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Impact of stored red cells on clinical outcome in critically ill

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Abstract:

BACKGROUND: The use and benefit of fresh blood and leuco-reduced blood for critically ill patients has been inconclusive. In this study we have tried to observe the same, in patients admitted to intensive care unit.

STUDY DESIGN AND METHODS: Prospective study was done to observe the effect of transfusion in critically ill patients in a tertiary care hospital. Clinical condition in cases and controls was assessed with the help of Simplified Acute Physiology Score II scoring tool. Clinical outcome among patients who received blood was compared using two cutoffs, 14 and 21 days of shelf life to delineate fresh from old blood. Length of hospital stay, length of stay in ICU, number of days on ventilator and number of hospital acquired infections were used as the surrogate markers for morbidity.

RESULTS: Of the 558 critically ill patients admitted during the study period, 427 received (cases) while 131 did not receive the transfusion (controls). Mean SAPS II scores of cases and controls were comparable. We observed a significantly higher rate of mortality among patients who received RBC units over 21 days. However morbidity parameters were affected even when the cutoff of 14 days is considered. Buffy-coat reduced blood did not influence the outcome in the study group.

CONCLUSION: Critically ill patients may be prioritized for receiving fresher units of packed red cells preferably less than 21 days old. Transfusion is an independent risk factor for morbidity. Hence the risk to benefit ratio should be carefully assessed for every red cell transfusion in critically ill patients.

Keywords:

Blood transfusion, critically ill, fresh blood, storage lesion, stored blood

Introduction

In vitro storage of red blood cells (RBCs) in a liquid medium at lower temperature slows down their metabolism; however, metabolic waste and cellular debris accumulate in the suspending fluid, and the RBCs undergo structural, functional, and biochemical alterations. These alterations in RBCs are termed as "storage lesions," and these changes tend to increase with the storage time.

The most characteristic event during RBC storage is the rapid fall in 2,3-diphosphoglycerate (DPG) levels. It is an allosteric modifier of hemoglobin, which helps in the release of oxygen at the end organ. The levels become undetectable within 2 weeks of storage. On transfusion, 2,3-DPG levels in transfused red cells return to 50% of normal in 7 h and to almost 95% at 72 h. The oxidized RBC membrane is pinched off and shed as microvesicles. Stored RBCs, as a result, change shape to become echinospherocytes characterized by increased fragility and loss of deformability.[1-3] In addition to this, the bioactivity of S-nitrosohemoglobin which is required for the normal physiological vasodilatation of the end arterioles rapidly falls with storage (within 3 hours *ex vivo*).[4]

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Bioactive substances, which are progressively released in the supernatant fluid during packed RBC (PRBC) storage, have the potential to prime neutrophils and mononuclear cells to produce cytokines and interleukins (ILs) such as IL-1b, IL-6, tumor necrosis factor-alpha, and RANTES which have a variety of inflammatory and immunomodulatory effects (transfusion-related immunomodulation [TRIM] effects) *in vivo*.[5] When stored blood is transfused to the recipient, it can lead to some inevitable adverse effects, which include immunomodulation and alterations in the physiology of vascular perfusion. These effects can manifest themselves, especially in the vulnerable critically ill patients owing to their already altered homeostasis and altered immunological status.[6-10] We aimed to observe the effect of transfusing stored blood on the clinical outcome of critically ill patients.

Materials and Methods

We conducted a prospective observational study which included patients admitted to the intensive care unit (ICU) at our tertiary care referral center, between October 2012 and April 2014. All those patients who received PRBC transfusions were taken as cases and those who did not receive PRBC transfusions served as controls. A transfusion event was defined as all PRBC transfusions received within 24 h in the ICU. The patients included were in the age group of 18 years and above. Patients satisfying the inclusion criteria were evaluated and severity of the disease was assessed by the Simplified Acute Physiology Score (SAPS II) calculation.[11] The SAPS II is a scoring tool, which predicts the mortality rate among patients through the multiple logistic regression modeling technique. This score was assessed using an online calculator. To eliminate bias and/or due to the inability to apply SAPS-II, patients on chemotherapy, patients undergoing transplantation, patients with the length of ICU stay <2 days and length of hospital stay <1 week, terminally ill patients with brain stem dysfunction, life expectancy <3 months, patients receiving autologous blood, patients admitted primarily for cardiovascular ailments, and patients admitted in the burns ICU were excluded from the study. The study was commenced after clearance from the Institutional Ethics Committee.

All transfusion decisions were left to the discretion of the patient's physician. Blood requests raised for PRBC transfusions from the ICU were reviewed daily on two occasions, once at 8 am and the other at 5 pm. Reason for ICU admission, indication for PRBC transfusion, the number of PRBC transfusion events in ICU and in hospital, the total number of PRBC units transfused, and concurrent blood components transfused were noted. Patients were followed up during their stay in ICU, until they were stepped down to a ward. Total number of blood components received by the patient, pre and posttransfusion hemoglobin, and hematocrit were noted from patients' records.

Outcome measured

For noting the effect of transfusion on mortality and morbidity, the patients with similar SAPS II score were segregated into comparable cohorts as follows:

1. Group which received transfusion (cases) versus which did not (control)
2. Group receiving fresh blood versus group receiving old blood (taking two cutoffs as 14 and 21 days to delineate fresh and old blood)
3. Group receiving leukoreduced (buffy-coat reduced) versus group receiving nonleukoreduced units.

Buffy coat removal was done to prepare the leucoreduced PRBC units. Anticoagulant and additive solutions used in non-leukoreduced and leukoreduced PRBC units were CPDA and CPD-SAGM respectively. The parameters compared among the above groups were condition during discharge, length of stay in hospital, length of stay in the ICU, and hospital-acquired infections. We tested the hypothesis that older blood is associated with an increase in complications and poor outcome of critically ill patients admitted to the ICU. We have also assessed the effect of transfusion of multiple units versus the single unit of PRBC and the effect of concurrent blood products.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software version 20 (IBM, Armonk, NY, United States of America). Comparison of mean values between two groups was done. The groups were compared using the Student's *t*-test. Kruskal–Wallis test was applied for nonparametric data. Chi-square test was applied to analyze 2 × 2 tables to know the *P* value. $P < 0.05$ was considered as statistically significant.

Results

Patient demographics

The study included 558 patients admitted to the ICU from October 2012 to April 2014, which included 427 cases and 131 controls. Various clinical parameters are compared between these two groups as detailed in Table 1. The patients were admitted for various medical conditions and were categorized broadly as trauma (92), nephrological (48), neurological (52), malignancies (34), and infection and patients with sepsis (158).

The effect of shelf life on the clinical outcome

We observed a significant increase in the mortality of patients receiving blood older than 21 days as shown in Table 2. However, parameters determining morbidity

Table 1: Demographical data of the study population

Demographical information	Mean (SD)		*P*
	Cases	Controls	
Age in years	48 (17.9)	52 (16.2)	0.77
Admission hemoglobin (g/dl)	10.3 (3.1)	10.3 (3.4)	0.28
Admission hematocrit (%)	31.5 (9.5)	31.3 (10.2)	0.34
SAPS II score	38.2 (13.2)	34.5 (13.7)	0.24
Days on ventilator	6.3 (6.8)	6.4 (4.5)	0.96
Length of hospital stay (in days)	21.8 (18.59)	15 (9.1)	0.001
Length of ICU stay (in days)	11.2 (10.8)	8.6 (6.8)	0.001
Mean hemoglobin on discharge (g/dL)	9.7 (2.1)	9.5 (2.1)	0.84
Mean hematocrit on discharge (%)	29.9 (7.41)	29.1 (6.9)	0.21
Mortality rate (%)	41	32	0.008

SAPS=Simplified Acute Physiology Score, ICU=Intensive Care Unit, SD=Standard deviation

Table 2: Age of blood versus clinical outcome

Fresh versus old	<14 days	>14 days	<21 days	>21 days
Improved (%)	156 (62.2)	96 (54.6)	213 (62.6)	39 (44.8)
Worsened (%)	95 (37.8)	80 (45.4)	127 (37.4)	48 (55.2)
P	0.116		0.003	

Table 3: Comparing morbidity markers among fresh and old blood

Fresh versus old	<14 days	>14 days	<21 days	>21 days
Average length of hospital stay (days)	20.1	24.4	20.6	27
P	0.018		0.005	
Average length of ICU stay (days)	10.2	12.7	9.3	15
P	0.019		<0.001	
Average ventilator days	5.8	7.1	6	8
P	0.207		0.173	

ICU=Intensive Care Unit

Table 4: Effect of buffy-coat reduction on clinical outcome

PRBC unit	Outcome		Total	*P*
	Improved	Worsened		
Buffy-coat reduced	54	42	96	0.53
Nonbuffy-coat reduced	198	133	331	
Total	252	175	427	

PRBC=Packed red blood cell

such as length of hospital and ICU stay were affected even when 14 days was taken as cutoff as shown in Table 3.

Effect of buffy-coat reduction on clinical outcome

As shown in Table 4, no significant influence on the clinical outcome was noted among patients who received the buffy-coat-reduced RBCs.

Effect of concomitant products on clinical outcome.

We observed significantly higher mortality (odds ratio = 2.4; $P < 0.0001$) in patients who received concomitant blood products such as fresh-frozen plasma (FFP), platelets, and cryoprecipitate as compared to those who received only PRBCs as shown in Table 5.

Effect of number of units on clinical outcome

The observed mortality rate was comparable to that of the expected mortality rate between the two groups of patients, who received single and multiple units of PRBC transfusion as shown in Table 6.

Discussion

Blood transfusion and its multitude discoveries instigate unlimited research and constant revision of policies regarding blood banking. As on the one hand, efforts are being made to discover novel additive solutions extending the shelf life beyond 42 days; there are researchers who propose a benefit of transfusing fresher blood due to the possible deleterious effects of transfusing older units. Researchers have taken several cutoffs such as 7, 14, 21, 28, and 30 days to delineate the fresh blood from the old blood.[12-18] Most of the studies done are retrospective. Prospective studies published on this subject are done mostly on a particular group of critical patients such as trauma patients receiving transfusion support, cardiac surgery, and in patients with sepsis.[18-20]

We conducted a prospective study to check the effect of transfusion of stored blood and thus to improve the quality of care of the critically ill patients admitted in the intensive care settings. Critically ill population was chosen as they are at a greater risk due to their altered physiology and any harmful effects of transfusing older RBCs may be more evident in these vulnerable patients. Till date, the data regarding the benefit of transfusing fresh blood, especially in cardiac surgical, critically ill and trauma patients requiring massive transfusion are inconclusive. Managing a blood bank inventory if the same is proven will become a mammoth task. The turnaround time for a unit of whole blood to be available for issue after component preparation and screening for transfusion-transmitted infections is around 2–3 days.[21] This reduces the actually available shelf life of blood. Aubron *et al*. reviewed the effect of age of RBC on clinical outcome of patients.[22]

In our study, the cases and controls had similar baseline characteristics and were comparable in terms of admission SAPS, admission hemoglobin, and hematocrit. However, the significant increase in mortality rate, length of stay in ICU, and length of stay in hospital among cases was noted. Increased mortality and morbidity observed in these patients probably indicated the TRIM effect and alteration of rheological properties of blood flow in blood transfusion recipients.[23-27]

Table 5: Effect of concomitant products on clinical outcome

Components transfused	Total patients (*n*)	Worsened (*n*)	Expected mortality rate (%)	Observed mortality rate (%)	*P*
Only PRBC	219	68	23.8	31	<0.0001
PRBC + other components	208	107	26.6	51.4	

PRBC=Packed red blood cell

Table 6: Comparison of patients receiving single and multiple packed red blood cell units

Patients receiving exclusively PRBCs	Total patients (*n*)	Worsened (*n*)	Expected mean mortality rate (%)	Observed mean mortality rate (%)	*P*
One PRBC	71	24	24	33.8	0.65
More than one PRBC	148	44	23.8	29.7	

PRBCs=Packed red blood cells

Effect of age of stored blood on clinical outcome

According to the hypothesis that storage lesions can affect clinical outcome, taking higher cutoff for defining old blood increases the probability of observing its adverse transfusion effect. In contrast to age of blood evaluation trial (ABLE) study (<8 days as cutoff), the adverse effect of old blood transfusion was more evident in our study (14 and 21 days as cutoff), and this could be due to the difference in the definition of old blood that is used for analysis. The overall mean age of PRBC issued in our hospital is 11.6 days (standard deviation: 1.7). The average shelf life of blood transfused in ICU patients is around 16–21 days in Europe and in the US.[28,29] Although we follow first-in first-out policy for the routine issue of blood units, we try to issue relatively fresher units to patients who are critically ill. Good inventory management, strict vigilance, and the use of dedicated blood bank software will help the blood bank personnel to keep a track on the blood units in stock.

The clinical outcome was not affected much when we considered 14 days as cutoff; however, the morbidity rate was high as shown in Table 3. The mechanisms involved in linking duration of red cell storage with adverse patient outcome are unclear and there are several contributing factors. The red cell storage also leads to depletion of nitrosohemoglobin. This could be a factor for causing microscopic multiple tissue ischemia and injury.[30] In addition, microparticles and other bioactive substances in packed red cell concentrates might have deleterious effects. Similar to our finding, Juffermans *et al*. noted that the transfusion of RBC stored for more than 14 days was associated with infections in trauma patients and they attributed it to the storage lesions.

Middelburg *et al*. retrospectively analyzed the data with varying cutoffs on clinical outcome.[31] They took 15 days as cutoff which was median age of RBC on issue for the entire patient population and did not find any correlation of age of issued PRBC with clinical outcome. Lelubre *et al*. identified 24 studies that evaluated the effect of age of RBC on clinical outcomes in adult patients and demonstrated their contradictory results.[32]

Effect of buffy-coat reduction on clinical outcome

As per the results of our study, 1-log reduction in leukocyte count may not be sufficient to show any beneficial effects of leukoreduction (LR) in critically ill patients. Our findings were similar to those of Englehart *et al.*, who compared the days on ventilator, the incidence of ARDS, the overall incidence of infectious complications, and mortality and they hypothesized that the use of LR blood does not improve outcome in trauma patients.[33] Karina *et al*. had studied the immunoregulatory effects of stored PRBC's and the effect of LR on storage. They noted a 50% reduction in percent hemolysis following a >3-log reduction in white blood cells. Although we did not observe any effect of LR on clinical outcome in terms of mortality and morbidity, we did observe two incidences of febrile nonhemolytic transfusion reactions occurring in those who received exclusively nonbuffy-coat reduced blood. This is in conformance with the findings of Pruss *et al*. and with the British Committee for Standards in Hematology guidelines, where the provision of buffy-coat reduced blood is the first option to decrease the incidence of febrile nonhemolytic transfusion reactions.[34-36]

Effect of number of red blood cell units transfused on clinical outcome van Straten *et al*. in a retrospective study found an association of mortality with the number of transfusions received. However, the sicker patients are more prone to receive transfusions as their length of stay is high.[15] We noted the similar mortality rate among the patients who received 1 unit and those who received more than 1 unit.

Effect of concomitant products on clinical outcome

The reason for the significantly higher mortality associated with those who have received concomitant products such as FFP, cryo, and platelets might be that, SAPS does not take the coagulation parameters such as prothrombin time, activated partial thromboplastin time, or international normalized ratio, neither does it take platelet count into account. However, the exact reason remains unclear.

The shortcoming of our study is that it is not a double-blinded study, the sample size is small and the measurement of SAPS was done only once at the time of admission to the ICU. Rate of transfusion-related attrition among controls was 40%.

Conclusion

We observed a significant difference in the mortality rates of those who received PRBCs versus those who did not receive any. The present study shows that the age of the blood influences the clinical outcome in critically ill patients. We observed higher mortality and morbidity in patients receiving older blood units. Blood transfusion as a treatment option should be carefully reviewed and administered only if the risk of not transfusing exceeds that of transfusing. Critically ill patients may be prioritized for receiving fresher units of packed red cells.

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Conflicts of interest

There are no conflicts of interest.

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