

Blood Transfusion and Nosocomial Infection in the Pediatric Intensive Care Units

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Abstract:

Objectives: We aimed to determine the association between red blood cell (RBC) transfusion and nosocomial infection (NI) in a Pediatric Intensive Care Unit (PICU) and its effect on absolute lymphocytic count (ALC) as a possible risk factor for transfusion-related immunomodulation..

Patients and methods: A prospective observational study carried out on 120 critically-ill patients <18 years old admitted to single-center, medical, closed pediatric intensive care unit of a tertiary university children hospital during a 6-month period from 1st of January to end of June, 2011.

Results: NIs (respiratory, urinary tract, and bloodstream infections) were the primary outcome measure and were defined as post transfusion if occurring within 14 days after RBC transfusion. Seventy patients (58%) received RBC transfusion: 44/70 (63%) once and 26/70 (37%) received repeated RBC transfusions. Patients with NI had higher Pediatric Index of Mortality (PIM), longer hospital stay and more frequent instrumentation compared to those without NI ($p=0.02$, 0.02 and 0.002 respectively). Among NI group; 67% received RBC transfusions versus 50% in other group (odds ratio, 2.1; 95% CI, 1.0-4.3; $p=0.06$). We found that patients receiving ≥ 2 RBC transfusions had a similar prevalence of NI compared with those receiving transfusion once (61% vs. 44%, $p=0.365$), but longer hospital stay ($p<0.001$) and greater mortality (62% vs. 23%, $p=0.002$). Transfused subjects had lower ALC compared with pre-transfusion levels ($p=0.04$).

Conclusion: a single blood transfusion lowers the ALC but is not associated with an increased infection risk in the PICU children; while repeated RBCs transfusion is associated with a longer hospital stay and a less favorable outcome.

Key words: blood transfusion; nosocomial infections; Pediatric intensive care unit (PICU), lymphopenia.

Introduction:

Anemia is a common problem in the intensive care unit (ICU). A great proportion of patients are found to be anemic at admission to the ICU **(1)**. Over one third of children receiving care in a pediatric intensive care unit (PICU) develop anemia **(2)**, and 15-50% of all PICU patients receive at least one blood transfusion during their stay **(3)**.

Potential risks of blood transfusion include pyrogenic and hemolytic reactions, transmission of viral infections [such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), cytomegalovirus (CMV)], bacterial contamination of blood components, adult respiratory distress syndrome (ARDS) and transfusion-related immune-modulation (TRIM). Basic mechanisms underlying TRIM may include soluble white blood cell-derived biological modifiers in allogenic red blood cell (RBC) transfusions that alter effector or suppressor T lymphocyte activity, suppression of natural killer cell function **(4)**, defective antigen presentation, and inhibition of lymphocyte proliferation in response to antigenic stimulus **(5)**.

Recent retrospective and prospective studies in adults revealed an association between blood transfusion and risk of nosocomial infections in medical/surgical ICU patients **(6)**. However, to the best of our knowledge, only a few published pediatric studies investigated the increased infection risk and altered immune status after blood and blood product transfusion(s). In a well-designed study of the outcomes related to blood transfusion practices in pediatric patients, *Lacroix et al* **(7)**, observed no differences in risk of mortality or infection in critically ill pediatric patients who were stratified to a high (hemoglobin [Hb] <9.5 g/dL) or low (Hb <7g/dL) transfusion threshold. A recent study concluded that RBCs transfusion in PICU patients is associated with an increased risk of nosocomial infections (NI) and reported an infection rate 51.1% in the RBCs group versus 5.5% in the non-transfused group (OR of 3.72 with 95% CI of 1.19-11.85) **(8)**.

Another study done on burned children receiving blood transfusion during their PICU stay suggested that administration of RBCs increases the risk of sepsis in pediatric burn patients **(9)**.

We aimed in this study to prospectively determine the association between RBC transfusion and NI in a PICU. We also investigated the effects of transfusion on the absolute lymphocytic count (ALC) as a possible risk factor for TRIM.

Patients and methods:

In a prospective case-control study, we enrolled 70 critically-ill children (aged 2 months to 13 years) admitted to our PICU at Cairo University Pediatric Hospital (tertiary referral teaching hospital), Cairo, Egypt, and received blood transfusion once or more during their hospital stay, and 50 critically-ill non-transfused age and sex matched patients admitted to our PICU as controls. Blood transfusions were given for critically-ill with system failure when Hb level ranged from 7 to 9 g/dL **(10)**. The study was carried out from 1st of January to end of June 2011. The study protocol was approved by the Institutional Ethical Committee and was conducted in accordance with the University bylaws for human research. The study was explained and consent was obtained from all parents/legal guardians before enrollment. The basic inclusion criterion was age ≤18 yrs for any patient admitted to the PICU. The exclusion criteria included, patients diagnosed with an infection <48 hrs before admission or within the first 48 hrs after admission to the PICU and patients diagnosed with primary immune deficiencies.

Full history was taken from all parents/legal guardians. Data collected included demographics (age and gender), diagnosis, Pediatric Index of Mortality (PIM) score, PICU length of stay (LOS), number of RBC transfusions, and presence of mechanical ventilation, presence of central venous catheter or urinary catheter.

Complete blood picture with blood indices by Coulter Counter (Cell-Dyn[®] 1700CS; Abbott) to record the baseline and post-transfusion Hb concentration. Post-transfusion samples always collected 12 to 24 hrs after transfusions. Differential leucocytic count was done on Leishman-Geimsa stained peripheral blood film **(11)** for calculation of absolute lymphocyte count (ALC). C-reactive protein was done using latex agglutination test **(12)**. Microbiologic methods (blood, sputum and urine cultures) were obtained as routine in all cases and performed using lysis direct plating and lysis centrifugation **(13)**. Plain chest radiography was performed for cases of suspected lower respiratory tract infections.

The main Primary outcome measure was documented post-transfusion infections (considered post transfusion if occurring ≤ 14 days after transfusion) **(8)**. Post-transfusion infections included: a) pneumonia as evident by positive bacterial cultures of tracheal aspirates and/or new evidence of airspace disease by plain chest radiograph or, in the absence of a new chest radiograph infiltrate, a clinical diagnosis of pneumonia in the attending physician's note, usually based on a combination of rales, hypoxia, elevated leukocytes in the tracheal smear, leukocytosis, and/or ventilation abnormalities. b) Urinary tract infection with positive bacterial culture, with colony counts $\geq 1,000$ CFU/mL or cm^3) Bacteraemia and clinical diagnosis of culture-negative sepsis. **The main Secondary outcome measures were** mortality during PICU stay and length of hospital stay.

Statistical Analysis: Data management and analysis were performed using SigmaStat program; version 3.5 (Systat Software, Inc., USA). The numerical data were statistically presented in terms of range, mean, standard deviation, median and interquartile range (IQR). Categorical data were summarized as percentages. Comparisons between numerical variables of two groups were done by unpaired Student's *t* test for parametric data or Mann-Whitney Rank Sum test for non-parametric data. Comparisons between numerical variables at pre and post transfusion time were done by Student's paired *t*-test for parametric data or Wilcoxon Signed Rank Test for non-parametric data. Comparing categorical variables were done by Chi-square test or Fisher exact test for small sample size. Pearson correlation was used to test for relationship of frequency of transfusion and other variables. Univariate regression analysis was performed to identify risk factors for nosocomial infection. *All p* values are *2-tailed* and considered statistically significant if < 0.05 .

Results:

During the study period, a total of 120 patients, 58 (48.3%) males and 62 (51.7%) females aged 2-156 months with a median age of 10 months were eligible for inclusion and enrollment. Of these, 70 (58.3%) patients received blood transfusion (Group 1) and 50 patients did not (Group 2). Group 1 was further divided into group 1A and 1B according to number of transfusions (once or more). The median PIM score of all studied cases was 2.4 (IQR: 1.3-5.75). Median PIM score was higher among the transfused group ($p < 0.05$). However, the majority of patients in this study were of the low risk category of illness severity on admission to the PICU. Baseline characteristics for the transfused and non-transfused patients are shown in Table 1.

Table 1: Patients' admission characteristics in both Groups:

Variable	Group 1 (n=70)	Group 2 (n=50)	p-value
Age (mo): Median (IQR)	7 (4-21.75)	18.5 (6-60)	0.004*
Sex (n;%): Males Females	31 (44.3%) 39 (55.7%)	27 (54%) 23 (46%)	0.4
Admission PIM score: Median (IQR)	2.85 (1.5-6.7)	1.9 (1.1-4.3)	0.01*
Instrumentation (n;%): Urinary catheter Central Venous Catheter	18 (26%) 16 (23%)	3 (6%) 2 (4%)	0.01* 0.01*
Admission hemoglobin: Median (IQR)	8.5 (7.8-9.9)	10.6 (9.6-11.8)	<0.001*
Platelet count: Median (IQR)	277.0 (150.8-432.8)	336.0 (215.3-466.0)	0.626
TLC: Median (IQR)	10.5 (7.1-16.0)	9.85 (6.10-14.0)	0.464
i/t ratio: median (IQR)	0.13 (0.1-0.2)	0.08 (0.03-0.22)	0.050
Absolute Lymphocytic count Median (IQR)	2520 (1521.8-4419.5)	2288.0 (1381.5-3380.0)	0.431
I/t ratio >0.2 (n,%)	20 (28.6%)	13 (26%)	0.837
Positive CRP (n;%)	31 (44.3%)	14 (28%)	0.087
Infection rate (%)	39 (55.7%)	19 (38%)	0.077

PIM, Pediatric Risk of Mortality score; TLC, total leucocytic count; I/t ratio, immature/total TLC ratio; n, number

Mortality was 37% in RBC group versus 16% in control group, presence and PICU LOS (10 days versus 4 days) are clinically significant variables that are notably different between the two groups (Table 2).

Table 2: Difference in LOS & mortality by transfusion status:

	Group 1 (n=70)	Group 2 (n=50)	p-value
Length of Hospital stay (LOS) (days): Median (IQR)	10 (6-15)	4 (2-6)	<0.001*
Outcome, n (%):			
Survived	44 (63%)	42 (84%)	0.014*
Died	26 (37%)	8 (16%)	

Continuous variables are expressed as median (interquartile range).

The median number of RBC transfusions per patient in the transfused cases was 1. In a dose-response analysis (Table 3), we noted a significant difference in mortality (23% vs. 62% for patients receiving one RBC transfusion versus ≥ 2 RBC transfusions, respectively; $p=0.002$), but no effect of RBC dose on frequency of NI.

Table 3: comparison of transfused patients according to frequency of transfusions:

	Group 1A (n=44)	Group 1B (n=26)	p-value
Age, mo			
Median (IQR)	6.0 (4.0-20.3)	8.0 (4.0-36.0)	0.280
Male, n (%)	18 (41%)	13 (50%)	
Female n (%)	26 (59%)	13 (50%)	0.619
PICU LOS, days:			
Median (IQR)	7.0 (5.0-11.00)	15.5 (10.0-20.0)	<0.001*
Positive cultures (n, %)			
Blood stream	7 (16%)	10 (38%)	
Urinary tract	2 (5%)	3 (14%)	0.498
Pneumonia	28 (64%)	22 (85%)	
Infection rate, (%)	19 (43%)	20 (77%)	0.01*
Outcome n (%):			
Survived	34 (77%)	10 (38%)	0.002*
Died	10 (23%)	16 (62%)	

PICU LOS, pediatric intensive care unit length of stay; n, number

A positive significant correlation between frequency of transfusion and PIM score ($r=0.2$, $p=0.02$), LOS ($r=0.5$, $p=0.000$), TLC ($r=0.2$, $p=0.02$) was detected but not significant negative correlation with ALC ($r=-0.2$, $p=0.07$).

The median Hb was significantly higher after transfusion and ALC was significantly lower at post transfusion time ($p < 0.05$). ALC and TLC before and after RBC transfusion are illustrated in Table (4).

Table 4: Laboratory characteristics before and after transfusion (n=70):

Variable	Before transfusion (n=70)	After Transfusion (n=70)	P-value
Hb (g/dl): Median (IQR)	8.50 (7.775-9.900)	10.70 (9.45-12.00)	<0.001*
Platelet count: Median (IQR)	277.00 (150.75-432.75)	295.0 (180.0-412.00)	0.526
TLC: Median (IQR)	10.45 (7.10-16.00)	11.30 (8.20-14.90)	0.504
I/t ratio: Median (IQR)	0.13 (0.08-0.228)	0.13 (0.045-0.305)	0.274
ALC: Median (IQR)	2520.0 (1521.75-4419.50)	2005.0 (1184.0-2900.0)	0.036
CRP, (n, %):			
Positive	31 (44.3%)	27 (38.6%)	0.607
Negative	39 (55.7%)	43 (61.4%)	
Positive Cultures:			
Sputum	15 (21%)	17 (24%)	0.632
Blood	9 (13%)	17 (24%)	
Urine	4 (6%)	5 (7%)	

Hb, hemoglobin; TLC, total leucocytic count; I/t ratio, immature/total TLC ratio; CPR, C-reactive protein; n, number

We found that ALC measured post transfusion was lower than pre transfusion; however, no statistically significant differences in ALC in transfused and non transfused patients, also white blood cell was unchanged (Table, 5)

Table (5): comparison of post transfusion absolute lymphocyte counts in transfused patients versus absolute lymphocyte counts in non transfused patients:

Variable	Group 1 (n=70)	Group 2 (n=50)	P-value
ALC (cells/micml)			
Pre transfusion	2520.0 (1521.75-4419.50)	2288.0(1381.5-3380.0)	0.431 0.416
Post transfusion	2005.0 (1184.0-2900.0)5		
TLC:			
Pre transfusion	10.45 (7.10-16.00)	9.85 (6.10-14.0)	0.464
Post transfusion	11.30 (8.20-14.90)		0.113

ALC, absolute lymphocytic count; TLC, total leucocytic count; n, number

Univariate analyses was performed to screen for risk factors for NI in the overall group of PICU patients. Variables that were significantly associated with NI are presented in Table (6). Of the three statistically significant variables—PIM score, PICU LOS, and presence of catheter. Catheter insertions were associated with the highest odds ratio for infection (odds ratio, 3.9; 95% confidence interval, 1.6–9.3).

Table (6): Comparison of patients with infection and patients without infection:

Variables	Infection (n=58)	No infection (n=62)	P value	Odds ratio	95% CI
Age, mo Median (IQR)	10.0 (4.0-36.0)	9.0 (4.8-48.0)	0.958	-	-
Sex (n; %): Male Female	31 (53.4%) 27 (46.6%)	27 (43.5%) 35 (56.5%)	0.361	1.4883	0.7245- 3.0574
PIM score Median (IQR)	3.9 (1.4-7.0)	1.95 (1.2-3.2)	0.021*	-	-
PICU LOS Median (IQR)	9.5 (4.0-19.0)	5.5 (3.0-9.0)	0.015*	-	-
Transfused Non-transfused	39 (67%) 19 (33%)	31 (50%) 31 (50%)	0.066	2.0526	0.9787- 4.3049
Catheter, No catheter	23 (39.7%) 35 (60.3%)	9 (14.5%) 53 (85.5%)	0.002*	3.8698	1.6036- 9.3389
Lymphopenia (%)	41 (70.6%)	37 (60%)	0.252	1.6296	0.7623- 3.4835

PIM, pediatric index of mortality; PICU LOS, pediatric intensive care unit length of stay; n, number; Catheter refers to blood and/or urinary catheter

Discussion:

Anemia and the need for allogenic RBC transfusions are exceedingly common among critically ill patients. Multiple pathologic mechanisms contribute to the genesis of anemia in these patients. Emerging risks associated with allogenic RBC transfusions including the transmission of newer infectious agents and immune modulation predisposing the patient to infections **(14)**. Currently, there are substantial data suggesting that exposure to allogenic transfusions may trigger an immune system response in the recipients, leading to an increased risk of infection and an increased likelihood of mortality **(15)**. To our knowledge, very few studies discussed this issue in critically ill children. In our prospective study we aimed to investigate allogenic blood transfusion as a possible risk factor of transfusion-related immunomodulation (TRIM) in critically ill medical children admitted to PICU and its possible underlying mechanism.

Among our cases; the infection rate reached 55.7% in group 1 versus 38% in group 2 , the odds ratio of transfusion related infection exceeded 2 with a 95% CI ranging from 0.9787 to 4.3049; however this difference did not reach a statistical significance

($p=0.08$). This is in agreement with the results reported in one of the well designed study of outcomes related to blood transfusion practices in pediatric patients, carried out by *Lacroix et al.*, (**7**) who reported no differences in risk of infection in critically ill pediatric patients who were stratified to a high ($Hb \geq 9.5$ g/dL) or low transfusion threshold ($Hb \leq 7$ g/dL).

Our findings disagree with numerous adult retrospective and prospective studies (**16, 17, 18, 19, and 20**) and with a single retrospective study carried out in pediatric ICU (**8**) that have investigated effect of blood transfusion on patients' clinical and immunological variables and clearly identified the increased risk of NI among critically ill transfused patients. However, we found a positive association between the number of transfusions and the rate of nosocomial infections (43% in group 1A versus 77% in group 1B ($p=0.007$)). This was in line with *Nichols and colleagues* (**19**) who reported that the number of blood transfusions positively correlated with the postoperative infection rate among their study population.

Based on our results, the PIM score, length of hospitalization and total leucocytic count were correlated positively with the frequency of transfusion. We observed a relationship between RBC transfusion and risk of mortality as well as a dose-response relationship between RBC transfusions and risk of mortality. We also observed that ALC correlated negatively with the frequency of transfusion, but this association didn't reach significance. It was found that poor PIM and instrumentations are still the major risk factors of infection. This agrees with some previous reports (**7,8,19**).

Although several studies have proved this association between blood transfusion and NI, a great debate is still present regarding this issue with no overwhelming clinical evidence to establish the existence of a TRIM effect that relates allogenic blood transfusion to post-transfusion infection in surgical or medical cases (**21**). Most of the previous studies have been flawed by retrospective design and make it difficult to establish a cause-and-effect relationship and to separate the effects of transfusion from those of the underlying condition. Our study was a prospective one carried out on medical patients but one of the limitations of our study was insufficient data to compare the changes in ALC after transfusion, with the corresponding change in ALC in those not transfused over the same time period.

Conclusions:

We found that blood transfusion lower the ALC but we failed to prove an association between RBC transfusion and infection risk in the PICU children. However, Patients with higher PIM score, longer hospital stay and more frequent instrumentation develop NI with a higher frequency. Repeated RBCs transfusion in PICU patients is associated with a longer hospital stay and a less favorable outcome. More studies targeted towards the mechanism(s) that predispose critically ill transfused children to the risk of NI have to be conducted.

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نقل الدم وعدوى المستشفيات في وحدات العناية المركزة للأطفال

الأهداف: نحن نهدف لتحديد الارتباط بين نقل خلايا الدم الحمراء (RBC) ونقل عدوى المستشفيات (NI) في وحدة العناية المركزة للأطفال (PICU) وتأثيره على العد الليمفاوي المطلق (ALC) كأحد عوامل الخطر التي قد تؤدي إلى الاختلال المناعي المصاحب لنقل الدم .

المرضى والطرق: دراسة وصفية مستقبلية أجريت على ١٢٠ من مريضى الحالات الحرجة اقل من ١٨ سنة المحجوزين بوحدة العناية المركزة للأطفال في مستشفى الأطفال الجامعي (جامعة القاهرة) خلال فترة ٦ أشهر من ١ يناير إلى نهاية يونيو ٢٠١١ .

النتائج: حدوث عدوى المستشفيات (بالجهاز التنفسي والمسالك البولية، والتهابات مجرى الدم) كانوا مقياس النتيجة الأولية وكانت تعرف بأنها مصاحبه لنقل الدم إذا حدثت في غضون ١٤ يوما بعده. تم نقل الدم لسبعين مريضا (٥٨٪): ٧٠/٤٤ (٦٣٪) مرة واحدة و٧٠/٢٦ (٣٧٪) مرتين او اكثر. وكان المرضى الذين حدثت لهم عدوى المستشفيات يعانون من ارتفاع مجموع نقاط مؤشر الوفيات (PIM)، طول مدة الإقامة في المستشفى والحاجة للأجهزة على نحو أكثر تواترا مقارنة بالمرضى الذين لم تحدث لهم عدوى المستشفيات (القيمة الاحتمالية= ٠,٠٢ و ٠,٠٢ و ٠,٠٠٢ على التوالي). من بين الجماعة التي اصيبت بعدوى المستشفيات ؛ تلقى ٦٧٪ نقل الدم مقابل ٥٠٪ في المجموعة الأخرى (نسبة الأرجحية، ٢,١ ، القيمة الاحتمالية=٠,٠٦).

وقد وجدنا ايضا أن المرضى الذين تلقوا نقل الدم مرتين او اكثر كان انتشار عدوى المستشفيات بينهم متشابه مع أولئك الذين تلقوا نقل الدم مرة واحدة (٦١٪ مقابل ٤٤٪، القيمة الاحتمالية=٠,٣٦٥)، ولكنهم بقوا في المستشفى لفترة أطول (القيمة الاحتمالية اقل من ٠,٠٠١)، كانت نسبة الوفيات فيهم اعلى (٦٢٪ مقابل ٢٣٪، القيمة الاحتمالية=٠,٠٠٢).

ومن الجدير بالذكر ان الاشخاص المنقول لهم الدم كان العد الليمفاوي المطلق لهم بعد نقل الدم أقل بالمقارنة مع مستويات ما قبل نقل الدم (القيمة الاحتمالية=٠,٠٤).

الخلاصة: عملية نقل دم مرة واحدة يقلل من العد الليمفاوي المطلق لكن لا يرتبط مع زيادة خطر عدوى المستشفيات في الأطفال المحجوزين بوحدة العناية المركزة للأطفال ، في حين يرتبط نقل الدم المتكرر مع إقامة أطول في المستشفى ونتيجة أقل موائمه.

الكلمات الدالة: نقل الدم؛ عدوى المستشفيات، وحدة العناية المركزة للأطفال ، نقص العد الليمفاوي المطلق