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Changes in Massive Transfusion Over Time: An Early Shift In The Right Direction?

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Abstract

Objective—Increasing evidence suggests that high fresh frozen plasma:packed red blood cell (FFP:PRBC) and platelet:packed red blood cell (PLT:PRBC) transfusion ratios may prevent or reduce the morbidity associated with early coagulopathy which complicates massive transfusion (MT). We sought to characterize changes in resuscitation which have occurred over time in a cohort severely injured patients requiring MT.

Methods—Data were obtained from a multicenter prospective cohort study evaluating outcomes in blunt injured adults with hemorrhagic shock. MT was defined as requiring ≥ 10 u PRBCs within 24hrs post-injury. Mean PRBC, FFP and PLT requirements (per unit, 6hr, 12hrs and 24hrs) were determined over time (2004–2009). SUB-MT, those patients just below the threshold for MT, were defined as requiring ≥ 7 and < 10 u PRBC's in the initial 24hrs. The % of resuscitation given at 6hrs relative to 24hrs total (6/24%) was determined and compared across EARLY (admission until 12/07) and RECENT (after 12/07) periods for each component.

Results—Over the study time period (2004–09) for the MT group (n=526), initial base deficit and presenting INR were unchanged, while ISS was significantly higher. The % of patients who required MT overall significantly decreased over time. No significant differences were found over

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time for 6hr, 12hr or 24hr FFP:PRBC and PLT:PRBC transfusion ratios in MT patients. SUB-MT patients (n=344) had significantly higher 6hr FFP:PRBC ratios and significantly higher 6hr, 12hr and 24hr PLT:PRBC ratios in the RECENT time period. The 6HR/24HR% total for FFP and PLT transfusion was significantly greater in the RECENT time period. (FFP 54% vs. 70%, $p=0.004$, PLT 46% vs. 61%, $p=0.048$)

Conclusion—In a severely injured cohort requiring MT, FFP:PRBC and PLT:PRBC ratios have not changed over time, while the rate of MT overall has significantly decreased. During the RECENT time period (after 12/7) significantly higher transfusion ratios and a greater % of 6hr/24hr FFP and PLT were found in the SUB-MT group, those patients just below the PRBC transfusion 1 threshold definition of MT. This data suggests early, more aggressive attainment of high transfusions ratios may reduce the requirement for MT, may shift overall blood requirements below those which currently define MT. Further prospective evidence is required to verify these findings.

Introduction

Despite the significant advances in trauma care delivery and post-injury management practices which have occurred over the last decade, uncontrolled hemorrhage remains one of the leading causes of trauma related deaths.^{1–4} A significant amount of recent attention has focused on the prevention and treatment of the early coagulopathy which complicates severe injury and massive transfusion (MT).^{5–8} Since 2007, both military and civilian evidence has suggested that ratio-based transfusion strategies targeting high fresh frozen plasma : packed red blood cell (FFP:PRBC) and platelet : packed red blood cell (PLT:PRBC) transfusion ratios reduces the morbidity and mortality associated with unbridled hemorrhage and MT post injury.^{9–16} These same studies revealed a lower overall blood transfusion requirement and shorter time intervals to receiving individual component transfusion, when MT resuscitation protocols were employed.^{10,13,17,18} Despite this increasing evidence, the effect that this evolving knowledge has had on clinical practice for these difficult patients remains unknown. The changes in MT resuscitation practice which have occurred over time, up until this point, have not been adequately characterized.

The main objective of the current analysis was to demonstrate how this recent evidence has impacted MT practice and to determine if changes have occurred over time regarding the attainment of high component transfusion ratios and the timing of such transfusion events, in a cohort of severely injured MT patients. We hypothesized that significant changes in MT resuscitation practice have occurred over time and that earlier, more aggressive attainment of high FFP:PRBC and PLT:PRBC transfusion ratios have occurred in more recent time periods corresponding to the expanding literature on MT resuscitation.

Methods

Data were derived from the ongoing multi-center prospective cohort study known as the *Inflammation and the Host Response to Injury Large Scale Collaborative Program*, (www.gluegrant.org) supported by the National Institute of General Medical Sciences (NIGMS), which is designed to characterize the genomic and proteomic response in injured patients at risk for multiple organ failure following traumatic injury and hemorrhagic shock.¹⁹ Standard operating procedures were developed and implemented across all institutional centers to minimize variation in post-injury care, including: early goal directed resuscitation, strict glycemic control, venous thrombo-embolism prophylaxis, appropriate low tidal volume ventilation, ventilator associated pneumonia management, and restrictive transfusion guidelines.^{19–24} Patients admitted to one of seven institutions, over a 6 year period (12/03–12/09), were included in the analysis. Inclusion criteria for the overall cohort

study included: blunt mechanism of injury, presence of pre-hospital or emergency department systolic hypotension (< 90 mmHg) or an elevated base deficit (≥ 6 meq/L), blood transfusion requirement within the first 12hrs, and any body region exclusive of the brain with an abbreviated injury score (AIS) ≥ 2 , allowing exclusion of patients with isolated traumatic brain injury. Patients < 16 or > 90 years of age and those with cervical spinal cord injury were also excluded from enrolment. Clinical data were entered and stored in TrialDb, a web-based data collection platform, by trained research nurses.²⁵ Integrity of the data was maintained through ongoing curation and external data review by an independent chart abstractor.

For the current secondary data analysis, transfusion practices for patients who required MT, defined as ≥ 10 units of packed red blood cells in the initial 24hrs post injury, were characterized over time for the primary analysis. SUB-MT patients, defined as patients requiring ≥ 7 and < 10 units PRBCs in the initial 24hrs post injury, were those patients who required PRBC transfusions just below the MT threshold and were similarly analyzed. With increased attention being paid to addressing the early coagulopathy which complicates severe injury and hemorrhagic shock, significant changes in resuscitative and transfusion practice following MT have potentially occurred over time. Because of these more recent changes, the study population was also divided into subgroups based upon time of enrollment into EARLY (admission until 12/07) and RECENT (admission after 12/07) cohorts to characterize any practice changes. Transfusion requirements for FFP, PLTs, and PRBCs (per unit) in the initial 24hrs were determined for each MT and SUB-MT patient. As transfusion volumes were recorded in milliliters for all components in the main data set, average blood bank transfusion volumes were used to determine per-unit quantities (PRBC= 300ml, FFP = 250ml, PLT = 300ml). The average volume of a '6-pack of platelets' was considered a single transfusion unit for all PLT comparisons. From these values, FFP:PRBC and PLT:PRBC ratios were determined for each MT and SUB-MT patient. To further characterize the timing of transfusion practice change in the first 24 hours post injury, the proportion of each individual component transfusion which was given in the first 6 hours relative to the total given in 24 hours was similarly determined (6HR/24HR%).

To first characterize changes over time, the requirement for MT was analyzed for the entire study cohort by comparing the annual incidence of MT (%MT) from 2004 to 2009 utilizing an independent samples Kruskal-Wallis test. To assess for differences in demographics and injury characteristics, MT patients were then compared across RECENT and EARLY time periods in a univariate fashion. FFP:PRBC and PLT:PRBC transfusion ratios at 6 hours, 12 hours, and 24 hours post injury were then compared annually over the same time period (2004–2009) for all MT patients. To verify these findings relative to potential changes in transfusion practice, FFP:PRBC and PLT:PRBC transfusion ratios at 6hr, 12hr and 24hrs and 6HR/24HR% were also compared across RECENT and EARLY time periods for MT patients. Finally, comparison of transfusion ratios and 6HR/24HR% for SUB-MT patients was then similarly performed across RECENT and EARLY time periods.

All data were summarized as mean $\pm$ SD, median [IQR, inter-quartile range], or percentage (%). Student-t or Mann-Whitney statistical tests were used to compare continuous variables, while Chi-Square or Fischer's Exact test were used for categorical variables. Independent samples Kruskal-Wallis test was utilized for all comparisons over time. The Institutional Review Board of each participating center approved the cohort study, while the Institutional Review Board at the University of Pittsburgh Medical Center approved this current secondary data analysis.

Results

Of the 1,961 blunt injured patients enrolled during the study period, 526 patients required ≥ 10 PRBCs in the first 24hrs post-injury and constituted the primary study population. When the rate of MT (MT%) for the entire injured cohort ($n=1,961$) was analyzed over time (2004–2009), there was a significant decrease in the requirement for MT despite a significant increase in ISS for the entire study population (Figure 1.). A concurrent significant decrease in the median 24 hour blood transfusion requirement for the entire cohort was also found over time.

Median PRBC, FFP, and PLT transfusion for the MT study cohort ($n=526$) over the initial 24 hours was 15.8 [12,24] units, 8.5 [4,13] units and 1.6 [0.6,3] units, respectively. The overall in-hospital mortality for the MT population was 21.7%. This cohort of massively transfused patients had a median age of 41 [26,55] years and, as expected, were significantly injured with a median ISS of 34 [25,45]. Overtime, for the MT population, initial base deficit, presenting international normalized ratio (INR) remained constant, however, ISS also significantly increased for the MT group over the same time period (2004–2009, $p=0.023$).

Those MT patients enrolled in the RECENT time period (admission after 12/07, $n=125$) as compared to those enrolled in the EARLY period (prior to 12/07, $n=401$) were similar across patient demographics, injury characteristic, shock parameters and 24 hour PRBC transfusion. (Table 1) Importantly, there were no differences in early central venous pressure (CVP) measurements, presenting coagulation status (INR), lowest body temperature in the first 24 hours, or the requirement of early vasopressors across the two time periods. Patients in the RECENT time period did have a significantly higher ISS but a lower overall mortality rate.

Despite the increasing evidence documenting improved outcomes using ratio based transfusion endpoints for MT patients and a decreased incidence of MT in this study cohort, 6 hour, 12 hour and 24 hour FFP:PRBC and PLT:PRBC transfusion ratios were unchanged over the 2004–2009 time period (Figure 2. and Figure 3.). These findings were consistent when stratified by different centers which participated in the study. When the same transfusion ratios were compared across EARLY and RECENT time periods, again no significant differences were found. When the proportion of blood product (FFP, PLT and PRBC) that was given in the initial 6 hours post injury relative to the 24 hour total (6HR/24HR%) was similarly compared, again, no significant differences were found for the MT group. (data not shown)

As expected, those patient who required just under the MT threshold, SUB-MT patients (≥ 7 and < 10 units PRBC in 24 hours), were also relatively common ($n=344$) and had a similarly high injury severity (median ISS of 34 [24, 41]). However, SUB-MT patients demonstrated less severe shock parameters, presenting coagulopathy, an improved temperature profile and an associated lower overall mortality relative to the MT cohort. (Table 2.) Interestingly, when the SUB-MT cohort was analyzed, those in the RECENT time period did have a significantly higher FFP:PRBC transfusion ratio at 6 hours post injury. (Figure 4.) SUB-MT patients in the RECENT time period also had significantly greater PLT:PRBC ratios for all 6, 12, and 24 hour time points. (Figure 5.) To determine if more aggressive attainment of high transfusion ratios was occurring earlier during resuscitation, 6HR/24HR% was again compared across RECENT and EARLY time periods for the SUB-MT group. A significantly higher percentage of FFP and PLTs were given in the first 6 hours post injury relative to the 24 hours total (FFP 54% vs. 70%, $p=0.004$, PLT 46% vs. 61%, $p=0.048$, Figure 6.), while no significant difference in the 6HR/24HR% for PRBCs

($p=0.089$) was found. These findings were consistent across all enrolling centers. Finally, when the percentage of patients who required SUB-MT for the entire cohort were analyzed overtime, no significant changes were found ($p=0.454$), with a relative constant percentage rate across the 2004–2009 period. The proportion of patients requiring SUB-MT remained stable despite a significant decrease in the MT% and the overall 24 hour median blood requirement for the entire cohort as shown in Figure 1.

Discussion

The effects of coagulopathy, hypothermia and acidosis, touted as the “lethal triad,” have long been known as important markers for mortality after traumatic hemorrhage.^{1,26–28} Increasing resources and attention has focused on the best methods to reverse or slow the development of coagulopathy and improve patient outcomes in those requiring MT.^{6,29–31} The presence of coagulopathy has been shown to not only be an important marker of mortality, but also presents early after injury and has been documented to be present at the time of arrival to the trauma center.^{30,32–34} Advancements in the area of damage control resuscitation and implementation of MT protocols in the early resuscitative period of the exsanguinating trauma patient have been shown to improve outcomes in these severely injured patients.^{11,13,17,18} These protocols employ earlier and more aggressive blood component transfusion by targeting high FFP:PRBC and PLT:PRBC transfusion ratios.^{9,10,16} Despite this expanding knowledge base, little is known regarding the incorporation of this growing evidence into clinical practice.

Characterization of any changes in practice that occur over time is important as it provides a benchmark for further improvement and is essential for planning future higher level clinical investigations that may be necessary. It is well known that there exists a ‘time gap’ between important clinical research findings and translation into common clinical practice.^{35–37} The results of the current analysis revealed that FFP:PRBC and PLT:PRBC transfusion ratios throughout the initial 24 hours (at 6, 12, and 24 hours post injury) have not significantly changed over time for those patients who required MT. Despite this transfusion ratio consistency, the requirement for MT (MT%) was found to have significantly decreased over time. The most intriguing results, however, revealed significantly higher FFP:PRBC and PLT:PRBC ratios and a greater percentage of component transfusion (FFP, PLT) being given in the first 6 hours for SUB-MT patients in the RECENT time period. SUB-MT patients (≥ 7 and < 10 units PRBCs) are those patients who were just below the transfusion threshold at 24 hours which currently defines MT.

These results suggest that earlier, more aggressive attainment of high transfusions ratios and earlier component transfusion may reduce the requirement for MT and may shift overall blood transfusion requirements below those which currently define MT (≥ 10 units PRBCs in 24 hours).

Assuming a relative consistency in the characteristics of the study cohort over time, when the incidence of MT significantly decreases over time, a corresponding increase of another subgroup of patients needs to occur. The primary mechanism for any transition due to the current MT cut-point (≥ 10 units PRBCs in 24hr) would be a shift toward lower blood transfusion quantities. Supporting this transitional explanation are the multiple studies which found that MT protocols which focus on earlier, more aggressive component transfusion are associated with decreased blood utilization, overall.^{10,13,17,18} When the SUB-MT group was characterized over time the percentage of patients remained stable despite the MT% decreasing and the overall median 24 hour blood transfusion requirement for the entire cohort decreasing. The results of the current analysis suggests that a transition or shift may

have occurred toward lower transfusion requirements, which corresponds to the time period of expanding literature on damage control resuscitation.

Another reasonable explanation for the relative stability of the transfusion ratios for those who required MT would be the well documented 'time gap' between noteworthy clinical research findings and the translation of such evidence into common clinical practice. However, this reasoning would equally pertain to the SUB-MT group where significant changes in the transfusion ratios in more recent time periods were indeed found. As equally plausible, it may be that transfusion ratios are not solely responsible for the improved outcomes and reduced blood transfusion requirements, but rather something inherent to implementation of MT protocols may be responsible, as demonstrated in prior literature.¹⁷

It may be that there exists a subgroup of patients who would of otherwise required MT as it is currently defined, but secondary to earlier and more aggressive component transfusion, require less blood transfusion overall and no longer meets the definition for MT. The remaining subgroup of patients who do meet the MT definition would be seemingly maximized relative to their transfusion ratios, as suggested by the current analysis. This is supported by the analysis as the mean FFP:PRBC ratio (0.46 ± 0.4) for all 526 MT patients represents a 1:2 FFP:PRBC ratio. On average 1 unit of FFP was given for every 2 units of PRBCs. This is comparably high relative to prior studies. Similar elevated mean ratios for PLTs in the MT cohort were found, as compared to prior literature¹⁵ (0.07 ± 0.1), suggesting relatively small room for significant improvement.

Our study does have several potential limitations. First, this analysis is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response following severe injury and hemorrhagic shock. As with any secondary analysis, data were not recorded to answer our specific hypothesis stated for this study. Potential unknown or unmeasured confounding variables may be responsible for the associations described and the conclusions formulated. No specific massive transfusion resuscitation guidelines were utilized throughout the time periods of the analysis. The cut point utilized for the RECENT and EARLY time periods was selected based up the timing of the majority of literature which focused on transfusion ratios. Prior research from earlier time periods also focused on the difficult problem of early coagulopathy which complicates severe injury.^{28–30,32} The results of this analysis may be altered by utilization of different time period cut points. There was a significant decrease in mortality over time for the entire enrolled cohort, particularly obvious for the RECENT and EARLY group comparison. Multiple changes in practice occurred over this time period and are not limited to changes in MT resuscitation. The over arching goal of this secondary analysis was to document changes in MT practice. Attributing any patient outcome improvements solely secondary to these changes in the MT or SUB-MT group is not the intent of, or within the feasible scope of this analysis.

In summary, this analysis suggests changes have occurred over time in patients requiring MT, with a significantly decreased incidence of MT over time and significantly higher transfusion ratios and 6 hour component transfusion in patients just below the threshold definition for MT.

These more recent time period changes correspond to the expanding literature on hemostatic resuscitation. Collectively, these data suggest earlier, more aggressive attainment of high transfusions ratios and component transfusion may reduce the requirement for MT and may shift overall blood requirements below those which currently define MT. Future studies documenting changes in MT practice will be needed to verify these findings and to continue monitoring and progress with the ultimate goal of improving outcome for these severely injured patients.

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Figure 1.

Incidence of MT, median 24 hour PRBC requirement, and ISS for the entire enrolled cohort over time (2004–2009). $*=p<0.05$, MT=massive transfusion, ISS=injury severity score, PRBC=packed red blood cells

MT FFP:PRBC Transfusion Ratios

Figure 2.
Mean FFP:PRBC transfusion ratios over time (2004–2009). NS=not significant (6hour $p=0.446$, 12hour $p=0.411$, 24hour $p=0.412$.)

Figure 3.
Mean PLT:PRBC transfusion ratios over time (2004–2009). NS=not significant (6hour $p=0.290$, 12hour $p=0.083$, 24hour $p=0.177$)

SUB-MT FFP:PRBC Transfusion Ratios

Figure 4. Comparison of mean 6hr, 12hr, and 24hr FFP:PRBC ratios for SUB-MT patients across EARLY and RECENT time periods. *= $p < 0.05$

SUB-MT PLT:PRBC Transfusion Ratios

Figure 5. Comparison of mean 6hr, 12hr, and 24hr PLT:PRBC ratios for SUB-MT patients across EARLY and RECENT time periods. * = $p < 0.05$

Figure 6. Comparison of the percentage of FFP and PLT transfusion in the first 6 hours relative to the total at 24 hours post injury across Early and RECENT time periods. *= $p < 0.05$

Table 1

Baseline demographics and injury and early resuscitation characteristics for patients from RECENT and EARLY time periods.

	RECENT (n=125)	EARLY (n=401)	p-value
Age (years)	44.5±19	42.0±18	0.186
Gender (%male)	76.0%	68.3%	0.102
ED GCS	7.9±5	7.8±5	0.859
ISS	38 [27,45]	34 [24,43]	0.037*
APACHE II score	32.3±7	32.4±6	0.946
Initial Base Deficit (meq/L)	10.1±5	10.3±6	0.772
24 Hour Lowest pH	7.16±0.1	7.15±0.1	0.234
6 Hour Lowest Central Venous Pressure (CVP)	10.4±6	11.3±6	0.402
Presenting ED INR	1.74±1	1.68±1	0.652
24hr Lowest Temperature (deg C°)	34.5±1	34.4±2	0.358
24 Hour Vasopressor Requirement	36.8%	33.9%	0.554
24 Hour PRBC Transfusion (unit)	15.8 [12,24]	16.0 [12,25]	0.763
Early (24hr) Operative Intervention (exlap/thoracotomy/sternotomy)	71.2%	65.1%	0.206
Length of Stay	32.2±34	29.3±29	0.354
ICU days	17.2±15	17.4±15	0.900
Ventilator Days	12.2±11	13.8±13	0.209
Mortality	14.4%	23.9%	0.024*

ISS=injury severity score, ED=emergency department, GCS = Glasgow coma scale, INR=International Normalized Ratio, PRBC=packed red blood cell ICU = intensive care unit

Table 2

Comparison of SUB-MT and MT groups across injury and shock severity and presenting coagulation parameters.

	Sub-MT (n=344)	MT (n=526)	p- value
ISS	34 [24,41]	34 [25,45]	0.067
APACHE II score	29.0±6	32.4±6	<0.001*
Initial Base Deficit (meq/L)	8.1±4	10.2±5	<0.001*
Presenting ED INR	1.40±1	1.69±1	<0.001*
24hr Lowest Temperature (deg C°)	34.8±1	34.4±2	<0.001*
Mortality	10.1%	21.7%	<0.001*