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Association between Transfusion of Red Blood Cells and Subsequent Development of Delirium in Critically ill Children

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Abstract

Objective: To determine the temporal relationship between the transfusion of red blood cells (RBC) and the subsequent development of delirium in a cohort of critically ill children.

Design: Nested retrospective cohort study within prospective cohort study

Setting: Urban academic tertiary care pediatric intensive care unit (PICU).

Patients: All consecutive admissions from September 2014 through August 2015

Interventions: Children were screened twice daily for delirium during their PICU admission

Measurements and Main Results: Among 1547 independent admissions screened for delirium, one hundred and sixty-six (10.7%) were transfused RBCs. Children who were transfused RBCs were more than twice as likely to be delirious during their admission compared to children who were never transfused, after controlling for known predictors of delirium development (adjusted odds ratio 2.16; 95% CI 1.38–3.37; $p = 0.001$). Among transfused children, a temporal relationship was observed between receipt of RBCs and the subsequent development of delirium. For each additional 10mL/kg of RBCs transfused, the recipients were 90% more likely to develop delirium or coma in the 72 hours following the transfusion, after controlling for confounders (adjusted odds ratio 1.90; 95% CI 1.14–3.17; $p = 0.01$). Anemia (represented by nadir hemoglobin prior to transfusion) was not associated with delirium development.

Conclusions: In this cohort of critically ill children, there is an independent association between the receipt of a RBC transfusion and the subsequent development of delirium. Further prospective studies are warranted to replicate this finding, and investigate possible pathophysiologic mechanisms for this association.

Keywords

Red blood cell transfusion; delirium; critical care; pediatric; children

INTRODUCTION

Delirium is the manifestation of global cerebral dysfunction caused by the direct physiologic consequences of a general medical condition or its treatment. It is characterized by an acute onset and fluctuating course during which the patient exhibits both disturbances of awareness and cognition. [1] Delirium is a common diagnosis in pediatric critical care. In a recent multi-institutional observational study, approximately one-quarter of all children admitted to the pediatric intensive care unit (PICU) screened positive for delirium.[2] Pediatric delirium is independently associated with mortality, duration of mechanical ventilation, length of PICU admission [3] and total hospital costs [4]. Given the high incidence of delirium in critically ill children, it is important to explore modifiable risk factors for delirium so as to potentially decrease the associated morbidity.

Inflammation has been postulated as a mechanism for the development of delirium.[5, 6] The transfusion of red blood cells (RBC) has also been associated with inflammation [7, 8] and may represent a modifiable risk factor for the development of delirium. The results from adult studies are conflicting.[9, 10] A recently published systematic review reported that there is no good quality evidence to suggest or refute an independent association between the receipt of an RBC transfusion and the subsequent development of delirium.[11]

The objective of this study was to explore a temporal relationship between a RBC transfusion and the subsequent development of delirium or coma in a cohort of critically ill children. In addition, we sought to assess for a dose-response relationship between the volume of RBCs transfused and subsequent delirium development.

MATERIALS AND METHODS

This study, approved by the Institutional Review Board at Weill Cornell Medicine, is a secondary analysis leveraging delirium data collected as part of a prospective, longitudinal study in an urban, academic, mixed PICU.[3] All patients admitted to the unit for at least 24 hours between September 1, 2014 and August 31, 2015 were included. Each patient, ages 0 to 21 years of age, was screened for delirium twice daily by the bedside nurse using the Cornell Assessment of Pediatric Delirium (CAPD) [12]. The CAPD has been validated for use in children on invasive mechanical ventilation, and is reliable for detecting delirium in children of all ages (including infants). A CAPD score of 9 or higher was considered positive. Children with developmental delay who screened positive on the CAPD had the diagnosis of delirium confirmed by an intensivist or psychiatrist prior to classification.

Each child was given a daily classification of either: “comatose” (unarousable to verbal stimulation -- generally due to deep sedation -- and thus impossible to assess for delirium), “delirious” (those with CAPD score ≥ 9 with diagnosis confirmed by a physician), or “normal” (those without coma or delirium). Demographic data, including severity of illness as measured by the Pediatric Index of Mortality-3 (PIM3) score [13], were collected at time of admission. Individual patient data, including sedation scores and CAPD assessments, as well as need for mechanical ventilation and medications received, were collected daily. Indications for transfusion were classified as intra-operative, post-operative, medical

bleeding (when a single direct cause of anemia identified, such as splenic laceration), or medical non-bleeding. Clinical outcomes data were recorded upon discharge from the hospital.

This cohort was included in a prior publication describing the epidemiology and outcomes of pediatric delirium. [3] All data in this manuscript regarding transfusions are novel and have never been published elsewhere.

Patients within the prospective, longitudinal study who received RBC transfusions were identified through SafeTrace Tx® Transfusion Management System, Haemonetics Corporation. Transfusion data, including RBC dose (in ml/kg), number of transfusions (defined as number of PICU days in which RBCs were transfused), and storage age of RBCs (in days), were collected retrospectively. The unit of analysis for assessing delirium as an outcome was an independent RBC transfusion event. Up to three RBC sequential transfusions during the same admission were accounted for in this analysis to study impact on outcomes. Delirium was assessed in two ways: a) being ever-delirious during the admission or b) being delirious-post-RBC-transfusion. To be classified as delirium-post-RBC-transfusion, a subject had to have documentation of normal mental status in the 24 hours prior to the RBC transfusion and then develop delirium or coma within 72 hours post transfusion. Delirium events without a prior normal mental status documentation were not included in this analysis. To establish a temporal relationship between the receipt of RBCs and the subsequent development of delirium, the cohort of those transfused was analyzed separately. As a secondary outcome, the relationship between anemia and the subsequent development of delirium was analyzed.

Statistical Methods

Quantitative variables were summarized as median and interquartile range and categorical data were summarized as count (%) and compared by the chi-square test. Univariate followed stepwise multivariable logistic regression was used for statistical analyses. Based on results of univariate analysis, the significant variables were added in a stepwise manner in a multivariable model. All hypothesis testing was two tailed and $p < 0.05$ was the threshold for significance. All analyses were conducted using SAS version 9.4 (Cary, NC).

RESULTS

The initial prospective cohort included 1547 independent admissions. Among those, a total of 220 RBC transfusions were administered to 166 subjects (overall transfusion rate 10.7%). The demographics of the transfused subjects are described in Table 1. The majority of transfusions were prescribed to patients undergoing surgical procedures (54%).

In this entire prospective cohort ($n=1547$), RBC transfusions were associated with a diagnosis of delirium in bivariate analysis (odds ratio 6.28 for delirium in patients who were ever transfused when compared to patients who were never transfused; 95% CI 4.46–8.85). In multivariate analysis, children who were transfused RBCs remained more than twice as likely to be delirious during their admission compared to children who were never transfused, after controlling for known predictors of delirium development including: age,

probability of mortality, gender, length of stay, receipt of benzodiazepines, deep sedation, mechanical ventilation and developmental delay (odds ratio 2.16; 95% CI 1.38–3.37; $p=0.001$).

Among the 220 transfusions, 79 patients (36%) were already either delirious or comatose prior to RBC transfusion. Among the 141 transfusions where the cognitive status of the recipient was normal at that time of transfusion, forty-three recipients (30%) developed delirium or coma within 72 hours post-transfusion.

RBC dose was available for 145 of the 166 transfused subjects. These subjects received a median dose (IQR) of 13.1 (9.5–15.1) mL/kg. The median age (IQR) of the transfused RBCs was 17.5 (1–24) days. In a univariate regression, for every additional 10mL/kg of RBCs transfused, the odds of transitioning from normal to delirium or coma increased by approximately 80% (odds ratio 1.79; 95% CI 1.1–2.9; p value 0.02). The multivariate model assessing the relationship between dose of RBC transfusion and the subsequent development of delirium is described in Table 2. For each additional 10mL/kg of RBCs transfused, the recipients were 90% more likely to develop delirium in the 72 hours following the transfusion, after controlling for age, gender, probability of mortality and PICU length of stay (odds ratio 1.90; 95% CI 1.14–3.17; $p = 0.03$). In addition, when comparing an additional 5mL/kg of RBCs transfused versus an additional 10mL/kg of RBCs transfused versus an additional 15mL/kg transfused, the odds of developing delirium in the 72 hours following transfusions steadily rose (odds ratio 1.38 versus 1.90 versus 2.61).

When transfusion burden was defined as number of RBC transfusions, the dose-response relationship between RBCs and delirium remained constant. In a univariate regression of number of transfusions, for each additional transfusion, the odds of transitioning from normal to delirium or coma increased by 36% (odds ratio 1.36; 95% CI 1.2–1.6; $p < 0.001$). The multivariate model assessing the relationship between number of RBC transfusions and the subsequent development of delirium is described in Table 3. For each additional RBC transfusion, the recipients were 27% more likely to develop delirium in the 72 hours following the transfusion, after controlling for age, gender, probability of mortality and PICU length of stay (odds ratio 1.27; 95% CI 1.04–1.56; $p = 0.018$).

The nadir hemoglobin prior to transfusion was not associated with development of subsequent delirium ($p=0.9$). In addition, there was no association between mean age of blood or maximum age of blood and the subsequent development of delirium ($p=0.39$ and 0.37, respectively).

DISCUSSION

This single-center, observational study is the first pediatric cohort reported to date examining the relationship between RBC transfusion and subsequent development of delirium. Nearly one-third of patients with a normal mental state prior to their transfusion went on to develop either delirium or coma within 72 hours following the RBC transfusion. We report a significant association between both dose and number of RBC transfusions and subsequent

delirium/coma. There was no association between anemia and delirium development in this cohort.

Though this association has not been explored previously in children, studies in adults have reported conflicting effects of RBC transfusions on the development of delirium. In a recent systematic review [9], twenty-three articles were included. All studies involved surgical patients; one also included medical patients[14]. Only four of the studies described the timing of delirium assessments in relation to the transfusions, thus establishing a temporal relationship [9, 15–17]. Only one of the 23 studies included relevant confounders in their analysis [7]. In that study, Behrends and colleagues described a cohort of 472 adults older than 65 years of age who underwent cardiac surgery. They reported that intra-operative blood transfusions with a transfusion volume of greater than one liter was the strongest independent predictor for the subsequent development of delirium on post-operative day 1 (odds ratio 3.68; 95% CI 1.32–10.94; $p < 0.001$). Our data in children suggest that a much lower exposure to RBCs may be associated with development of pediatric delirium/coma as a composite outcome.

Adult studies have also explored anemia, rather than RBC transfusion, as a risk factor for delirium development. In a recent study, van der Zanden and colleagues enrolled 415 adults older than 65 years of age admitted for hip fracture surgery in a substudy of a multicenter randomized controlled trial [18]. They concluded that mild anemia (defined as hemoglobin < 9.7 g/dL) was associated with delirium (odds ratio 1.81; 95% CI 1.15–2.86). However, they analyzed delirium occurring at any time during the hospitalization, rather than showing a temporal relationship. We report that the nadir hemoglobin in our subjects (prior to the transfusion) was not associated with the subsequent development of delirium ($p = 0.9$). Our data suggest that it is not the anemia, but the RBC transfusion itself, that is the risk factor for the development of delirium.

Though there are no additional pediatric reports of an association between RBC transfusions and delirium to support our findings, these associations are scientifically plausible. RBC transfusion in children has been independently associated with the subsequent development of new or progressive multiple organ dysfunction syndrome (MODS) [19]. A two-hit model has been suggested in which (1) critically ill children have systemic inflammation secondary to their underlying illness and (2) the RBC transfusion amplifies the primed inflammatory response [20]. In-vitro studies have also demonstrated the ability of washed red blood cells to prime the respiratory burst of neutrophils [21]. Because delirium is thought to be a result of neuro-inflammation in a brain with reduced functional reserve [22, 23], RBC transfusion can conceivably contribute to the inflammatory process and increase the risk of delirium.

Our study has several limitations. Foremost, it is an observational study and can only suggest an association and not establish causality. There are factors that may contribute to the development of delirium, such as ambient noise level, the use of restraints, concurrent infections or the transfusion of other blood products, which we did not include in our analyses. In addition, though we controlled for benzodiazepine exposure in the initial cohort, we did not include it in our multivariate model involving transfused children. It is an important element to include in future, larger cohorts. The association between RBC

transfusion dose and delirium must be interpreted with caution as patients who are sicker are often more heavily transfused and although we controlled for severity of illness in our analyses, this confounding likely cannot be accounted for entirely. Finally, this study was conducted in a single PICU with an established focus on delirium prevention; it is likely that delirium rates in this cohort are lower than delirium rates in other PICUs, and therefore the findings may not be widely generalizable. Multi-institutional studies are needed to further explore the relationship between red blood cell transfusions and subsequent delirium.

CONCLUSIONS

In this cohort of critically ill children, there is an independent association between the receipt of an RBC transfusion and the subsequent development of delirium. Future multi-institutional studies should be conducted to replicate this finding, and explore pathophysiologic mechanisms related to inflammation.

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Table 1.

Patient Characteristics

Patient Variable	N=166
Age (yr), median (IQR)	2.79 (0.58–10.9)
Sex (male), n (%)	67 (40)
Mechanical Ventilation, n (%)	133 (80)
PIM-3 Score, median (IQR)	1.8% (1.3–4.8%)
Most Common Admitting Diagnoses, n (%)	
Respiratory Insufficiency/Failure	47 (28)
Cardiac Disease	36 (22)
Neurologic Disorder	29 (17)
Indications for Transfusion, n (%)	
Intra-operative	51 (38)
Post-operative	38 (23)
Medical Bleeding	7 (4)
Medical Non-bleeding	70 (42)
Hospital length of stay (days), median (IQR)	9 (5–25)
PICU length of stay (days), median (IQR)	6 (3–15)

Table 2.

Multiple Logistic Regression Model of Dose of RBCs and the Subsequent Development of Delirium in Transfused Patients

Predictor Variables	OR (95% CI)	p-value
Dose RBC transfusion		
5 mL/kg	1.38 (1.07–1.78)	0.014
10 mL/kg	1.90 (1.14–3.17)	0.014
15 mL/kg	2.61 (1.21–5.63)	0.014
Age (> 13 years as reference)		
< 1 year of age	1.87 (0.47–7.47)	0.940
1–3 years of age	1.54 (0.33–7.14)	0.612
3–6 years of age	3.68 (0.83–16.32)	0.112
6–12 years of age	2.45 (0.55–10.93)	0.552
Gender (male as reference)	1.38 (0.60–3.17)	0.456
PICU LOS (days)	0.99 (0.97–1.02)	0.501
Probability of mortality	1.22 (0.08–19.24)	0.889

Probability of mortality was determined by the Pediatric Index of Mortality-3 score.

Table 3.

Multiple Logistic Regression Model for Number of RBC Transfusions and the Subsequent Development of Delirium in Transfused Patients

Predictor Variables	OR (95% CI)	p-value
Number of RBC transfusions	1.27 (1.04–1.56)	0.018
Age (> 13 years as reference)		
< 1 year of age	1.47 (0.49–4.38)	0.478
1–3 years of age	0.96 (0.27–3.37)	0.608
3–6 years of age	1.52 (0.47–4.86)	0.470
6–12 years of age	1.06 (0.31–3.60)	0.777
Gender (male as reference)	1.71 (0.81–3.61)	0.163
PICU LOS (days)	1.01 (0.98–1.05)	0.458
Probability of mortality	7.57 (0.52–110.31)	0.139

Probability of mortality was determined by the Pediatric Index of Mortality-3 score.