Influence of Blood Transfusion on the Clinical Course and Immediate Outcome of Trauma Patients: Retrospective Study in a Tertiary Trauma Care Centre in Northern India

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Abstract: *Background:* Red blood cell transfusion is a prominent faction of the standard protocol for management of trauma patients. Clinical research over the past two decades has linked RBC transfusion with increased odds of morbidity and mortality. We conducted a study to assess influence of transfusion on survival and the clinical course of trauma patients in a level I trauma care center.

Methodology: Retrospective review of the blood bank registry was conducted (Jan-June 2012). 100 acutely injured trauma patients who received blood transfusion were selected and categorized based on the number of units transfused; group I (1-5 units) n= 40; group II (6-9 units) n=40 & group III (≥10 units) n= 20. Study control were trauma patients who did not receive transfusion group IV (n= 40). The clinical course of the patients was followed via computerized patient record system maintained by our institution. Analysis was done to compare outcome (in hospital mortality, organ failure, infections, length of stay) between the study and control groups, also between groups based on units transfused.

Results: Severity of injury was significantly higher in patients who received transfusion than those who did not ($p< 0.001$). Transfusion was associated with high rate of infection (62%), organ failures (43%) and mortality (39%). Number of units transfused also correlated with injury severity ($p< 0.001$). Incidence of renal failure (20%), liver failure (35%) was high in group II. Also 50% developed sepsis in group II compared to 13.6 % in group I, and 31.8 % in group III. ($p< 0.001$). Highest mortality rate was observed in group II (67.5%), followed by 60% in group III and lowest in group IV 2.5% ($p< 0.001$).

Conclusion: We observed a surrogate relationship between severity of injury and transfusion requirements. Transfusion-related adversities may be more reflective of the confounding effect of severity of injury than RBC transfusion. Therefore evaluating the risks and benefits of blood transfusion in trauma management is recommended.

Keywords: RBC transfusion, Trauma, Organ failure, Infection, Mortality.

INTRODUCTION

Allogeneic blood transfusion is life saving in severely injured patients. However, transfusion of packed red blood cells (PRBCs), may contribute to sepsis and organ failure in a variety of ways that are only partially understood [1].

Stored RBCs contain a complex assortment of natural antibodies, polymorphic neutrophils (PMN's), cytokines, complement proteins along with bioactive lipids and lysophosphatidycholine (LPC) that favors complement activation and production, when transfused into a trauma patient. The Ag-Ab complexes, generated from natural and allogeneic-specific antibodies from both the donor and host to alloantigen and neoantigens derived from damaged and apoptotic cells, and LPC-CRP (C reactive protein) complexes formed post transfusion are excellent activators of complement through the classical pathway [1]. In addition, bioactive lipids and other subcellular components activate the alternative complement pathway [2]. The end result is an augmented acute phase response that, in the appropriate clinical setting contributing to increased morbidity and mortality. The kinetics of such a response is consistent with studies demonstrating that transfused blood is an independent risk factor for multi-organ failure in trauma patients [3-4].

Despite several studies depicting the contrary effect of transfusion on clinical outcome of trauma patients, management approach remains to entail a copious transfusion approach. Our aim was to assess influence of transfusion, and the number of units transfused on the clinical course of hospital stay and outcome in North Indian population following trauma.

PATIENTS AND METHODS

This is a retrospective study performed in the Department of Blood Bank and Laboratory Medicine of

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Jai Prakash Narayan Apex Trauma Centre, AIIMS for a period of six months (Jan-June 2012). Patient data as retrieved from the patient record system and - blood bank registry. Patients who were issued blood units to be transfused were selected, screened and categorized on the basis of number of PRBC units of blood transfused throughout hospital stay. Based on which the patients were categorized into four groups. First group included 40 patients who received 1 to 5 units of PRBCs, second group included 40 patients who received 6 to 9 units of PRBCs and third group included 20 patients who were massively transfused. Massive transfusion was defined as the transfusion of 10 or more than 10 units of blood to a severely injured patient in less than 24 hours [5]. Fourth was a control group that consisted of 40 patients who underwent trauma but did not receive any blood during their whole hospital stay.

Clinical and blood bank details such as age, gender, injury mechanism, site of injury, BP, shock and mechanical ventilation were recorded at the time of admission into the hospital. Also details such as surgical procedure, length of stay in hospital, ventilator associated pneumonia (VAP) if there was growth of *Pneumonia bacterium* in microbial culture of trachea, infection, splenectomy, organ failure mortality and cause of death were noted.

GCS (Glasgow Coma Scale), ISS (Injury Severity Score) and New Injury Severity Score (NISS) were assessed. Transfusion specifics like, the number of packed cells, platelets and fresh frozen plasma (FFP) units transfused in the first 24 hours of injury and total units transfused during their hospital stay were noted.

The data was expressed in the form of mean ± S.D. Data were compared between transfused and non-transfused patients using Student *t* test. Continuous variables were dichotomized by using clinically relevant cutoffs, and compared using Pearson χ^2 test and contingency table analysis. Non-categorical data was subjected to Bonferroni's test. For inter-group analysis, ANOVA (Analysis of variance) and Bartlett's test was done. A p value of ≤ 0.05 was statistically significant. Data were analyzed using STATA (Stata Corp, TX, and USA) statistical software.

RESULTS

Hundred patients receiving transfusion were included in the study and overall mortality rate was 52% with road traffic accident being the most common cause of trauma. The severity of head injury in transfused patients was [GCS 11.2 ± 4.5], significantly higher than the non-transfused patients with mean ± SD, GCS of 14.4 ± 2.3 ($p< 0.001$). Similarly severity of injury was significantly higher in patients who received transfusion than those who did not ($p< 0.001$). Table **1**

On arrival, 86% of the patients on mechanical ventilation received blood transfusion and 14% did not ($p= 0.006$). 96.6% patients who suffered liver trauma were transfused blood, while only 3.4% did not receive blood transfusion. 96.2% of the patients who were hypotensive on admission, received transfusion; also 57.7% patients had normal blood pressure and still received blood transfusion. Post trauma hypotensive and shock patients were transfused with blood. The admission mean prothrombin time (PT) for transfused patients was significantly higher (19.7 ± 5.7) than non-transfused patients (15.9 ± 1.5).

Patients who received transfusion had high rate of infection (62%) and organ failures (43%) of which 13 had renal failure, 30 had liver failure, and 63 had respiratory failure. None of the patients in the non-transfused group had renal and liver failure, but 36 had respiratory failure.

Of the patients receiving transfusion 15% developed VAP, 62% developed infection, however these incidences were much lower in the non-transfused group, 7.5% and 15% respectively.

Mortality in non-transfused patients was 2.5% and in case of transfused patients was 39%.

Severity of head injury was significantly high in group II (GCS 10.4 ± 4.8), whereas the severity of injury was highest in group III (ISS 17.6 ± 9.1). Transfusion volumes correlated with injury severity score ($p< 0.001$; 0.005). Patients in the massive transfusion group also had significantly elevated prothrombin and activated partial thromboplastin time (aPTT), and decline in hemoglobin levels as compared to the other groups ($p< 0.001$; < 0.001; < 0.001, Table **2**).

Incidence of renal failure was high (20%) in patients who were transfused with 6-9 units and 35% had liver failure. 10% of the patients receiving massive transfusion developed renal failure and 55% developed liver failure Figure **1**.

Table1: Comparison of Clinical and Laboratory Parameters among Transfused and Non-Transfused Group of Trauma Patients

Parameters		Transfused (n=100)	Non Transfused (n=40)	P Value
Age#		31(17-82)	25.5(17-65)	0.3
Gender*	Male	90 (70.9)	37(29.1)	0.7
	Female	10 (76.9)	3 (23.1)	
Severity Of Head Injury*	Minor (GCS 13-14)	55(59.1)	38(40.9)	<0.001
	Moderate (GCS 9-12)	11(100)	0 (0)	
	Severe (GCS ≤ 8)	33(33.3)	2(5.7)	
Severity Of Injury*	Low (ISS<24)	79(67.5)	38(32.5)	0.02
	High (ISS>25)	21(91.3)	2(8.7)	
New Injury Severity Score (NISS)_		15±5.6	11.8±7.2	0.34
Weighted Revised Trauma Score (RTS)		6.8±1.3	7.7±0.3	<0.001
Systolic Blood Pressure (mm/hg)		111.9±25.5	114.8±10.2	0.5
	Normal (BP=120mm//Hg)	49(57.7)	36(42.4)	<0.001
	Hypotension (BP<120mm//Hg)	25(96.2)	1(3.9)	
	Hypertension (BP>120mm//Hg)	20(90.9)	2(9.1)	
Liver Trauma*	Yes	28(96.6)	1(3.4)	<0.001
	No	72(64.9)	39(35.1)	
Length Of Stay (Days)#		14(1-74)	7(1-60)	<0.001
Mechanical Ventilation*	Yes	43(86)	7(14)	0.006
	No	57(63.3)	33(36.7)	
Splenectomy*	Yes	3(100)	0(0)	0.6
	No	97(70.8)	40(29.2)	
Hemoglobin (g/dl)		10.2±2.6	12.2±1.6	<0.001
Hemoglobin*	Anemia ≤9 (g/dl)	33(100)	0(0)	<0.001
	≥9 (g/dl)	62(71.3)	25(28.7)	
Total Leukocyte count*	4000-1100/cumm	32(69.6)	14(30.4)	0.04
	<4000 &>1100/cumm	63(85.1)	11(14.9)	
Platelets*	1-4(lacs/cumm)	62(72.1)	24(27.9)	<0.001
	<1 (lacs/cumm)	33(100)	0(0)	
Prothrombin Time (Sec)		19.7±5.7	15.9±1.5	0.002
	12-16sec	18(54.55)	15(45.45)	<0.001
	>16 sec	71(89.9)	8(10.13)	
Activated partial thromboplastin time (Sec)		32.6±10.9	36.1±4.4	0.007
	28-36sec	27(87.1)	4(12.9)	0.3
	>36 secs	61(77.2)	18(22.8)	
Infection*	Yes	62(91.2)	6 (8.8)	<0.001
	No	38 (52.8)	34 (47.2)	
Renal Failure*	Yes	13(100)	0(0)	0.02
	No	87(68.5)	40(31.5)	
Liver Failure*	Yes	30 (100)	0(0)	<0.001
	No	70(63.6)	40(36.4)	
Respiratory* Failure	Yes	63(63.6)	36(36.4)	0.002
	No	37(90.2)	4(9.76)	

Coagulopathy*	Yes	16 (100)	0(0)	0.006
	No	84 (67.7)	40(32.3)	

Values are expressed as mean ± S.D; or n (%)*; or median (minimum-maximum) #.

Table 2: Comparison of Clinical and Laboratory Parameter amongst Groups Based on the Volume of RBC Transfusion

Parameter	Group 1 (1-5 units)	Group 2 (6-9 units)	Group 3 (>10 units)	Group 4 (No Transfusion)	Statistical Significance	Post hoc Analysis
Age	31.5(20-47.5)	33.5(24-45.5)	28.5(22-38)	25.5(22-38)	F -0.1 P-0.9	-
Length of stay	19.0±15.0	17.1±18.835	22.05±19.82	13.1±15.870	F -1.5 P -0.2	-
Glasgow coma scale	11.7±4.0	10.4±4.8	11.7±4.8	14.5±2.4	F- 7.3 P-< 0.0001	1 vs. 4: p 0.02 2 vs. 4: p <0.0001
ISS	14.5(9.0-16.0)	16.0(9.0-23.5)	1	9.0(4.0-16.0)	F -4.35 P-0.005	2 vs. 4: p 0.01 3 vs. 4: p 0.03
Weighted revised trauma score	7.3±0.9	6.4±1.6	6.8±1.4	7.8±0.3	F 9.11 P < 0.001	2 vs. 4: 0.000 3 vs. 4: 0.023
24hrs red blood cells (units)	2.8±1.1	5.6±2.3	4.8±2.7	—	F -20.1 P < 0.001	1 vs. 2: 0.000 1 vs. 3: 0.001
24hrs fresh frozen plasma (units)	3.5±1.4	5.7±2.9	5.1±4.2	—	F- 4.6 P - 0.01	1 vs. 2: 0.010
24hrs platelet (units)	3.3±0.8	4.6±3.2	7.5±3.0	—	F 4.7 P 0.01	1 vs. 3: 0.029 2 vs. 3: 0.046
Total red blood cell (units)	2.9±1.1	7.3±1.4	17.5±7.6	—	F 163.9 P <0.001	1 vs. 2: 3 0.000 2 vs. 3: 0.000
Total fresh frozen plasma (units)	3.5±1.7	8.6±8.7	24.8±17.7	—	F 24.3 P <0.001	1 vs. 3: 0.000 2 vs. 3: 0.000
Total platelet (units)	3.7±1.3	9.0±11.7	23.1±23.6	—	F 5.3 P 0.008	1 vs. 3: 0.033 2 vs. 3: 0.021
hemoglobin(g/dl)	±±2.4	9.6±2.5	9.3±2.8	12.2±1.6	F 8.7 P <0.001	1 vs. 2: 0.026 1 vs. 3: 0.037 2 vs. 4: 0.000 3 vs. 4: 0.001
total leucocyte count(/cumm)	13800(9300-16800)	11000(7600-14700)	11300(6300-15000)	9900(7500-13200)	F 1.68 P 0.1748	-
platelet count (lacs/cumm)	178(102-262)	146(80-225)	92(45-176)	176(133-228.5)	F 3.67 P 0.0143	1 vs. 3: 0.008
prothrombin time(sec)	17.6±2.9	20.1±4.2	23.2±9.8	15.8±1.6	F 9.1 P <0.001	1 vs. 3: 0.001 3 vs. 4: 0.000
activated partial thromboplastin time(sec)	28.1±4.9	33.3±9.5	39.4±16.8	26.1±4.3	F 8.82 P <0.001	1 vs. 3: 0.000 2 vs. 4: 0.030 3 vs. 4: 0.000

15.7% developed sepsis of which 13.6 % had received 1-5 units, 50% received 6-9 units, and 31.8 % had undergone massive transfusion (p< 0.001) Figure **1.**

45% of the patients who underwent massive transfusion had coagulopathy (p< 0.001).

Highest mortality rate was observed in group II *i.e*. 67.5%, followed by 60% for group III, 32.5% in group I and lowest in group IV 2.5% (p< 0.001) Figure **1.**

DISCUSSION

Red blood cell (RBC) transfusion is the most common life-saving medical intervention. However

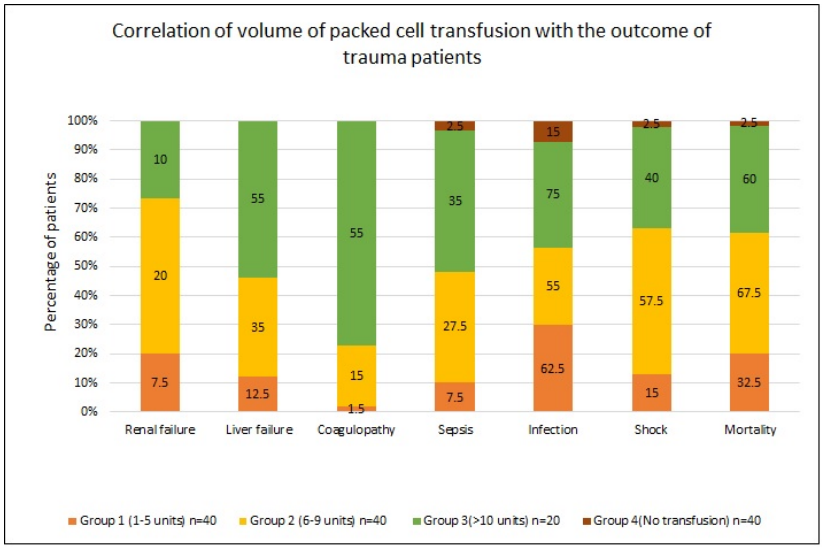

Figure 1: Correlation of volume of packed cell transfusion with the outcomeof trauma patients.

RBC transfusion has come under intense scrutiny over the last few decades [6]. Liberal use of transfusion may result in an increased loss of life. RBC transfusion in the first 24 hours following admission is associated with an increase in mortality. In a recent review of 45 observational studies that had reported the impact of transfusion on outcomes in trauma, RBC transfusion was an independent predictor of death, infectious complications and acute respiratory distress syndrome (ARDS). 91% of the studies on trauma patients showed a deleterious impact of older RBCs on any endpoint [6]. Agarwal *et al*. demonstrated an association between blood transfusion and infection in a trauma patient cohort in the early 1990s [7]. Various studies have identified post-injury transfusion to be a significant predictor of pulmonary morbidity, multi-organ failure, infection, and death [8-10].

Patel *et al*., conducted a metaanalysis to determine the association between RBC transfusion and patient outcome following trauma, 40 observational studies were included and after pooling the results, they report odds of multiorgan failure increasing with each additional unit of blood transfused (OR 1.08, 95%CI 1.02–1.14, P = 0.012, I2 = 95.9%), patients those who received ≤6 units vs. >6 units found very strong evidence of an increased odds of multiorgan failure with >6 units transfused (OR 4.30, 95%CI 2.36– 7.85, P < 0.001, I2 = 65.9%). There was an increased odds of ARDS/ALI with transfusion (OR 2.04, 95%CI 1.47–2.83, P < 0.001, I2 = 0%) [11].

Suppression of innate immune responses by allogeneic blood may contribute to the development of nosocomial infection and aggravate their severity [1]. We report 62% incidence of infection among the transfused patients, significantly higher than the non-transfused (15%). Similarly Taylor *et al*. studied 1,717 intensive care unit (ICU) patients to compare the rates of nosocomial infection between transfused (n= 416) and non-transfused (n= 1,301) patients. Transfused group had a significantly higher rate (six fold increase) of nosocomial infection (15.38% vs. 2.92%, $p< 0.05$). Transfusion cannot be the predominant cause for development of infection in these individuals since the severity of injury and length of ICU stay were more in transfused patients which could have been adding factors. Furthermore, for each unit of blood transfusion risk of infection was increased by a factor of 1.5 ($p< 0.0001$).

Vandromme *et al*., evaluated the temporal relation-ship between transfusion and pneumonia and the influence of blood age on it, overall, no significant association between transfusion and pneumonia was observed, however transfusion of exclusively old blood versus no blood was significantly associated with development of pneumonia, whereas the receipt of exclusively young blood and mixed units were not [12].

Mortality rate was significantly higher in transfused group (24.0% vs. 10.2%, $p< 0.05$) [13]. Beale *et al*. [14] reported that 52% of their study population with major trauma developed systemic inflammatory response syndrome (SIRS) (54 patients), followed by septic complications (31 patients, 30%), any organ failure (27 patients, 26%) and ARDS (9 patients, 9%). However they regarded that these complications were not

directly related to transfusions. Multivariate analysis identified >4 units blood transfusion as an independent risk factor for SIRS.

In studies that focused just on trauma patients, similar results were found. Dunne *et al*. found that blood transfusions within the first 24 h resulted in longer ICU stays, and were independent predictors of mortality [15].

Claridge *et al*. had reported the relationship between transfusion and infections in trauma patients within the first 48 hours of admission. The infection rate was significantly higher (p< 0.0001) in those who had transfusion in comparison to those who had not received transfusion (33.0% versus 7.6%). Multivariate analysis of this study had confirmed that blood transfusion was an independent risk factor for infection in trauma patients [8].

A dose-response relationship between early blood transfusion and the later development of multi organ failure (MOF) was identified by Moore *et al*. and concluded that blood transfusion is an early consistent risk factor for post injury MOF, independent of other indexes of shock [16]. In this study 13 patients developed renal failure and 61.5% (n= 8)were transfused with 6-9 units. Michael *et al*. reported that unmatched PRBCs administered during resuscitation were independent risk factors for (AKI) Acute Kidney Injury (OR, 1.13 per unit; 95% confidence interval [CI], 1.04-1.23; p= 0.004) in trauma patients [17].

Malone *et al*. had analyzed outcomes of transfusion in more than 15,000 trauma patients and concluded that blood transfusion was a strong independent predictor of mortality (odds ratio [OR], 2.83; 95% CI, 1.82-4.40; p< 0.001), ICU admission (OR, 3.27; 95% CI, 2.69-3.99; p< 0.001), ICU LOS (p< 0.001), and hospital LOS (Coef, 4.37; 95% CI, 2.79-5.94; p< 0.001) when stratified by indices of shock. Patients who underwent blood transfusion were almost three times more likely to die and more than three times more likely to be admitted to the ICU [5].

In another retrospective cohort of 820 transfused trauma patients, the total number of RBC units but not older (> 14 days old) units transfused were independently associated with increased mortality [1].

Metaanalysis by Patel *et al*., report an increased odds of mortality in those transfused compared to those not transfused (OR 3.15, 95%CI 1.82–5.46, P < 0.001), also an increase in the odds of mortality with each additional unit transfused (OR 1.07, 95%CI 1.04–1.10, P < 0.001) [11].

Influence of blood transfusion on the immediate outcome of trauma patients are mainly observational studies and should be interpreted with caution. This applies to our study as well. Such studies cannot clearly demarcate whether RBC transfusion is responsible for post trauma complications or whether those who received transfusion were having severe trauma which itself had led to complications. Definitive conclusion can be withdrawn with randomized prospective trials only. Since conducting such trial is extremely difficult and laborious, so most were retrospective randomized studies.

The present study did not take into account the confounding factors such as trigger for transfusion, the age or duration of PRBC storage, PBRC's transfusion timing; which is a limitation to this study. Another limitation was the inclusion of study subjects with shorter length of stay. Few in non-transfused group could be due to death before initiation of transfusion.

The results of our study are coherent with previous studies. We found a 3 folds significantly higher rate of infection in massive transfused patient. Blood transfusion was found to be significantly associated with mortality, infection and organ failure. Moreover, the patients who required massive blood transfusion had a very high admission ISS score, suggesting that allogeneic transfusion is an underlying phenomenon for adverse outcomes in trauma patients, and is a surrogate marker of injury severity.

CONCLUSION

Transfusion in trauma patients was associated with substantially increased odds of an adverse outcome, in particular higher incidence of post trauma infection & mortality. Adoption of a more restrictive transfusion strategy may be safely applied to trauma patients.

Transfusion requirements are directly proportional to the severity of injury, thus it can be said that the significant association of transfusion with adverse outcome seen in our results is actually due to the fact that transfusion is functioning as a surrogate for severity of injury. Patients receiving more blood are likely to be more severely injured. Thus, the observed associations between the transfusion and morbidity or mortality may be more reflective of the confounding effect of severity of injury than RBC transfusion.

Restricted use of blood and blood products is advised, Transfusion should only be regarded as a life-saving intervention.

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