time of transfused RBCs and patient outcome [12–16]. A possible explanation for these discrepancies may lie in the heterogeneity of the study designs and patient groups, the use of different outcome parameters, and the various cut-offs of RBC age (5–27 days). Many of these studies were retrospective [3, 8, 10, 16], lacking a stringent differentiation between groups that had exclusively received ‘new’ or ‘old’ blood during observation. Thus, conclusions have been largely based on the transfusion of RBCs with mixed ages. Only 2 studies have reported on the exclusive transfusion of patients with either ‘new’ or ‘old’ RBCs, with controversy surrounding the results [5, 9].

Transfusion of RBCs is common in pediatric open-heart surgery patients via cardiopulmonary bypass (CPB) due to

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Table 1. Primary diagnoses of pediatric patients

Primary diagnosis	RBC storage time	
	≤3 days (n = 26)	≥3 days (n = 113)
Ventricular septal defect	6	43
Complete atrioventricular septal defect	3	15
Dextro-transposition of the great arteries	7	11
Tetralogy of Fallot	1	13
Hypoplastic aortic arch	3	2
Total anomalous pulmonary venous connection	1	4
Other	5	25

Only primary diagnoses are listed. The majority of the patients presented with combined congenital cardiac defects.

the imbalance between the patients' blood volume and the priming volumes of the CPB circuits. 2 recent studies reported on the profound influence of the RBC storage time on post-operative morbidity by using either a cut-off of <5 days for fresh RBCs [17] or by applying the storage time as a continuous variable in patients receiving >4 red cell units or a volume exceeding 150 ml/kg [18]. The authors of the latter study recommended the use of the freshest available RBC in such pediatric patients, preferably not older than 14 days. This has been the policy in our institution for several years, although the supply of fresh RBCs is not invariably possible. In addition, a dedicated group of surgeons, anesthetists, and perfusionists apply a comprehensive blood-sparing approach to avoid or minimize the need for transfusion [19–22]. Here, we present results on pediatric patients who underwent open heart surgery and received RBCs from a single unit with a storage time ranging from 0 to 14 days. Multivariate analyses were performed to assess the association of RBC storage time with clinical outcome, namely the prospectively selected parameters: transfusion requirements, post-operative morbidity (lengths of ventilation and intensive care unit (ICU) stay), and post-operative peak C-reactive protein (CRP) concentration as an inflammatory parameter.

Material and Methods

Between February 2009 and January 2012, 147 pediatric patients underwent cardiac surgery via CPB and received RBCs from a single unit. First, the storage times of the RBC unit were analyzed. Since in most cases the unit was between 0 and 14 days old, 8 patients who had received RBCs that had been stored for 15–32 days were excluded to avoid a potentially stronger impact of a few very old RBCs on the outcome parameters. Informed written parental consent for the surgical, anesthesiological, and monitoring procedures was obtained. The retrospective data analysis was approved by the Institutional Review Board.

CPB circuits were adjusted to the patients' body weights, with the goal of minimizing the priming volumes, which were 95, 110, and 200 ml for patients with body weights of <3, 3–5, and 5–16 kg, respectively [19–21]. The priming solution was enriched with RBCs only when the expected hemoglobin concentration was less than 7.0 g/dl. Tranexamic acid was used in all patients for anti-fibrinolysis at a concentration of 10 mg/kg/h. Moderate hypothermia was induced, except in 5 cases requiring deep hypothermic circulatory arrest where the temperature was decreased to approximately 16 °C. The necessitation for transfusion during CPB was triggered by a hemoglobin concentration of <7.0 g/dl.

During the postoperative period, the decision for transfusion was at the liberty of the attending critical care physicians. Low hemoglobin concentration due to blood loss and hemodynamic instability were the major reasons for post-operative transfusion. The transfused RBCs were leukocyte depleted. RBCs used intra-operatively were washed with cell saver prior to use and transfused within 4 h. Intra-operative transfusions were administered to 99 patients (71%). The remaining patients were transfused within 48 h following surgery.

Statistical Analysis

The effects of storage time on the transfusion requirements, i.e. volume of RBCs per kilogram body weight and incidence of fresh frozen plasma (FFP) administration, were analyzed by multivariate backward stepwise linear regression and by multiple logistic regression, respectively. The effects on post-operative morbidity, represented by length of mechanical ventilation and length of ICU stay, were analyzed by the Cox regression proportional hazards model. The effect on the degree of post-operative inflammatory response as assessed by peak CRP concentration was analyzed by multivariate backward stepwise linear regression. Covariates included in the multivariate models were body weight, previous sternotomies, and the risk adjustment in congenital heart surgery (RACHS) score, as well as the transfused volume of RBCs. The RACHS score is a consensus-based risk score estimating the risk of in-hospital mortality according to the severity of the congenital heart defect and the complexity of surgery [23]. Its validity has been confirmed to predict post-operative mortality and morbidity for a large European patient population [24]. Assignment to groups of patients receiving fresh versus stored RBCs was performed using sliding time cut-offs between <3 days and <11 days to identify the optimal cut-off (according to correlation coefficient, odds ratio (OR), or hazard ratio (HR), as appropriate, and P values) for each outcome parameter.

Data on the patient characteristics of groups of patients differentiated according to RBC storage time were compared by rank sum test or χ^2 tests as appropriate.

Results

In this study, 139 pediatric patients were included. The median age of the patients was 14 days (ranging from 2 days to 4.1 years), with a median body weight of 5.4 kg (ranging from 2.2 to 16.2 kg). The most frequent primary diagnoses are listed in table 1. However, many patients presented with a combination of defects. 23 (17%) patients had previous sternotomies.

Table 2. Patient characteristics

	RBC storage time cut-off		P value	RBC storage time cut-off		P value
	≤3 days	>3 days		≤6 days	>6 days	
N	26	113		45	94	
Storage time, days	1 (1–1)	9 (7–10)	n.d.	2 (1–5)	9 (8–11)	n.d.
Age, days	108 (8–165)	145 (89–234)	0.01	121 (8–183)	146 (94–242)	0.02
Body weight, kg	4.4 (3.6–6.1)	5.5 (4.1–7.2)	0.03	4.7 (3.6–6.7)	5.5 (4.3–7.2)	0.04
RACHS score	3 (2–4)	2 (2–3)	0.01	3 (3–3.25)	2 (2–3)	0.013
RACHS 2	8 (31)	58 (51)	0.09	15 (33)	51 (54)	0.03
RACHS 3	(31)	40 (35)	0.83	19 (42)	29 (31)	0.26
RACHS 4	10 (38)	15 (13)	0.006	11 (24)	14 (15)	0.26
Previous sternotomy, N (%)	4 (15.4)	19 (16.8)	0.91	8 (18.2)	15 (16.0)	0.93
CPB, min	104 (56–114)	87 (69–112)	0.72	97 (69–112)	85 (67–115)	0.64
Transfused RBCs, ml/kg	19 (15–23)	25 (19–34)	0.003	19 (16–29)	25 (19–33)	0.02
FFP, N (%)	9 (35)	82 (73)	0.0006	19 (43)	72 (76)	0.0003
FFP, ml/kg[a]	26 (11–29)	18 (13–28)	n.d.	23 (14–34)	17 (13–28)	n.d.
Platelet concentrate, N (%)	1 (4)	9 (8)	0.76	2 (5)	8 (8)	0.63
Pre-OP platelets, 1,000/μl	359 (297–414)	382 (324–463)	0.23	357 (293–418)	387 (331–465)	0.06
Post-OP platelets, 1,000/μl	189 (142–230)	174 (140–216)	0.42	186 (141–226)	169 (139–213)	0.49
Pre-OP fibrinogen, mg/dl	259 (222–307)	249 (216–292)	0.29	262 (221–307)	245 (219–277)	0.14
Post-OP fibrinogen, mg/dl	159 (136–183)	159 (138–185)	0.97	159 (128–182)	159 (142–186)	0.37
Pre-OP CRP peak, mg/dl	0.06 (0.03–0.31)	0.04 (0.02–0.16)	0.06	0.07 (0.03–0.31)	0.03 (0.02–0.15)	0.06
Post-OP CRP peak, mg/dl	6.3 (4.6–10.2)	7.6 (5.2–10.2)	0.41	6.1 (3.8–8.6)	8.1 (5.6–10.4)	0.009
Length of ventilation, h	31 (19–47)	30 (20–62)	0.61	33 (18–53)	29 (20–73)	0.62
Length of ICU stay, days	3 (2–4)	3 (2–5)	0.98	3 (2–4)	3 (2–5)	0.83

RBCs = Packed red blood cells, RACHS = risk adjustment for congenital heart surgery, CPB = cardiopulmonary bypass time, FFP = fresh frozen plasma, Pre-OP = pre-operative, Post-OP = post-operative, CRP = C-reactive protein, ICU = intensive care unit, n.d. = not determined.
Data on patient characteristics, transfusion requirements, and post-operative morbidity are listed. Data are presented as the median (interquartile range) or number N (%). Groups receiving fresh or stored RBCs (for cut-offs of ≤3 and ≤6 days) were compared by rank sum or χ^2 tests as appropriate. P values were not adjusted for test repetitions on multiple parameters, and false-positive results cannot be excluded.
An increasing RACHS score represents increasing risk of in-hospital mortality. The median RACHS score for each group is provided. In addition, the numbers of patients with RACHS scores of 2, 3, or 4 are presented; RACHS scores of 1, 5, or 6 were not present in our patient population.
[a]The median volume relates only to patients who received FFP.

Table 3. Results of sliding cut-off analyses

		Cont	Cut-off, days										
			≤1	≤2	≤3	≤4	≤5	≤6	≤7	≤8	≤9	≤10	≤11
RBC	P	0.00026	0.00041	*0.00013*	*0.00014*	0.0011	0.016	0.007	0.023	0.012	0.015	0.079	0.068
Linear	Coeff	0.91	9.15	*9.31*	*9.06*	7.34	5.09	5.34	4.22	4.61	4.81	4.08	5.63
FFP	P	0.003	0.07	0.018	0.0035	*0.0011*	0.00085	0.0011	0.0086	0.0083	0.58	0.53	0.54
Logistic	OR	1.04	2.6	3.5	4.7	*5.1*	4.5	4.0	2.8	2.9	1.3	1.4	1.5
LoV	P	0.034	0.076	0.041	0.071	0.10	0.022	*0.009*	0.097	0.35	0.95	1	0.27
Cox	HR	1.06	1.61	1.69	1.59	1.45	1.64	*1.72*	1.37	1.30	0.99	1.00	1.39
LoICU	P	0.26	0.57	0.64	0.49	0.66	0.44	0.16	0.15	*0.054*	0.66	0.81	0.31
Cox	HR	1.02	1.18	1.36	1.19	1.11	1.19	1.33	1.32	*1.43*	1.09	0.95	1.35
CRP	P	0.33	0.99	0.83	0.62	0.33	0.11	*0.009*	0.20	0.56	0.79	0.89	0.45
Linear	Coeff	0.11	–0.01	0.23	0.54	0.98	1.48	*2.27*	1.02	0.47	–0.21	–0.14	1.00

RBC = Volume of transfused RBC, FFP = incidence of transfusion of fresh frozen plasma, LoV = length of ventilation, LoICU = length of ICU stay, CRP = post-operative peak concentration of C-reactive protein, Coeff = coefficient, OR = odds ratio, HR = hazard ratio.
Multivariate analyses were performed with RBC storage duration as continuous variable (Cont) and as dichotomous variable using sliding cut-offs between ≤1 and ≤11 days. P values and regression coefficients (for backward stepwise linear regression), ORs (for multiple logistic regression) or HRs (for delayed extubation or delayed release from ICU by Cox regression proportional hazards model) are provided. The values for the cut-offs selected for further analyses are shown in italics.

Table 4. Results of multivariate analyses with the optimal cut-offs from table 3

	Coeff		p value
Transfusion requirement, ml RBCs/kg: multiple linear regression, cut-off ≤ 2 days			
Body weight, kg	9.06		<0.001
Previous sternotomy	0.21		0.86
RACHS score	0.61		0.68
RBCs older than 3 days	9.06		<0.001
	OR	CI	
FFP requirement: multiple logistic regression, cut-off ≤ 4 days			
Body weight, kg	1.07	0.89–1.30	0.47
Previous sternotomy	1.15	0.35–3.80	0.81
RACHS score	1.73	0.97–3.09	0.06
RBCs, ml/kg	1.04	0.99–1.08	0.06
RBCs older than 4 days	5.13	1.92–13.72	0.001
	HR	CI	
Length of ventilation, days: Cox regression proportional hazards for delayed extubation, cut-off ≤ 6 days			
Body weight, kg	0.80	0.72–0.88	<0.001
Previous sternotomy	1.19	0.71–2.00	0.50
RACHS score	1.64	1.25–2.17	<0.001
RBCs, ml/kg	1.03	1.01–1.05	<0.001
RBCs older than 6 days	1.72	1.15–2.63	0.009
Length of ICU, days: Cox regression proportional hazards for delayed release from ICU, cut-off ≤ 8 days			
	HR	CI	
Body weight, kg	0.93	0.85–1.02	0.12
Previous sternotomy	0.88	0.53–1.47	0.64
RACHS score	1.59	1.23–2.08	<0.001
RBCs, ml/kg	1.02	1.00–1.03	0.06
RBCs older than 8 days	1.43	0.99–2.08	0.054
	Coeff		
Post-OP-CRP peak, mg/dl: backward stepwise regression, cut-off ≤6 days			
Body weight, kg	0.007		0.97
Previous sternotomy	4.9		<0.001
RACHS score	–0.22		0.68
RBCs, ml/kg	–0.04		0.27
RBCs older than 6 days	2.27		0.009

For each outcome parameter, the results for the optimal cut-off with best separation between fresh and old RBCs as given in table 3 are listed. In addition to the significance levels P, regression coefficients for linear regression, ORs with confidence intervals (CI) for use of FFP calculated by logistic regression and HRs with CI for delayed extubation or delayed release from the ICU calculated by Cox regression are listed.

RBCs that were stored for up to 3 days (median storage time, 1 day) were received by 26 patients and 113 patients received RBCs with a storage time of >3 days (median storage time, 9 days). The patients receiving the RBCs stored for >3 days were older (median age of 145 vs. 108 days; p = 0.01) and heavier (median body weight of 5.5 vs. 4.4 kg; p = 0.03) (table 2) than those receiving fresher RBCs. The rate of previous sternotomies was similar between both groups, while the median RACHS score was lower in the patients receiving RBCs >3 days old. The pre- and post-operative platelet counts and fibrinogen concentrations did not differ between groups. Patients who received fresh RBCs required a smaller volume than those who received older RBCs (median (interquartile range) 19 (15–23) versus 25 (19–34) ml/kg; p = 0.003). In addition, a larger number of patients in the latter group required FFP (73% vs. 35%; p < 0.001). The rate of patients receiving platelet concentrates was quite low and was therefore not included as covariable in the multivariate analyses. The post-operative peak CRP concentrations were similar between groups, as were the lengths of ventilation and ICU stay.

Multiple multivariate analyses with sliding cut-offs provided the best prediction of transfusion requirements of RBCs and FFP for cut-offs of ≤2 and ≤4 days, respectively (table 3), and these were applied in the multivariate analyses reported below and in table 4. Because the difference between the cut-offs of ≤2 and ≤3 days was very small (p = 0.00013 vs. p = 0.00014, with only 2 patients receiving RBCs stored for 3 days), the group stratification presented in table 2 is according to the cut-off of ≤3 days, which is closer to the best cut-off for the FFP requirement of ≤4 days.

Low body weight ($p < 0.001$) and RBCs older than 3 days ($p = 0.001$), but not previous sternotomies or the RACHS score, were independently associated with the transfused volume of RBCs (table 4). The odds for administration of FFP as analyzed by multiple logistic regression increased with the transfusion of older RBCs ($p = 0.001$ for RBCs ≤ 4 days old vs. 5–14 days old). In contrast, body weight and previous sternotomies had no effect on the FFP transfusion requirements while the RACHS score and the volume of transfused RBCs tended to be associated with the incidence of FFP transfusion ($p = 0.06$; table 4).

The optimal cut-offs for parameters of post-operative morbidity were at markedly longer storage times of ≤6 days, or ≤8 days for length of ventilation, post-operative peak of CRP concentration, and length of ICU (table 3). Data on patient characteristics for the separation of patients according to RBC storage time of ≤6 days are presented in table 2. Patients who received RBCs > 6 days old were older and heavier, had a lower RACHS score, received greater RBC volumes and more frequently FFP, and demonstrated higher post-operative peak CRP concentrations than patients who received RBCs ≤ 6 days old. The indicators of post-operative morbidity, lengths of ventilation and of ICU stay, were not different between groups. Only after correction by multivariate analyses for body weight, previous sternotomies, RACHS score, and transfused volume of RBCs, an effect of RBC storage time on post-operative morbidity became apparent.

Multivariate analyses revealed that the hazard for late extubation decreased with larger body weight ($p < 0.001$), but increased with greater RACHS score ($p < 0.001$), transfusion of a larger amount of RBCs per kilogram body weight ($p < 0.001$), and with transfusion of RBCs > 6 days old ($p = 0.009$; table 4). The hazard for late release from the pediatric ICU increased with greater RACHS score ($p < 0.001$) and tended to increase with the volume of transfused RBCs ($p = 0.06$) and a storage time of >8 days ($p = 0.054$; table 4).

The post-operative inflammatory response as assessed by peak CRP concentration was independently associated with previous sternotomies ($p < 0.001$) and RBCs > 6 days old ($p = 0.009$), while body weight, RACHS score, or volume of transfused RBCs did not demonstrate an effect.

Discussion

The results from this study support the prioritization of the use of fresh RBCs in pediatric cardiac surgery patients. The transfusion requirement was observed to continuously increase with longer duration of RBC storage. The optimal RBC storage time cut-offs for transfusion of greater volumes of RBC and requirement of FFP were ≤2 and ≤4 days, respectively. In addition, the post-operative duration of ventilation and the peak CRP concentration were affected by RBCs stored for more than 6 days.

Since the transfusions were given from 1 single RBC unit, yet in most cases transfused in increments, the independence between age and amount of transfused RBCs may be challenged. Also, the mean difference in the transfused volumes of RBCs of only 6 ml/kg may be of little clinical relevance. However, previous studies [14, 16] and the differences in FFP transfusion support the notion that the age of RBCs is associated with the overall transfusion requirement. Potential bias by transfusion of RBCs with mixed ages was avoided by including patients who had only received RBCs from a single unit, as part of a comprehensive blood-sparing approach [21], thus requiring only a small volume of RBCs. Our findings are supported by the comprehensive review by van de Watering [1] who identified several pitfalls in the design of observational studies concerning the effect of RBC storage time on clinical outcome. One of these concerns was the heterogeneous amount of RBC units in the different groups. This problem could not be resolved, even by adjusting the data for the number of transfused RBC units, as patients receiving additional RBC units have a greater chance of receiving either a very fresh or an old unit. In comparison to other studies, we avoided the problem of stratification of RBC units with different storage times for either the mean age or the oldest/freshest unit [1].

The selection of risk factors as potential confounders influencing the outcome parameters is largely based on our recent analyses of pediatric patients treated with the same comprehensive blood-sparing approach [22]. The major general limitation of retrospective studies that only retrospectively available covariates can be included in the analyses also applies to this study [25].

In contrast to previous studies [2–16, 18], the age of the transfused RBC units in the present study was invariably <14 days. Due to the institutional policy of using the freshest available blood units for pediatric patients, the individual storage times depended only on availability. Because previous studies do not provide cut-offs for the differentiation between fresh and old RBC units for such a cohort of patients, analyses were performed with multiple cut-offs for each outcome parameter and optimal cut-offs were defined retrospectively. However, these cut-offs may not be applicable to other patient cohorts with greater RBC storage time variability. Surprisingly, even within this cohort of patients receiving RBCs that had been considered fresh in most of these previous studies, the storage time still has a profound effect on the transfusion requirements and the post-operative morbidity.

The effect of the storage time on the transfusion requirements following cardiac surgery in adults has been described previously [14], although the storage time was not observed to have an independent effect on the mortality or the length of the ICU stay when adjusting for the number of transfusions. Similarly, in another study based on early outcomes following cardiac surgery, the total number of RBC units transfused was associated with early mortality, renal failure, pneumonia, length of ventilation and ICU stay, but no effect was observed for the RBC storage time [16]. In contrast, a study on cardiac surgery patients conducted by Koch et al. [5] revealed that a storage time > 14 days was independently associated with post-operative short- and long-term mortality, intubation beyond 72 h, renal failure, and sepsis, but not with the number of transfused units. In the present study, pediatric patients received transfusions from a single RBC unit. Therefore, we included the volume of RBC per kilogram body weight as a confounder in the multivariate analyses of the effects of storage time on the need for FFP and on post-operative outcome parameters. Contrary to previous studies, we found that the storage time independently influenced the volume of transfused RBCs, the length of ventilation, and the peak CRP concentration.

In conclusion, a short RBC storage time may have a profound independent effect on both transfusion requirements and early post-operative morbidity. In consideration of all aspects related to the production and management of allogeneic RBCs, further randomized controlled trials of no transfusion versus transfusion of fresh or old RBCs are required prior to drawing any final conclusions.

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Disclosure Statement

The authors state no conflict of interests.

References

1 van de Watering L: Red cell storage and prognosis. Vox Sang 2011;100:36–45.
2 Zallen G, Offner PJ, Moore EE, Blackwell J, Ciesla DJ, Gabriel J, Denny C, Silliman CC: Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg 1999;178:570–572.
3 Purdy FR, Tweeddale MG, Merrick PM: Association of mortality with age of blood transfused in septic ICU patients. Can J Anaesth 1997;44:1256–1261.
4 Offner PJ, Moore EE, Biffl WL, Johnson JL, Silliman CC: Increased rate of infection associated with transfusion of old blood after severe injury. Arch Surg 2002;137:711–716.
5 Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH: Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008;358:1229–1239.
6 Leal-Noval SR, Munoz-Gomez M, Arellano-Orden V, Marin-Caballos A, Amaya-Villar R, Marin A, Puppo-Moreno A, Ferrandiz-Millon C, Flores-Cordero JM, Murillo-Cabezas F: Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury. Crit Care Med 2008;36:1290–1296.
7 Kneyber MC, Hersi MI, Twisk JW, Markhorst DG, Plotz FB: Red blood cell transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med 2007;33:1414–1422.
8 Spinella PC, Carroll CL, Staff I, Gross R, Mc Quay J, Keibel L, Wade CE, Holcomb JB: Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. Crit Care 2009;13:R151.
9 Vandromme MJ, McGwin G Jr, Weinberg JA: Blood transfusion in the critically ill: does storage age matter? Scand J Trauma Resusc Emerg Med 2009;17:35.
10 Weinberg JA, McGwin G Jr, Vandromme MJ, Marques MB, Melton SM, Reiff DA, Kerby JD, Rue LW III: Duration of red cell storage influences mortality after trauma. J Trauma 2010;69:1427–1431.
11 Mynster T, Nielsen HJ: Storage time of transfused blood and disease recurrence after colorectal cancer surgery. Dis Colon Rectum 2001;44:955–964.
12 Leal-Noval SR, Jara-Lopez I, Garcia-Garmendia JL, Marin-Niebla A, Herruzo-Aviles A, Camacho-Larana P, Loscertales J: Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. Anesthesiology 2003; 98:815–822.
13 Walsh TS, McArdle F, McLellan SA, Maciver C, Maginnis M, Prescott RJ, McClelland DB: Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? Crit Care Med 2004;32:364–371.
14 van de Watering L, Lorinser J, Versteegh M, Westendord R, Brand A: Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion 2006; 46:1712–1718.
15 Kneyber MC, Gazendam RP, Markhorst DG, Plotz FB: Length of storage of red blood cells does not affect outcome in critically ill children. Intensive Care Med 2009;35:179–180.
16 Yap CH, Lau L, Krishnaswamy M, Gaskell M, Yii M: Age of transfused red cells and early outcomes after cardiac surgery. Ann Thorac Surg 2008;86: 554–559.
17 Ranucci M, Carlucci C, Isgro G, Boncilli A, De Benedetti D, De la Torre T, Brozzi S, Frigiola A: Duration of red blood cell storage and outcomes in pediatric cardiac surgery: an association found for pump prime blood. Crit Care 2009;13:R207.
18 Manlhiot C, McCrindle BW, Menjak IB, Yoon H, Holtby HM, Brandao LR, Chan AK, Schwartz SM, Sivarajan VB, Crawford-Lean L, Foreman C, Caldarone CA, Van Arsdell GS, Gruenwald CE: Longer blood storage is associated with suboptimal outcomes in high-risk pediatric cardiac surgery. Ann Thorac Surg 2012;93:1563–1569.
19 Koster A, Huebler M, Boettcher W, Redlin M, Berger F, Hetzer R: A new miniaturized cardiopulmonary bypass system reduces transfusion requirements during neonatal cardiac surgery: initial experience in 13 consecutive patients. J Thorac Cardiovasc Surg 2009;137:1565–1568.
20 Redlin M, Huebler M, Boettcher W, Kukucka M, Schoenfeld H, Hetzer R, Habazettl H: Minimizing intraoperative hemodilution by use of a very low priming volume cardiopulmonary bypass in neonates with transposition of the great arteries. J Thorac Cardiovasc Surg 2011;142:875–881.
21 Redlin M, Habazettl H, Boettcher W, Kukucka M, Schoenfeld H, Hetzer R, Huebler M: Effects of a comprehensive blood-sparing approach using body weight-adjusted miniaturized cardiopulmonary bypass circuits on transfusion requirements in pediatric cardiac surgery. J Thorac Cardiovasc Surg 2012; 144:493–499.
22 Redlin M, Kukucka M, Boettcher W, Schoenfeld H, Huebler M, Kuppe H, Habazettl H: Blood transfusion determines postoperative morbidity in pediatric cardiac surgery applying a comprehensive blood-sparing approach. J Thorac Cardiovasc Surg 201;146:537–542.
23 Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI: Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002;123:110–118.
24 Boethig D, Jenkins KJ, Hecker H, Thies WR, Breymann T: The RACHS-1 risk categories reflect mortality and length of hospital stay in a large German pediatric cardiac surgery population. Eur J Cardiothorac Surg 2004;26:12–17.
25 DeCampli WM: Invited commentary. Ann Thorac Surg 2011;91:210–211.