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LIQUID PLASMA USE DURING “SUPER” MASSIVE TRANSFUSION PROTOCOL

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CJA is directly responsible for all aspects of this study. He participated in the collection, analysis and interpretation of data; drafting and revision of the manuscript, figures and tables. JPM, MMH, JM and JJR participated in the revision of the manuscript, figures and tables. NN and RD were medically responsible for the patients and participated in the review and revision of the manuscript, figures, and tables. KGP had overall responsibility for the study; including conception and experimental design; analysis and interpretation of data; drafting and revision of the manuscript, figures and tables; statistical expertise and evaluation; obtaining funding for this project; supervision.

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ABSTRACT

Background: A massive transfusion protocol (MTP) presents a logistical challenge for most blood banks and trauma centers. We compare the ratio of packed red blood cells (PRBC):plasma transfused over serial time points in those requiring MTP (10-30 units PRBC/24hrs) to those requiring “super” MTP (S-MTP; >30 units PRBC/24hrs), and test the hypothesis that changes in allocation of blood products with use of readily transfusable liquid plasma (LP) improves the ratio of PRBC:plasma during S-MTP.

Materials and Methods: All transfused trauma patients (n=1,305) from 1/09 to 3/15 were reviewed. PRBC:plasma was compared for MTP (n=277) and S-MTP (n=61) patients, before and after the availability of LP at our institution. Data are reported as mean±standard deviation or median(interquartile range).

Results: Age was 41±19y, 52% blunt mechanism, injury severity score 32±16, and 46.3% mortality. In 24 hr, requirements were 17(14)units PRBC, 10(11)units plasma, with a PRBC:plasma of 1.6(0.8). Within the first hour, PRBC:plasma for S-MTP vs MTP was 2.1:1 vs 1.7:1 (p=0.017). With LP, S-MTP patients received significantly lower PRBC:plasma at the first hour (p<0.001). Before institutional changes, PRBC:plasma positively correlated with PRBC transfused at hour 1 (r=0.410, R²=0.168, p<0.001); after institutional changes and the advent of LP there was no correlation (r=0.177, R²=0.031, p=0.219).

Conclusion: Within the first hour of transfusion, units of PRBC transfused positively correlated with PRBC:plasma ratios, and patients receiving S-MTP had higher PRBC:plasma ratios than those receiving MTP. Changes in our institution’s MTP protocol to include LP improved the early ratio of PRBC:plasma transfused in patients requiring S-MTP.

Level III Evidence

INTRODUCTION

Hemorrhagic shock remains the leading cause of death in trauma patients aged 1 to 44 years old [1, 2]. A massive transfusion protocol (MTP) is activated in many level 1 trauma centers when a patient presents with uncontrolled, life-threatening bleeding [3]. During MTP, the goal is to transfuse packed red blood cells (PRBC), plasma, and platelets in a similar ratio to that of whole blood; this minimizes dilutional coagulopathy and hypovolemia, and improves hemostatic resuscitation and subsequent outcomes [4-9]. Most recently, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial showed evidence of benefit of an early 1:1:1 transfusion [10]. Along with recent recommendations by the US Food and Drug Administration (FDA) including a 3-hour end point for studies focusing on traumatic hemorrhage [11], it is clear the goal therapy for hemostatic resuscitation is an immediate and balanced blood component delivery. The American College of Surgeons Trauma Quality Improvement Project issued guidelines for trauma resuscitation in November 2013, recommending that “Universal donor products should be immediately available on patient arrival to support ratio-based transfusion,” and “If MTP triggers are met, transfuse universal plasma and RBC in a ratio between 1:1 and 1:2” [12]. These new guidelines represent a major shift in the paradigm of trauma resuscitation and blood product provision, and are likely to become accreditation requirements in the near future.

Proper implementation of an MTP depends on a 24/7/365 state of readiness in the blood bank for rapid delivery of components to the bedside. Practically, it may be difficult to continuously maintain a desired ratio of transfused components at least during active bleeding and ongoing resuscitation [13]. It is not unusual at urban trauma centers for an occasional patient to require

“super” massive transfusion protocol (S-MTP; >30 units PRBC in 24 hr), which poses an extraordinary logistical challenge for most blood banks and trauma centers. The term “super” MTP is not a generally recognized classification, but it has been used in few reports [14, 15], to represent that fraction of the population that requires an exorbitant amount of blood products. Our institution has recently changed its blood product delivery method during MTP activations to make more plasma capable of immediate transfusion (thawed fresh frozen plasma [FFP] or liquid [never thawed] plasma [LP]) in higher quantities; see [Table 1](#).

The purpose of this study was to compare the ratio of PRBC:plasma transfused over serial time points immediately following transfusion initiation in those requiring MTP vs S-MTP. We test the hypothesis that changes in the availability of readily transfusable plasma, made possible with LP, improves the ratio of PRBC:plasma transfused in patients requiring S-MTP.

MATERIALS AND METHODS

With the approval of the Institutional Review Board of the University of Miami Miller School of Medicine (Miami, FL) and Jackson Memorial Hospital, and waiver of informed consent, we reviewed all patients requiring blood component transfusions within six hours of arrival to the Ryder Trauma Center from 1/1/09 to 3/4/15.

Demographics, injury patterns, procedures, total fluid and transfusion requirements, and outcomes were analyzed in those who received >10 units PRBCS or plasma over 24 hr. Each component was recorded at serial time increments during MTP (10-30 units PRBC and S-MTP (>30 units PRBC). The institutional MTP policy and procedure changes on July 1, 2014 are

detailed in [Table 1](#).

To match cohorts of each era, propensity scores were assigned for each patient based on a logistic regression model using patient and injury characteristics (i.e., age, injury severity score [ISS], systolic blood pressure [SBP], heart rate [HR], Glasgow Coma Score [GCS], base excess [BE], hematocrit [Hct]). A 1:1 fixed ratio nearest neighbor matching was performed to compare mortality between the cohorts to minimize bias without sacrificing power [16].

Statistical analyses were performed using SPSS version 22 (IBM Corporation; Armonk, NY). Parametric data are reported as mean $\pm$ standard deviation and non-parametric are reported as median (interquartile range). Data were compared using a t-test or Mann Whitney U test, as appropriate. Categorical variables were compared using a chi-square or Fisher’s exact test, as appropriate. Pearson correlation coefficient (r) tests were performed to detect correlations between units PRBC transfused and PRBC:plasma ratios. Statistical significance was determined at alpha level 0.05.

RESULTS

A total of 1,305 patients were transfused, with 277 MTP and 61 S-MTP. For a more complete description, [Table 2](#) details the overall population. In 24 hr, transfusion requirements were 17(14)units of PRBC and 10(11) units of plasma, with a PRBC:plasma of 1.6(0.8). In comparing population differences between those who received MTP versus S-MTP, [Table 3](#) shows how those who receive S-MTP are inherently more severely injured, require more fluids and blood products, and have a significantly higher rate of mortality.

To identify how blood component ratios differed according to time between these populations, the PRBC:plasma ratio for each patient was calculated at serial time increments and median values were plotted in [Figure 1](#). Notably, within the first hour, S-MTP patients received a higher PRBC:plasma ratio of 2.1:1 vs 1.7:1 in MTP patients ($p=0.017$).

When comparing the patient populations before and after the institutional protocol changes, [Table 4](#) shows that patient demographics were similar yet ISS (31 ± 16 vs 46 ± 19 , $p<0.001$) and mortality (43.8% vs 59.3% , $p=0.038$) were significantly different. As the difference in injury severity could account for the differences in mortality, we used a 1:1 fixed ratio nearest neighbor propensity score match. With this, 62 patients with similar patient characteristics (age, ISS, BE, SBP, HR, Hct) were compared and there was no difference in mortality (54.8% vs 58.1% , $p=1.000$).

In assessing the effectiveness of institutional changes, [Figure 2](#) shows the PRBC:plasma ratio during MTP and S-MTP at serial time points. S-MTP patients received significantly lower PRBC:plasma ratios within the first two hours following initial transfusion (all $p<0.05$) following the advent of LP use.

To assess the change in PRBC:plasma ratio as a function of total blood requirements, [Figure 3](#) shows that, in all patients, PRBC:plasma positively correlated with units PRBC transfused at hour 1 ($r=0.343$, $R^2=0.118$, $p<0.001$). Before institutional changes, units PRBC transfused

positively correlated with PRBC:plasma at hour 1 ($r=0.410$, $R^2=0.168$, $p<0.001$), but not after the advent of LP ($r=0.177$, $R^2=0.031$, $p=0.219$).

DISCUSSION

There are three major findings of this study: (1) PRBC:plasma positively correlated with units PRBC transfused within the first hour immediately following initial transfusion during MTP, (2) PRBC:plasma was higher in S-MTP vs MTP, and (3) the changes in our institution’s availability of readily transfusable plasma improved early ratio of PRBC:plasma in patients requiring S-MTP. These results support the conclusion that early resuscitation during MTP is improved by making more plasma readily available for immediate transfusion and adapting protocols to encompass the most efficient delivery system of blood products.

In trauma, the “golden hour” is critical to survival [17]. Only 3-5% of all trauma patients require MTP but it is important to quickly identify these patients [3, 5, 18]. A PRBC:plasma ratio between 1:1 and 2:1 during initial transfusion has a survival benefit during MTP [19-21]. Duchesne et al. reported that survival was improved with PRBC:plasma of 1:1 vs 4:1 [19]. Sperry et al. reported lower 48hr mortality rates with a ratio of FFP:PRBC $\geq$ 1:1.5 [21]. A ratio of PRBC:plasma:platelets of at least 1:1:1 is associated with reduced mortality [9, 22, 23]. The recent evidence of benefit of a 1:1:1 transfusion was also found in the PROPPR trial [10]. The early availability of blood products within minutes of arrival using a transfusion ratio of 1:1:1 was associated with more patients achieving hemostasis and decreased hemorrhage-related deaths [10]. Based on recommendations from the FDA [11] and the guidelines set by the ACS [12], it is clear the goal therapy for hemostatic resuscitation is an immediate and balanced blood

component delivery. Unfortunately, as our results show, it is not always possible to deliver the desired ratio during most extreme conditions. Logistical improvements on our MTP seem to solve this problem of the delivery of immediate and balanced blood components.

It is important to note that the goal ratios were between 1:1 and 2:1 during the study period, and the changes in MTP were made to improve allocation to facilitate that delivery. Those with MTP alone (10-30 units PRBCs) did not experience deficits in delivery prior to institutional changes (see [Figure 1](#)). When assessing the effects of the protocol changes (and LP) on regular MTP, there was no significant difference in delivery but it was still within the goal of 1:1 to 2:1 at all time points (see [Figure 2A](#)). Still, to this point, [Figure 3](#) shows that, regardless of MTP or S-MTP, there was a correlation of increased PRBC:plasma ratio with total blood requirements, and this was not seen after institutional changes.

There are no studies assessing blood component ratios with >30 units PRBC during MTP. [Figure 2](#) showed that there was a lag phase in the first hours in those requiring S-MTP suggesting the need for more immediately available plasma. The inability to maintain the target ratio in S-MTP may be complicated by multiple factors.

Plasma is ideally given with the first unit of PRBC [24, 25]. Whereas PRBCs are stored in a refrigerator, plasma is stored frozen. It must be thawed in a water bath over 20 to 30 min [26], which can delay its administration during MTP [27]. Waiting for FFP to thaw makes this concurrent administration of blood components difficult to maintain the desired 1:1 to 2:1 ratio throughout the critical resuscitation period. After 24 hr, FFP is relabeled as “thawed plasma” and

can be stored and/or utilized for four more days [28]. This product is immediately transfusable, but supply may be limited because of shelf-life. Another concern is the limited donor pool of AB type FFP – only 4% of the population of the United States. There has been an increasing push for the use of LP over thawed plasma due to these logistical issues [13, 29]. With LP, there is no delay waiting for a thaw. This product can be available in higher quantities as it can be stored for up to 26 days [28, 30], which can preserve the supply of AB FFP.

The PROPPR trial was potentially limited by the low number of units of plasma available from blood suppliers [31]. Additionally, there was concern that there would be excessive wastage if plasma was routinely thawed in advance [31]. Several centers experienced significant wastage due to their need to have more plasma available (thawed and discarded) for the study protocol; yet the single institution which used LP (Houston) experienced one of the lowest wastage rates of 0.4% [31]. This utilization improvement may be even more pronounced in smaller hospitals with less volume of patients requiring MTP. As plasma use and turnover is likely less in these hospitals, we can speculate that they may benefit more from the wastage advantage LP offers.

Trauma centers have variable blood product allocation strategies for MTP [3, 5, 7, 8] and very few institutions use LP at their hospitals [31]. With the advent of LP, our institution changed its MTP policy; see [Table 1](#). Jackson Memorial Hospital’s “Policies and Procedures: Massive Transfusion Protocol” changes took effect on 6/1/14. Prior to that date, five units of uncrossmatched PRBC and two units of group AB plasma were available until a type-and-crossmatch was obtained and type-specific FFP was thawed and delivered. Upon MTP activation, blood components were delivered via the TransLogic® Pneumatic Tube System from

the blood-bank to the trauma resuscitation unit. With the new policy, eight units of universal donor, uncrossmatched PRBC and eight units of readily transfusable plasma (thawed AB plasma and LP) are immediately available. All blood products are now transported in a cooler by a laboratory “runner” with instructions to stay one round/batch ahead for the duration of the MTP activation. Prior to this protocol, there was still blood immediately available for massive transfusion. Therefore, the new protocol would not have any effect on time until first unit transfused, regardless of PRBC or plasma component. The changes were made to address the availability of readily transfusable plasma in order to keep up with the 1:1 to 2:1 ratio required by the American College of Surgeons. As time-to-transfusion may vary depending on patient situation, the PRBC:plasma ratio should be maintained 1:1 to 2:1. Therefore, this is the end-point assessed in our report.

With this institutional change, the early PRBC:plasma ratio in patients requiring S-MTP improved toward the 1:1 target. It is difficult to determine whether this improvement is due to LP, to the change in blood products allocation methodology, or to a combination of the two factors. To be clear, no unit of plasma is specifically designated as LP or thawed FFP during a MTP. LP has been added to our existing blood bank to have readily available plasma for transfusion. Our blood bank still uses FFP as it has a longer shelf life; most patients can wait the 20-30 min for it to thaw. Sometimes, FFP may be thawed but not transfused for one patient, and then must be used within 5 days. Depending on the situation, there may be an abundance of thawed FFP readily available for MTP, and these would be the first units allocated. However, in times of exorbitant blood requirements (S-MTP), this supply might not be enough to keep up with the 1:1 to 2:1 required, thus LP is available. In another scenario, the blood bank may not

have much recently thawed FFP for MTP use, thus LP would be employed much earlier following protocol activation. Ultimately, even if LP is not directly used in each MTP, its availability is what facilitates our new capability to balance blood product ratios.

We cannot explain why the mortality rate of those requiring MTP was higher after our institutional changes, however any apparent difference in outcomes is probably confounded by the small sample size and by differences in injury severity. No attempt was made to measure the effects of ratios on coagulation function; hence, little can be ascertained about the effects of liquid plasma. Also, the results of our propensity score match to control for these patient and injury differences showed no difference in mortality between eras. However this was not the goal of this study. It is already established that a PRBC:plasma ratio between 1:1 and 2:1 has an added survival benefit to patients requiring MTP [19-21]; with most recently 1:1 being the gold standard [10]. The purpose of this study was not to assess if these changes directly provide a mortality benefit, rather if LP facilitates the delivery of this target ratio that is becoming a guideline set by both the FDA and the ACS.

This is one of the first reports on the use of LP during MTP [29, 32], and an obvious limitation is the small number that received MTP after institutional changes. The fact is that this sample may not represent the entire trauma population. However, the differences in blood product administration were significant. The term “super” MTP is not a generally recognized classification, but the term has been used in few reports, with the definition varying (>25-40 units PRBCs) [14, 15]. For the purposes of this study, we identified those that required the top 20% of total blood component requirements amongst all patients who receive MTP and

arbitrarily set the value at >30 units. Another limitation is that this is a single institution review of observational data without randomization, and therefore baseline differences between groups could not be directly controlled. Aside from the MTP, resuscitative and operative strategies were based upon physician discretion without a set protocol. However, our group of trauma surgeons and anesthesiologists follow current guidelines and resuscitate to similar hemodynamic parameters. The timing of blood products transfused was according to first unit of PRBC given. As our institution has uncrossmatched, universal donor PRBCs immediately available for all trauma patients, it is likely these patients were initially transfused units not a part of the MTP. Therefore, initial ratios may be skewed towards a higher PRBC component, but this bias would have been imposed equally on all subgroups. Another limitation is that we did not directly measure the effect of LP but rather the logistical benefits it offers. Finally, the purpose of this study was not to determine optimal blood component ratios to improve patient outcomes. This study was based on the assumption that a balanced ratio of blood components is the goal during MTP.

CONCLUSIONS

In summary, within the first hour immediately following initial transfusion during MTP, (1) PRBC:plasma ratios positively correlated with units PRBC transfused, (2) patients receiving >30units PRBC in 24hrs (S-MTP) had significantly higher PRBC:plasma transfusion ratios than those of MTP, and (3) the improvements in allocation of blood products with use of readily transfusable plasma (enabled with use of LP) improve the ratio of PRBC:plasma transfused within the first hours in patients requiring S-MTP. Making more plasma readily available for immediate transfusion and adapting protocols to encompass the most efficient delivery system of

blood products from the blood-bank to the resuscitation unit improves the process of early resuscitation during MTP.

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TABLES/FIGURES

Table 1: Policy and Procedural changes at Ryder Trauma Center, massive transfusion protocol (MTP).

* 4-round cycle, repeated as needed.

Round-1: 5 units PRBC, 5 units plasma.

Round-2: 5 units PRBC, 5 units plasma, 10 units platelets.

Round-3: 5 units PRBC, 5 units plasma.

Round-4: 5 units PRBC, 5 units plasma, 10 units platelets, 10 units cryoprecipitate.

Table 2: Characteristics of all patients who receive MTP (n=338). Data are reported as mean $\pm$ standard deviation and median (interquartile range).

Table 3: Comparison of patients who receive MTP (10-29 total units PRBCs) to those of S-MTP (≥ 30 units PRBCs) (n=338). Data are reported as mean $\pm$ standard deviation and median (interquartile range).

Figure 1: Ratio of PRBC:Plasma Administered at serial time points, MTP vs SMTP (n=338). Data points are reported as median values for the population. Data were compared using a Mann Whitney U test. *Denotes statistical significance of $p < 0.05$.

Table 4: Comparison of patients who receive any MTP before and after institutional change (n=338). Data are reported as mean $\pm$ standard deviation and median (interquartile range).

Figure 2A: Ratio of PRBC:Plasma Administered during MTP at serial time points, before and after institutional change (n=277). Data points are reported as median values for the population. Data were compared using a Mann Whitney U test. *Denotes statistical significance of $p < 0.05$.

Figure 2B: Ratio of PRBC:Plasma Administered during S-MTP at serial time points, before and after institutional change (n=61). Data points are reported as median values for the population. Data were compared using a Mann Whitney U test. *Denotes statistical significance of $p < 0.05$.

Figure 3: Correlations between units PRBC transfused and PRBC:plasma ratios, before and after institutional changes (n=338).

Table 1: Policy and Procedural changes at Ryder Trauma Center, massive transfusion protocol (MTP).

Pre-institutional change (before July 1, 2014)	Post-institutional change (after July 1, 2014)
Two (2) units of group AB FFP available immediately until type and crossmatch obtained	Eight (8) units of thawed group AB plasma or liquid plasma (LP) available immediately until type and crossmatch obtained
Five (5) units universal donor, uncrossmatched PRBCs available immediately until type and crossmatch obtained	Eight (8) units universal donor, uncrossmatched PRBCs available immediately until type and crossmatch obtained
Blood components delivered via TransLogic® Pneumatic Tube System from blood-bank to trauma resuscitation unit	In the hands of a "runner", all blood products transported via cooler with set PRBC:plasma ratio of 1:1 with addition of other product (platelet, cryoprecipitate) as determined by batch number*
Additonal plasma for subsequent batches* available upon thawing of FFP	Additonal plasma for subsequent batches* available upon thawing of FFP or with LP

* 4-round cycle, repeated as needed.

Round-1: 5 units PRBC, 5 units plasma.

Round-2: 5 units PRBC, 5 units plasma, 10 units platelets.

Round-3: 5 units PRBC, 5 units plasma.

Round-4: 5 units PRBC, 5 units plasma, 10 units platelets, 10 units cryoprecipitate.

Table 2: Characteristics of all patients who receive MTP (n=338)

Age, years		41±19
Gender	Male	81%
	Female	19%
Mechanism of Injury	Blunt	52%
	Penetrating	48%
SBP, mmHg		96±35
HR, bpm		108±31
GCS		10±5
Base Excess, mEq/L		-9±7
Hematocrit, %)		33±6
ISS		33±17
Time to OR, min		30(68)
24h crystalloids, mL		9605±5889
S-MTP		18%
24h PRBC, units		17(14)
24h Plasma, units		10(11)
24h PRBC:Plasma		1.6(0.8)
LOS, days		9(34)
Mortality		46.3%

Parametric data are reported as mean ± standard deviation and non-parametric are reported as median (interquartile range)

Table 3: Comparison of patients who receive MTP (10-29 total units PRBCs) to those of S-MTP (≥ 30 units PRBCs)

		MTP (n=277)	S-MTP (n=61)	p value
Age, years		41 $\pm$ 20	37 $\pm$ 16	0.107
Gender	Male	81%	77%	0.477
	Female	19%	23%	
Mechanism of Injury	Blunt	53%	46%	0.396
	Penetrating	47%	54%	
SBP, mmHg		97 $\pm$ 35	94 $\pm$ 33	0.564
HR, bpm		106 $\pm$ 32	117 $\pm$ 28	0.018
GCS		10 $\pm$ 5	9 $\pm$ 5	0.524
Base Excess, mEq/L		-8 $\pm$ 7	-9 $\pm$ 7	0.958
Hematocrit, %		33 $\pm$ 6	33 $\pm$ 7	0.576
ISS		33 $\pm$ 17	34 $\pm$ 16	0.620
Time to OR, min		30(70)	27(50)	0.749
24h crystalloids, mL		9024 $\pm$ 5265	12214 $\pm$ 7649	<0.001
24h PRBC, units		15(9)	41(24)	<0.001
24h Plasma, units		9(6)	31(14)	<0.001
24h PRBC:Plasma		1.6(1.1)	1.4(0.6)	0.012
LOS, days		10(39)	3(23)	0.274
Mortality		42.3%	63.9%	0.003

Parametric data are reported as mean $\pm$ standard deviation and non-parametric are reported as median (interquartile range).

Table 4: Comparison of patients who receive any MTP before and after institutional change (n=338)

		Pre-institutional change (n=281)	Post-institutional change (n=57)	p value
Age, years		40±19	44±19	0.178
Gender	Male	79.7%	84%	0.582
	Female	20.3%	16%	
Mechanism of Injury	Blunt	52.3%	47%	0.562
	Penetrating	47.7%	53%	
SBP, mmHg		97±34	92±37	0.334
HR, bpm		110±30	102±34	0.123
GCS		10±5	9±5	0.140
Base Excess, mEq/L		-9±7	-8±5	0.519
Hematocrit, %		33±6	34±6	0.229
ISS		31±16	46±19	<0.001
S-MTP		19%	18%	1.000
24h PRBC, units		17(14)	16(10)	0.860
24h FFP, units		10(11)	10(6)	0.543
24h PRBC:FFP		1.6(1.0)	1.6(0.8)	0.473
Mortality		43.8%	59.3%	0.038

Parametric data are reported as mean ± standard deviation and non-parametric are reported as median (interquartile range).

Figure 3A: Correlation between units PRBCs transfused and PRBC:Plasma ratio at hour 1, MTP before LP Era. n=281

Figure 3B: Correlation between units PRBCs transfused and PRBC:Plasma ratio at hour 1, MTP after LP Era. n=57