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Rapid release protocol optimizes product utilization compared with massive transfusion protocol in selected patients

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ABSTRACT

Background: While massive transfusion protocols (MTPs) are effective means of expeditiously delivering blood products to patients with exsanguinating hemorrhage, activation often occurs in cases with small blood volume deficits, leading to product wastage and overtransfusion. We sought to determine whether the additional implementation of a new protocol (called Rapid Release [RR]), which uses less resources, would result in decrease in blood product wastage. We hypothesized that RR would result in the reservation of MTPs for sicker patients and that blood product wastage would decrease.

Methods: All MTP activations 1.5 y pre-RR and 1.5 y post-RR were analyzed. Compared with MTP (six units packed red blood cells [pRBCs], six units fresh frozen plasma [FFP], six units platelets), RR only releases four units pRBCs and one unit FFP per activation. MTP resource utilization and wastage was compared before and after RR in trauma and nontrauma populations. $P \leq 0.05$ was considered significant.

Results: One hundred nine MTPs were activated pre- ($n = 48$) to post-RR ($n = 61$), with 69 RRs activated in the post-RR period. Of these 69 RRs, 10 (14.5%) were eventually upgraded to MTP. Compared with the pre-RR group, significantly higher transfusion rates were observed for FFP and platelets. FFP wastage increased (pre: 0.65 ± 1.78 *versus* post: 3.46 ± 4.29; $P < 0.001$) over the study duration with no differences between the trauma and nontrauma populations.

Conclusions: Contrary to our hypothesis, institution of the RR protocol resulted in higher mean wastage of FFP per activation despite the appropriateness of the RR protocol. Further efforts are warranted to refine the MTP to increase efficiency.

Introduction

Massive transfusions of blood products are often critical to the successful resuscitation of actively bleeding patients, regardless of the underlying etiology of hemorrhage (trauma, obstetrical, gastrointestinal bleed). Appropriate management of intravascular volume loss is critical as inadequate resuscitation may lead to significant hypoperfusion, organ failure,

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and poor outcomes.[1] Historically, there have been three common definitions of massive transfusions: transfusion of ≥10 units of packed red blood cells (pRBC) within 24 h, transfusion of more than four units pRBC in 1 h with ongoing need for blood, and replacement of >50% of total blood volume within 3 h.[2]

Besides rapid control, management of hemorrhage has traditionally focused on infusions of crystalloid and infusion of blood products. Current practices place a greater emphasis on prevention of coagulopathy and advocate transfusion of platelets and plasma along with pRBC in a bid to resuscitate effectively.[3] This concept has led to the development of standardized massive transfusion protocols (MTP) to mobilize transfusion efforts for those patients that are anticipated to need massive transfusions. While massive transfusion is inherently a retrospective definition based on the amount of blood transfused over a given duration, the need for massive transfusion can be anticipated in certain patient populations. These patients would greatly benefit by the existence of a protocol (MTP) that establishes a systematic approach to care with predetermined ratios of transfusion, which have been shown to improve outcomes.[4,5]

Despite the tremendous benefits associated with MTPs, transfusion on this scale comes with its own risk. Studies have shown massive transfusions are associated with increased risk of respiratory and infectious complications along with 30-d mortality.[6,7] In addition, with any activation of MTP, there exists a possibility of inappropriate overactivation, which can lead to blood product wastage. Because the indications for a massive transfusion in nontrauma patients are often less clear, there may be even more striking wastage in these patients. Further obscuring this, outcome data may not show whether the massive transfusion itself, or the expeditious start of blood product infusion that is a characteristic of the MTP, is the true contributor to positive outcomes when combined with rapid control of hemorrhage.

At our level II trauma center, it was noted on review of massive transfusion events that many inpatient nontrauma MTPs were terminated rapidly, as well as launched with unclear diagnoses. This raised the concern that MTPs were being inappropriately activated for patients who did not meet specific evidence-based criteria used to determine the need for MTP activation. Examples of inappropriate activation include patients in need of rapid infusion of blood products and those suspected of ongoing bleeding, but not undergoing true exsanguinating hemorrhage. To curtail these inappropriate MTP activations, a new protocol called Rapid Release (RR) of Blood Products was developed, which releases four units of pRBC and one unit of thawed fresh frozen plasma (FFP) on verbal activation from an attending physician. The RR protocol was introduced to address the identified need for expeditious delivery of blood products to patients with ongoing blood loss who were not necessarily high-level trauma activations suffering from exsanguinating hemorrhage. This protocol was an additional measure introduced and did not replace existing protocols designed to respond to trauma activations with known or suspected massive hemorrhage. In addition to the blood products available for release via the MTP, the blood bank ensures there is ready availability of six units of uncrossed and unmatched pRBC for emergent situations. These patients would likely require multiple units of pRBC delivered on an emergent basis, but would not require the volume of blood products or the 1:1:1 ratio associated with a modern MTP.

Our goal was to determine whether implementation of the RR protocol, which uses less resources, would impact the number of MTPs that were activated in our level II trauma center and whether there would be any associated changes in blood product wastage, especially as there is not consistent data on wastage of blood products in an MTP.[8,9] We hypothesized that introduction of the RR protocol would result in reservation of MTPs for sicker patients and subsequently lead to decreased blood product wastage per MTP activation.

Methods

This study was reviewed and approved by the Lancaster General/Penn Medicine Institutional Review Board. Informed consent was waived given the minimal risk nature of the study. All activations of MTP are thoroughly documented and reviewed by the blood bank and Blood Utilization Review Committee. Information collected includes number of blood products transfused, wastage occurred per activation, and patient outcome at deactivation of protocol. Trauma MTP activations are additionally reviewed by Performance Improvement Coordinators within the trauma department and were all available for review. RR protocol activations are also documented by the blood bank with only patient outcome data collected. Records on blood product transfusion and wastage are not maintained for exclusively RR activations but those upgraded to MTP have product transfusion and wastage information collected.

All MTP activations 1.5 y before and 1.5 y after implementation of the RR protocol were analyzed. Blood product utilization, wastage, and mortality rates were compared before and after introduction of RR protocol in both trauma and nontrauma populations. A retrospective chart review of MTP trauma patients in the pre-RR period was conducted to determine the appropriateness of MTP activations. The analysis was limited to trauma patients as there exist a defined criteria (detailed below) in this population for MTP activation. Nontrauma MTP activations are not held to the same criteria and thus more difficult to assess retrospectively regarding appropriateness of MTP activation. In addition to the MTP activations, a subanalysis of RR activations (separate from the MTP activations) was also conducted. Univariate analysis using two-sample *t*-test and Fischer's exact tests were performed to determine differences between the two cohorts. Statistical significance was set at $P < 0.05$.

MTP is initiated by the attending physician in the setting of known or suspected massive hemorrhage. MTP was implemented in our institution in 2011 and initially comprised a ratio of 1.5 pRBC and one unit of FFP with no platelets. At the start of the study period, the protocol was updated to the 1:1:1 ratio of pRBC to FFP to platelets given the results of the PROPPR study.[5] The blood bank also made a commitment to keep thawed FFP available for MTPs to minimize delay in initial administration of FFP. Indications for activation include Assessment of the Blood Consumption (ABC) score as well as

clinical judgment of attending physician. The ABC scoring system assigns a point for each variable present: systolic blood pressure <90 mm Hg, heart rate >120, penetrating torso trauma, positive focused ultrasound assessment for trauma with a score of two or more warranting MTP activation. Once initiated, the blood bank prepares six units of pRBC, six units of FFP, and one pooled unit (consists of six units of random donor) of platelets. MTP process dictates that transfusion be continued in a 1:1:1 ratio until bleeding is adequately controlled or transfusion is no longer deemed appropriate by the physician. There is no limit on the quantity of blood products administered, only that they be transfused in the appropriate ratio. Each MTP activation is monitored and formally deactivated by the attending physician. In addition, supplementary blood products, such as tranexamic acid (TXA) and cryoprecipitate, although not formally included in the MTP, may be administered at the discretion of the attending physician. There has been unclear data[10] regarding appropriate patient selection for TXA as well as narrow time frame of administration for mortality benefits so it was deemed more appropriate to offer TXA on a discretionary basis. Utilization of these additional products is frequently dependent on laboratory values, such as thromboelastogram results.

By contrast, the RR protocol is activated for patients that do not meet MTP indications yet still require rapid blood product transfusions and compels the RR of only four units of pRBC and one unit of FFP, although further units of blood products can be ordered by the attending physician on a discretionary basis. Indications for RR activations include evidence of inadequate organ perfusion including moderate hypotension and ongoing blood loss that does not meet ABC criteria but with a predicted need for multiple units of pRBC over an hour. Physician judgment is exercised to decide whether there is a need for rapid administration of blood products to warrant RR as opposed to the normal process to type and cross-match patients. Thus, the criteria for RR activation rely heavily on clinical judgment and are therefore inherently subjective. In the event the RR fails to restore stability, the RR can be upgraded to an MTP if patients require additional blood products.

Results

During the 3-y study period, there were 109 MTP activations, with 48 MTP activations occurring pre-RR and 61 MTP activations in the post-RR period. Figure depicts the breakdown of MTP activations before and after RR protocol implementation for trauma and nontrauma cohorts. Patient demographics, injury severity, and outcomes for all MTP activations before and after RR protocol are included in Table 1. With the exception of average composite GCS score, no significant differences were observed in patient characteristics before and after RR. In addition to the MTPs, the post-RR period also included 69 RR activations, with 30 secondary to trauma and 39 secondary to nontrauma patients (Table 2). About 14.5% (10/69) of RRs were eventually upgraded to MTP with no significant differences in percentage of trauma *versus* nontrauma MTP upgrades (4/30 *versus* 6/39; $P = 1.00$). Retrospective chart review of MTP trauma activations in the pre-RR period revealed that 11 of the MTP activations were appropriate activations as defined by the ABC criteria and 11 of the activations did not meet ABC criteria. The remaining MTP activation did not have sufficient documentation in the chart to accurately determine whether ABC criteria were met.

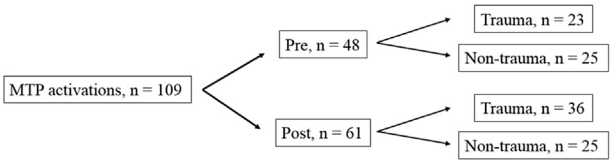

Fig – Breakdown of MTP activations over the study period.

Blood product utilization for MTP and RR activations during the study period is presented in Table 3. Higher overall trends were observed in product transfusion from pre- to post-RR for MTP activations with FFP and platelets transfused at significantly higher rates after RR. Both trauma and nontrauma populations had higher product utilizations, albeit nonsignificant, pre- to post-RR. Analysis of RR product utilization per activation (Table 3) reveals that on average, fewer blood products are transfused (2.81 ± 1.36 pRBC and 0.84 ± 1.11 FFP) than released by the protocol (four units of pRBC and one unit of FFP). There were no significant differences in the mean number of units of pRBC and FFP transfused between the trauma and nontrauma populations.

Table 4 depicts the blood product wastage associated with MTPs before and after RR. There was a significant increase in FFP wastage over the study period (pre: 0.65 ± 1.78 *versus* post: 3.46 ± 4.29; $P < 0.001$). This trend was observed in both trauma and nontrauma populations. Overall unadjusted mortality was not significantly different (pre: 16.67% *versus* post: 27.87%; $P = 0.25$) for the MTPs. There were no significant differences in mortality between trauma and nontrauma populations, pre-RR (21.74% *versus* 12.0%; $P = 0.45$) and post-RR (25.0% *versus*

Table 1 – Demographics of MTP patients.

Variable	Pre ($n = 48$)	Post ($n = 61$)	P
Age, y, mean ± SD	53.08 ± 21.22	48.97 ± 23.75	0.342
Median (IQR)	58.0 (29.5-68.7)	52.0 (25.0-69.5)	
Gender (male), *n* (%)	29 (60.42)	37 (60.66)	1.000
MOI (trauma only)			
Blunt, *n* (%)	17 (73.91)	28 (77.78)	
Penetrating, *n* (%)	6 (26.09)	8 (22.22)	0.762
ISS (trauma only)	31.96 ± 16.84	29.34 ± 12.37	0.526
GCS (trauma only)	9.32 ± 4.92	11.97 ± 4.48	0.048*
Hospital LOS	8.02 ± 6.79	9.52 ± 12.94	0.437
Mortality (deactivation), *n* (%)	8 (16.67)	17 (27.87)	0.251

SD = standard deviation; IQR = inter-quartile range; MOI = mechanism of injury; ISS = injury severity scale; GCS = Glasgow coma scale; LOS = length of stay.
* $P < 0.05$ = statistical significance.

Table 2 – Demographics of RR activation patients.

Variable	Trauma ($n = 30$)	Nontrauma ($n = 39$)	P
Age, y, mean ± SD	54.80 ± 21.49	63.03 ± 13.88	0.075
Median (IQR)	57.0 (33.75-70.50)	64.5 (54.25-73.25)	
Gender (male), *n* (%)	23 (76.67)	24 (61.54)	0.204
MOI (trauma only)		—	—
Blunt, *n* (%)	30 (90.0)		
Penetrating, *n* (%)	3 (10.0)		
MTP upgrade	4 (13.13)	6 (15.38)	1.000
Mortality (deactivation), *n* (%)	1 (3.33)	11 (28.21)	0.009*

SD = standard deviation; IQR = inter-quartile range; MOI = mechanism of injury.
*$P < 0.05$ = statistical significance.

32.0%; $P = 0.57$). Mortality for RR activations was 17.39%. There was a statistically significant difference in mortality between trauma and nontrauma RR activations (trauma: 3.33% *versus* nontrauma: 28.21%, $P = 0.0098$).

Discussion

Contrary to our hypothesis, MTPs after introduction of the RR protocol had a higher mean wastage of FFP per activation, despite the overall appropriateness of the RR activations. Given that most of the RR activations did not progress to MTPs, it is unlikely that post-RR MTP wastage is a reflection of RR activations that were upgraded to MTPs. A more likely reason for the wastage observed is that the blood bank and clinicians were more inclined to maintain a "stay ahead" process for blood products in the recent past compared with its more conservative approach in preparing blood products at the onset of the study period. This included a more aggressive approach in thawing of FFP to ensure proper ratios were maintained. If a unit of FFP is thawed and not given, it is returned to the blood bank for other potential patients. However, if no suitable recipients are identified within 5 d, the unit is discarded and recorded as wasted. This is generally carried out at other institutions as well.[11] This increased diligence in preparation of units likely inflated the increase in FFP wastage observed in MTPs after introduction of the RR protocol. FFP wastage in relation to MTPs has been reported previously by Balvers *et al.*,[12] who noted a significant increase in wastage of FFP (but not other blood products) after introduction of a hospitalwide MTP. They also credit the higher FFP wastage rates to its notoriously limited shelf life of ~3 d and reported that introduction of an intervention prolonging storage time of FFP to 7 d led to a reduction in prethawed FFP wastage. We have introduced a similar process at our institution, which extends the shelf life of thawed FFP to 5 d, although given its recent introduction, it is too early to determine whether it has been successful in decreasing our wastage.

Another factor to consider is that the MTP is now reserved for sicker patients with higher volumes of hemorrhage. As these patients will have higher intrinsic rates of hemorrhage with the move to balanced resuscitation, there will be more "rounds" of products issued in the 1:1:1 ratio, with a consequent increase in the likelihood that some of these products will be wasted. As we captured all of our MTPs, we do not believe there is any "survivor bias" that affects our ratios or the amount of blood products wasted; both survivors and nonsurvivors contributed toward wasted units.

Given these results, while the goal is to always maximize efficiency of blood products, attempts to drastically curtail product wastage may be impractical, as there is a lack of consensus in the medical community regarding acceptable utilization/wastage rates of blood products per MTP activations. While we use thromboelastogram assays to guide transfusions and MTPs, and employ a coordinated team managed in crew resource fashion (like most institutions) to manage these complex events, we still see blood product wastage. The underlying reasons could be attributed to a variety of causes, including termination of the MTP before proper ratios are given, as well as occasional mishandling of the blood products themselves. Thus, overall education regarding appropriate MTP activations and encouragement of

Table 3 – Mean product utilization per activation.

Blood products	MTP			RR
	Pre	Post	P	
pRBC (mean ± SD)	6.77 ± 7.98	9.34 ± 10.93	0.159	2.81 ± 1.36
FFP (mean ± SD)	4.42 ± 6.45	8.11 ± 9.32	0.016*	0.84 ± 1.11
Pooled platelets (mean ± SD)	0.79 ± 1.18	1.46 ± 1.60	0.013*	—

MTP = massive transfusion protocol; RR = rapid release; SD = standard deviation; pRBC = packed red blood cells; FFP = fresh frozen plasma.
*$P < 0.05$ = statistical significance.

Table 4 – Mean product wastage per activation.

Blood products	MTP			RR
	Pre	Post	P	
pRBC (mean ± SD)	0.06 ± 0.43	0.02 ± 0.13	0.479	—
FFP (mean ± SD)	0.65 ± 1.78	3.46 ± 4.29	<0.001*	—
Pooled platelets (mean ± SD)	0.00 ± 0.00	0.05 ± 0.22	—	—

MTP = massive transfusion protocol; RR = rapid release; SD = standard deviation; pRBC = packed red blood cells; FFP = fresh frozen plasma.
* $P < 0.05$ = statistical significance.

prompt return of unused products are an ongoing effort. These efforts will likely continue even if standards regarding MTP product wastage are established, which seems unlikely given the emergent and somewhat chaotic nature of the event, particularly in centers that have lower but significant rates of MTP activation.

It was interesting to note that the number of MTP activations increased after implementation of the RR protocol with the increase in MTPs exclusive to the trauma population. During the study duration, especially with the introduction of the RR protocol, there was a robust effort underway to increase education on both MTP and RR processes. Increased awareness and comfort with the MTP process could have contributed to the increase in number of MTP activations observed in the post-RR period. Alternatively, the increase may also have been a reflection of increase in patient population during the latter period. Superficially, the increase in MTPs overall, and the unchanged number of nontrauma MTPs after RR implementation, somewhat contradicts our hypothesis. However, we believe the RR protocol appears to play a role in limiting MTP overactivations given only 10 of the RRs were upgraded to MTP. Without the existence of the RR protocol, it is possible that greater than 10 of the 69 RR activations would otherwise have been MTP activations. This is especially true as 11 of 23 MTP trauma patients in the pre-RR period did not warrant MTP activation as defined by the ABC criteria, suggesting these patients were likely MTP overactivations. The RR protocol thus fulfills an essential role in the gap that exists in the continuum of care of patients who require rapid transfusions.

While O'Keeffe *et al*. reported a decrease in blood product utilization after introduction of MTP, no definitive rates of acceptable product utilization and wastage with MTPs have been established. Cotton *et al*.[13] found that failure to send type and screen from the ED is an independent predictor of wasted blood products, which indicates that this metric is susceptible to performance improvement. In a retrospective cohort study, Kreuziger *et al*.[14] found that MTP can be used both in trauma and nontrauma settings without significantly impacting overall blood product utilization, and that these patients should be included in studies that assess the benefits and risks of a massive transfusion. Finally, Khan *et al*.[15] showed that an updated massive hemorrhage protocol can show improvement in blood utilization and wastage over an older protocol, even decreasing the wastage of platelets, suggesting that continuous performance improvement is possible.

The need for better criteria to help predict massive transfusion has been previously recognized in the trauma literature. While the advantage of utilizing the ABC criteria lies in its simplicity, it is not an entirely reliable tool in predicting massive transfusion and would perhaps be of best utility in conjunction with other criteria. Another metric that has demonstrated success in identification of severely ill trauma patients and, may be a better predictor of massive transfusion, is the critical administration threshold (CAT).[16] Cognizant of the importance of both volume and rate of blood products transfused, CAT was defined as administration of three units of pRBC over a 60-min period and proved to be a more reliable predictor of mortality than standard definition of massive transfusion.[17] Although analysis using CAT appears to have been limited to the trauma population, it can perhaps also serve as an indicator for massive transfusion events in nontrauma patients. The disparity in prospective predictions of massive transfusion between trauma and nontrauma patients is vast as there is considerably less published data on the results of MTP activations in nontrauma patients.

This study does have significant limitations. The study relied on single institution data, as no large databases yet exist that provide extensive documentation regarding blood product utilization and wastage. In addition, as with any retrospective study, there were possible confounders that may have contributed to the increased wasting of blood products that were independent of the institution of our RR protocol, as our transfusion process, like most institutions undergoes continued review and quality improvement. We do feel that despite the limited sample size, the data itself is robust given the meticulous documentation and subsequent review of every MTP and RR by the institution's blood bank and Blood Utilization Review Committee, so it is unlikely that any massive transfusions were missed during the study period. In addition, despite the inherently dynamic nature of the MTP and the RR processes, no changes were made to the actual number of products transfused per protocol.

Conclusions

The RR protocol bridges a much-needed gap in patients requiring rapid transfusions as it better matches the administration of blood products to a patient's needs. However, it does not affect efficiency of product utilization within resuscitation ratios of MTP. Given the fundamental role MTPs play in trauma care, improvement in criteria for predicting massive transfusion is vital as are continued efforts to refine the process.

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Authors' contributions: S.J. participated in study design, data analysis, and article preparation. J.A.M. participated in study design, and data collection. C.A.M. participated in study design, article preparation, and editorial oversight.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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