

# Massive transfusion protocol: Need of the hour – A tertiary care centre experience

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## Abstract

**Background and Aims:** Massive transfusion (MT) in critically ill patients during major volume losses can lead to serious adverse outcomes. Studies have reported that rampant red cell infusion for maintaining perfusion support has had detrimental effects on patients' short- and long-term survival rates. Evidence-based studies quote the importance of maintaining blood product ratio during massive hemorrhage and ensuring good outcomes with the least morbidity and mortality.

**Material and Methods:** It is an observational study to compare the ratio of usage of blood products and their role in the outcome of MT cases.

**Results:** A total of 70 patients (29 females and 41 males) who received MT were included in the study. There was no fixed ratio of packed red blood cells (PRBC) to blood components for patients with massive hemorrhage. The average ratio of PRBC: fresh frozen plasma (FFP):platelet concentrate (PC) was 1:0.9:0.6. However, blood component therapy with PRBC: FFP ratio between 1 and 2 was associated with a significant rise in post-acute phase hemoglobin value ( $P$  value = 0.018).

**Conclusion:** Appropriate blood component therapy during the acute bleeding phase in massively transfused patients can further decrease the transfusion demand and transfusion-related complications. There is a need to adhere to the MT protocol for the clinical areas requiring MT in the developing world too.

**Keywords:** Damage control resuscitation, Fresh frozen plasma, Massive transfusion protocol, Packed red blood cells, Platelet Concentrate

## Background

Transfusion in critically ill patients undergoing major volume replacements within short intervals frequently can be life-saving but have often led to serious hazardous outcomes in various trauma care and other specialties requiring massive transfusion (MT).<sup>[1-3]</sup> In the era of damage control resuscitation (DCR), where the role of crystalloid-based management has reduced, the rapid release of predefined blood products in a constrained ratio has played a pivot role to control life-threatening hemorrhage.<sup>[4]</sup> Evidence-based studies quote the importance of blood product ratio (packed red cells: plasma: platelets) in trauma management and in the outcomes of MT

cases.<sup>[5]</sup> Whereas revision of the definition of MT helped us understand the pathophysiology of the condition, the therapeutic application of the protocol development still requires fine-tuning and a stepwise time-constrained approach, categorized case wise and based on associated variables.<sup>[6]</sup> This is important as each case of MT stands unique from the point of view of therapeutic approach owing to various case-specific factors like diagnosis, pre-transfusion hemoglobin, underlying coagulopathy, and dialysis dependency that yields outcome of morbidity and mortality of these patients.<sup>[7,8]</sup> Considering the various factors that interplay, our study aimed to compare the ratios of usage of blood products and their role in the outcome of MT cases.

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## Material and Methods

This was a retrospective observational study conducted over 12 months (October 2016 to September 2017). We obtained approval from the institutional ethics committee (letter no. INT/IEC/2020/SPL-1427, dated 06.11.2020) to publish collected data from the cases requiring and fulfilling the criteria of MT. Cases were registered from the emergency medicine, accident and trauma ward of the institute and were followed up based on clinical and investigational parameters till death or discharge in the institute. MT was considered when a patient underwent a total body blood volume replacement within 24 hours (approximately equals >10-unit packed cell transfusion) or replacement of half the total blood volume in less than 3 hours or transfusion of >4 packed red cell unit(s) in an hour.<sup>[6]</sup> Initially, transfusion was performed depending on the clinical status of the patient. Transfusion was guided by the laboratory parameters on receiving the laboratory parameters. The quantity of products utilized in the time frame noted as short-term (less than 24 hours) and long-term controls (more than 24 hours), diagnosis, age, gender, antibody screening status, dialysis requirement, trends in hemogram parameters, and the onset of Disseminated Intravascular Coagulation (DIC) were taken as composite factors influencing patient outcomes and total length of hospital stay.

Statistical analysis was done using the following parameters:

1. Blood group, diagnosis, component ratio distribution
2. Closeness of a ratio to 1:1:1 and its impact on the outcome
3. Post-acute phase transfusion parameters and the role of chronic hemotherapy (post-day 1) and its impact on the outcome.

## Results

During the study period, a total of 70 cases (29 females and 41 males) received MT in emergency areas and were followed up from the acute phase till the post-acute phase to study outcomes. The distribution of the cases with MT on the basis of diagnosis is shown in Table 1. There were 36 cases of trauma, 21 obstetric, and 13 major surgical cases registered in the study.

### Outcome data

Of the 70 cases who received MT, 6 had DIC (8.5%), of which 2 were having DIC at admission and 4 had DIC after the massive transfusion episode. The case-fatality ratio was 35.7% on follow up and 2 (2.8%) went LAMA (left against medical advice) in the course. As shown in Table 2, the case fatality and mean number of red cell component required

per person were higher in trauma patients as compared to non-trauma patients. Ten patients (14.3%) developed acute kidney injury and required dialysis of which six expired (60%) in the course of complications and one went LAMA. Fifty-eight required (82.8%) prolonged inotrope support and forty-eight (68.5%) required prolonged intubation in the post-acute phase. Of the 70 cases, 3 developed antibodies against red cell antigens and 1 developed febrile non-hemolytic transfusion reaction. Further immunohematological workup of patients with red cell antibodies showed anti-c in a patient with ruptured aortic aneurysm. The other two patients were obstetric patients who developed anti-E and anti-D antibodies. Anti-c and anti-E antibodies developed during the patient's hospital stay and made it difficult for arranging the antigen-negative crossmatched blood for subsequent transfusion. The other obstetric patient with anti-D tested positive for anti-D on the first day of admission, and hence, may be due to pregnancy-related alloimmunization and not related to the red cell transfusion during the hospital stay. Fifteen deaths occurred due to cardiac arrest, five due to renal failure, and one death each due to cerebral ischemia, sepsis, ARDS, DIC, and respiratory failure.

The ratio of PRBC to FFP transfusion and FFP to PC transfusion in the patients in the acute phase and their outcomes were compared.

Among 70 patients, 44 had pre- and post-acute phase set of hemoglobin values and 30 had prothrombin index (PTI) set of values which were compared as shown in Table 3 and 4 respectively. On doing paired sample *t*-test on the pre- and post-acute phase parameters, it was found that in the group with PRBC: FFP ratio 1:2, the change in the hemoglobin level in patients in the post-acute phase was significantly better and there was a rise in the post-acute phase (*P* value = 0.018). This shows that in bleeding patients, replacement of clotting factors to stop bleeding is as important as red cell and

**Table 1: Distribution of cases based on their diagnosis**

	Number of cases (%)
Blunt trauma abdomen	21 (30%)
Post-partum hemorrhage	27.1 (25.7%)
Ruptured aorta	9 (12.8%)
Vascular injury	6 (8.5%)
Coronary artery bypass surgery	4 (5.7%)
Upper GI bleed	4 (5.7%)
Antepartum hemorrhage	2 (2.8%)
Carotid blowout	2 (2.8%)
Liver transplant	1 (1.4%)
Extradural hemorrhage	1 (1.4%)
Renal cell carcinoma	1 (1.4%)
Total	70

hemoglobin restoration. In the group where PRBC was used to FFP at a ratio  $<1$  or  $>2$ , no clinically significant rise in the post-acute phase Hb was found in the group alarming that underlying coagulopathy might super add to the post-acute phase blood loss ( $P$  values 0.09 and 0.913). No significant change in PTI was found in the post-acute phase for patients receiving FFP: PC at 0.5 $<$ , 0.5–1.5,  $>1.5$  ratios ( $P$  values 0.103, 0.160, respectively).

## Discussion

MT is frequently encountered in tertiary care setups as a life-saving modality in trauma and operative cases. However, previous studies have deeply probed into the need of a protocol development in such cases and rampant reply to the clinicians' request for blood products is not the answer. Excessive usage of PRBC has shown to have detrimental effects on the long-term outcomes in bleeding and trauma patients.<sup>[3,5,8]</sup> As known by the name "Trauma Triad of Death"—hypothermia, acidosis, coagulopathy,<sup>[9]</sup> the pivotal causes of death in trauma and bleeding patients, failure of correction of any of the above factors may hamper the hemostasis and alter outcomes in the post-acute phase. The Trauma Associated Severe Hemorrhage Score and McLaughlin scores can predict outcomes in such situations.<sup>[4]</sup> Indeed studies have shown that the correction of coagulopathy<sup>[9]</sup> is as important as the volume and red cell mass replacement in acutely bleeding patients and overcorrection of the hemoglobin does not lead to a significant change in morbidity or mortality in these patients.<sup>[10]</sup> Although the ratio of PC: FFP did not have any positive effect on the laboratory parameters in the post-acute phase, maybe a larger sample size might yield a significant result. Major causes included trauma, obstetric conditions<sup>[11]</sup> like Antepartum and postpartum haemorrhage (APH and

PPH), ruptured major vessels like aorta, or abdominal arteries, or major operative requirements. In most cases, cardiac arrest, or acute renal failure<sup>[7]</sup> have been the major implicating causes of mortality. In view of the varied spectrum in the outcomes of the cases in a tertiary setup, where availability of blood products is possible, it seems logical to envisage a protocol of ratio of blood component issue in response to a triggering event of MT requirement.<sup>[11,12]</sup> A release of PRBC and FFP in equivocal ratios along with a liberal transfusion of platelet concentrates might be the answer to defend coagulopathy, third-space sequestration, and colloid deficits besides maintenance of hemoglobin and perfusion requirements.<sup>[13]</sup>

A recent systematic review and meta-analyses comprising two randomized-controlled trials and 53 observational studies were performed. The randomized trials showed no difference in the outcome of the patients who received a higher ratio of FFP to PRBC when compared to the patients who were managed with standard care. However, the observational studies showed conflicting results with improvement in coagulopathy and survival benefits in patients who were transfused with a fixed ratio of FFP to PRBC.<sup>[14]</sup> In our observational study also, the rise in hemoglobin was higher in the group which received FFP to PRBC in the ratio between 1 and 2. Patients with less FFP transfusion (FFP: PRBC  $<1$ ) probably had a fall due to deranged hemostasis. This is supported by a randomized control trial conducted in North America which showed the advantage of giving FFP and PRBC in the ratio of 2:1 in maintaining the homeostasis and fewer deaths due to exsanguination during the acute phase (within 24 hours) but failed to demonstrate any difference in mortality at 24 hours and 30 days.<sup>[15]</sup> In our study, the non-significant rise in hemoglobin in the patients who were transfused with higher ratio ( $>2$ ) of FFP to PRBC is probably due to the under transfusion of PRBC and hemodilution due to excess plasma transfusion. In another multicentric, observational cohort study, the early initiation of balanced transfusion regime in trauma patients was associated with a decreased 24-hour mortality.<sup>[16]</sup> Hence, there is a need for further studies to determine the most appropriate and balanced ratio of blood components for improving the outcome of the patient requiring MT.

**Table 2: Distribution of cases with case fatality rates and red cell requirements**

Type of case	Number	Deaths	Mean number of PRBC (s) required per patient
Trauma cases	36	16 (44.4%)	12.2
Non-trauma cases			
Obstetric cases	21	3 (14.2%)	9.0
Major surgical cases	13	6 (46.1%)	10.6

**Table 3: The table shows the ratio of PRBC: FFP and its effect on the post-acute phase hemoglobin rise**

Ratio of PRBC: FFP	Mean of acute phase hemoglobin	Mean of post-acute phase hemoglobin	Total number of cases	$P$ (rise in Hb in the post-acute phase compared to the pre-acute phase)
Used in the acute phase				
$<1$	6.279	7.264	14	0.090
1-2	7.050	8.088	26	0.018
$>2$	6.725	7.000	4	0.913

**Table 4: The table shows the ratio of PRBC: PC and its effect on the post-acute phase prothrombin index (PTI) rise**

Ratio of FFP: PC	Total number of cases	P (rise in PTI) in the post-acute phase compared to the pre-acute phase
Used in the acute phase		
0.5-1.5	9	0.103
0.5 < and > 1.5	21	0.160

Our study has certain limitations. First, the study conducted was retrospective, observational, and included a small sample size with a short follow-up period. All the patients who developed massive hemorrhage during the study period could not be included, and hence, parameters like maternal mortality due to hemorrhage could not be calculated. Second, other parameters like volume of resuscitation fluids, use of any anti-fibrinolytics, hypocalcemia, acidosis, urine output, INR (international normalized ratio), D-dimers, fibrin-degradation products (FDPs), and hypothermia which can affect the prognosis in the patient with massive bleed could not be reported due to retrospective data. The prothrombin index was the most common reported laboratory parameter used to assess coagulation profile in the majority of the patients although INR is preferred over PTI nowadays. The study was intended to observe the patient blood management practices, and hence, any intervention was out of the scope of this study. Our observation can be utilized to draft an interventional study with a wider range of parameters and a large sample size may yield newer horizons in the management of MT cases in our developing world.

In terms of outcome, adequate coordination between transfusion and clinical services is important in trauma setups as the initial loop of fluid management and its time of delivery is always a deciding factor to cut-off additional transfusion requirements in the post-acute phase.<sup>[6]</sup> A stepwise protocol for MT management can actually be helpful to train the clinical and laboratory staff to bring uniformity in the process towards an improvement step for trauma care. From the inventory management point of view, maintenance of a stock of AB group plasma and O-negative packed red cells easily accessible to the trauma patients in the form of fixed ratio packages might be a crucial time-saving factor. However, the decision to provide crossmatched or typed and screened unit is always debatable and case-specific and requires coordinated judgment of the clinician and the transfusion specialist. In our study, two patients developed antibodies anti-c and anti-E during their hospital stay. Hence, we recommend that if a patient has received uncrossmatched massive blood during the initial resuscitation phase, then the antibody screen should be performed in all the patients for subsequent transfusion. These red cell antibodies have the potential to cause hemolysis if the antigen-matched blood is not given.

Unlike the Trauma Associated Severe Hemorrhage (TASH) and McLaughlin scores which were used previously to predict the outcomes of patients with massive hemorrhage requiring transfusion, the triggering need for MT can be decided using the assessment of blood consumption score (ABC score) on clinical basis and other point-of-care tests.<sup>[6]</sup> Once the protocols are debated and institutionalized, the process improvement steps can help in further fine-tuning of the trauma blood management system.

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### Conflicts of interest

There are no conflicts of interest.

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