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Massive Transfusion Protocol in Adult Trauma Population

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Abstract

Background: Acute blood loss in trauma requires quick identification and action to restore circulating volume and save the patient. Massive transfusion protocols (MTPs) have become standard at Trauma Centers, in order to rapidly deliver blood products to bleeding patients. This literature review presents current standards of transfusion ratios, as well as insights into adjuncts during massive transfusions.

Methods: PubMED was searched for articles from 2005-2020 on MTPs, the article were assessed for single vs. multi-institutional, mechanism of injury, type of MTP, timing in which blood products should be administered, timing of delivery of blood products to trauma bay, pre-hospital treatment and adjuncts, and outcomes.

Results: Eleven studies addressed transfusion ratios. Seven studies looked at timing of blood products. Nine studies addressed MTP pre-hospital treatment and adjuncts. Prior to 2015, studies supported the benefits of a balanced transfusion ratio, which was then confirmed by the PROPPR randomized controlled trial. The shorter the time to blood product delivery the better the outcomes. New advances in technology have allowed us to measure different patterns of coagulation, allowing more individualized approaches to the bleeding patient.

Conclusion: Current massive transfusion protocols should utilize between 1:1:1 and 1:1:2 ratios of the 3 main products; plasma, platelets, and red blood cells. Massive transfusion protocols are effective in decreasing mortality. Better resuscitation efforts were seen when blood products were readily available in the trauma bay when the patient arrived and the faster the replacement of blood, the better the outcomes.

Key words: Acute Blood Loss; Massive Transfusion Protocol; Blood Products; Balanced Transfusion Ratio; Coagulopathy; Trauma Mortality

Background:

Acute blood loss in the setting of trauma is a life-threatening condition in which medical professionals must work expediently in order to deliver optimal care. Massive transfusion (MT) is commonly defined as a transfusion of 10 or more packed red blood cells (PRBCs) within a 24-hour period with the goal being to limit complications and limit critical hypoperfusion while surgical hemostasis is achieved (1). The indications for PRBC transfusions in the setting of trauma and acute blood loss have been identified (2, 3). The American College of Surgeons (ACS) has also outlined the indications for a Massive Transfusion Protocol (MTP) (4). The Trauma Quality Improvement Program (TQIP) of the ACS suggests a transfusion ratio of plasma and PRBCs between 1:1 and 1:2 and to transfuse one single donor apheresis or random donor platelet pool for each six units of RBC (5). This is often called a "six pack of platelets." Having an MTP in place is critical, as its compliance is associated with lower mortality rates (6).

Discussions have revolved around the administration of plasma, platelets and PRBCs at a ratio between 1:1:1 and 1:1:2. Earlier studies have advocated that in the civilian population, early transfusions of plasma and platelets, in addition to PRBCs during MTs in the setting of trauma may improve survival and reduce incidence of trauma-induced coagulopathy (7, 8). A multicenter study suggested that increased ratios of plasma and platelets within the first 6 hours of admission provided the largest difference in mortality (9). Another multicenter cohort supported this data (10).

A landmark randomized controlled trial in 2015 known as the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial has concluded there is no significant difference in mortality within the first 24 hours or at the 30 day mark regardless if patients were transfused at a 1:1:1 or 1:1:2 ratio (11). The PROPPR trial also noted that more patients who received 1:1:1 ratio achieved earlier hemostasis and fewer deaths due to exsanguination, but statistically similar results for all deaths (11). Hence the current guidelines recommending the administration of plasma to PRBCs in a ratio between 1:1 and 1:2 (4).

These findings encouraged researchers in the field of trauma to further investigate the matter of a universal MTP and strive to make sense of how a higher plasma and platelet ratio could provide some benefits in hemostasis but not impact patient outcomes in terms of mortality. It is also important to note that these studies were not able to stratify the outcomes of patients who received the massive transfusion based on injury types (penetrating vs. blunt trauma).

Subsequent analyses have re-tested the principle of higher plasma and platelet ratios to PRBCs. A systematic review by McQuilten et al. yielded similar results as the PROPPR trial, stating that there was no significant difference in morbidity and mortality with increased plasma and platelet ratios and that there was insufficient evidence to recommend transfusions at a 1:1:1 ratio over a 1:1:2 ratio as the standard of care for patients with critical bleeding (12). Another recent meta-analysis that compiled the literature on MT patients with critical bleeding was not able to provide a distinct answer to the impact of component therapies and ratios to PRBCs on patient outcomes (13). Thus, illustrating the gap in evidence needed to determine the exact ratios in which blood components should be transfused as well as calling for further trials to provide illumination to the matter.

The scope of an MTP extends beyond just the ratios of blood components and also explains why a universal MTP has yet to be adopted. As previously mentioned, there may be a time-dependent relationship to obtain a significant difference in outcomes of transfusions with high components of plasma and platelets (9, 10). Current ACS guidelines recommend early initiation of an MTP with blood bank cooler deliveries to the trauma bay within15 minutes of an MTP activation (4). A recent randomized controlled trial with planned subset analysis verified that delays in MTP activation and delivery of first cooler prolonged time to hemostasis and increased mortality (14).

Many other factors involved in an MTP must be considered in addition to the timing in which the blood products are delivered. The utilization of thromboelastography (TEG) or rotational thromboelastometry

(ROTEM) and the role of therapeutic adjuncts such as tranexamic acid (TXA), pro-thrombin complex concentrates (PCC) and activated factor VIIa are all potential useful adjuncts. The latest research on the applications of TEG in MTs should be considered when identifying transfusion thresholds (15). TXA in the milestone CRASH 2 trial was associated with less death if given within 3 hours of injury and the complication rate was similar to placebo. (16, 17).

Overall, MTPs in trauma settings and among practitioners are widely variable with an abundance of tools and markers that could assist in unifying a set of recommendations based on patient outcomes. The primary objective of this literature review is to determine the optimal ratio of blood products (plasma, platelets and packed red blood cells) that should be administered during an MTP. Secondary objectives include the timing in which these blood products should be administered during the MTP, timing of delivery of blood products to the trauma bay, the role of therapeutic adjuncts in an MTP and the mechanism of injury (blunt vs. penetrating trauma) on patient outcomes during an MTP. These objectives are also key to the emergency medicine physician as they are often the first provider available to these trauma patients and time is of essence when a trauma patient is rapidly hemorrhaging.

Methods:

A literature search was conducted using PubMed for studies in the English-language using the keywords "trauma and massive transfusion protocols" or "adult, trauma, and massive transfusion protocols." Adult trauma patients are those trauma patients age ≥15 years old as defined by The American College of Surgeons. Titles and abstracts of the results were screened for relevance with the last study accessed on July 2020. Case reports, incomplete studies, irrelevant population, non-English language studies, and repeated studies were excluded. References from included articles were also searched for relevant manuscripts. Thirty-four studies were initially excluded, as they were not in the English language. Articles were searched and initially reviewed by two authors (EM and DB) and reviewed again by the senior author (AE). Additionally, the search terms "trauma, prehospital treatment, and massive

transfusion protocols" or "trauma, adjuncts, and massive transfusion protocols" was used to identify studies that included prehospital treatment and adjuncts for trauma patients who received massive transfusion protocols. Titles and abstracts were once again screened for relevance with the same exclusion criteria similar to the previous search. There was a total of 450 studies from 2005 to 2020 that were eligible for inclusion. After applying exclusion criteria, a total of 11 studies were included for MTP ratios, 7 studies included for timing in which blood products should be administered during MTP and timing of delivery of blood products to trauma bay, and 9 studies included which looked at MTP pre-hospital treatment and adjuncts (Figure 1).

Data Search Strategy

Articles were assessed for single vs. multi-institutional, United States (US) vs. non-US, study design, age of patient population, mechanism of injury, type of MTP used, timing in which blood products should be administered during MTP and timing of delivery of blood products to trauma bay, pre-hospital and adjunct treatment to MTP, and outcomes (Figure 1). Studies were chosen for the primary outcome of our study if they compared different blood component transfusion ratios among trauma patients and looked at the outcome, which totaled to 11 studies (Table 1).

Results:

Optimal Ratio of Blood Products

Prior to the PROPPR trial, transfusion practices in the acutely bleeding trauma patient varied substantially between institutions. MTPs were initially only present at a relatively small number of large trauma centers throughout the US and non-US hospitals (19).

Studies in the late 2000s and early 2010s began analyzing the most appropriate PRBC:FFP:platelet ratios. In a study by Johansson et al. in 2009, an early balanced transfusion therapy consisting of 5 RBC, 5 FFP, and 2 platelet concentrates was introduced into their institution due to a noted increased mortality in patients at their institution who were inadequately transfused (20, 21). As early as 2009, Snyder

concluded that there was an association between higher FFP:PRBC ratios at 24 hours and improved survival. However, after adjustment for survival bias in the analysis, the association was no longer statistically significant (22). Progress was made on a national level as evidenced by Schuster et al. who in 2010 surveyed 59 trauma centers and showed that 85% had an MTP in place with FFP:PRBC ratios of 1:1 (23).

In a study by Duchesne et al., it was concluded that FFP to PRBC ratio close to 1:1 confers a survival advantage in patients requiring MTP (24). Similarly, this was seen with Teixeria et al. (25). In contrast to this, two studies, Kashuk et al. and Scalea et al. found no benefit in balanced transfusion (26, 27). In a study by Shaz et al. a high vs. low (PLT:PRBC >1:1 vs <1:2 and Plasma:PRBC ≥1:2 vs. <1:3) were associated with improved 30 day survival (28). In a study by Dente et al. a PRBC:platelet transfusion ratio >3:1 or a PRBC:FFP ratio > 3:1 fared worse. Patients whose PRBC:FFP transfusion ratio or PRBC:platelet between 2:1 to 3:1 had statistically similar early and late outcomes compared to 1:1 to 2:1. The patients in this study that received PRBC:FFP ratio >3:1 had significantly worse early outcomes with an early mortality of 57% vs 31% and 36% for the 1-2:1 and 2-3:1 groups respectively. This worse outcome was also seen in patients whose PRBC:platelet ratio was >3:1, with early mortality of 50% vs 10% and 18% for patients whose ratio was 1-2:1 and 2-3:1 respectively. Late mortality was numerically worse in both the >3:1 groups, but this did not reach statistical significance (29). In Hallet et al. there was insufficient evidence to strongly support the use of a precise platelet:PRBC ratio for trauma resuscitation (30). From Borgman et al. patients who were in combat-related trauma who received MTPs with a plasma:PRBC ratio of 1:1.4 were associated with improved survival to hospital discharge. This was compared to low ratio (1:8) and medium ratio (1:2.5) (31). Sperry et al. demonstrated that patients who received transfusion products in ≥ 1:1.50 FFP:PRBC ratio versus < 1:1.50 FFP:PRBC ratio required significantly less blood transfusion at 24 hours (16 ± 9 units vs. 22 ± 17 units, p = 0.001) (32).

In a study by Maegele et al. an association between PRBC:FFP transfusion ratios and mortality favored early aggressive FFP (33). In addition, Holcomb et al. found that increased platelet ratios were associated with improved survival at 6 hours, 24 hours, and 30 days, ideally with a platelet:PRBC ratio of 1:1 (34) (Table 1).

Within the past several years, MTPs have consisted of similar products. Haider et al. performed a multi-center US survey that showed 95% of centers surveyed had a MTP with 68% consisting of a plasma:platelets:PRBC ratio of 1:1:1 (34). Another study by Treml et al. surveyed multiple US centers and showed the relative target goal MTP plasma:PRBC was between 1:1 and 1:2 (36). Interestingly, a study by Innerhofer et al. in 2017 showed the importance in early and effective fibrinogen supplementation in patients who were identified by abnormal fibrin polymerization or prolonged coagulation time using rotational thromboelastometry (ROTEM) (37).

A challenge to individual component transfusion therapy is the use of whole blood. In 2013, Nessen et al. saw improved survival in those who received uncrossmatched Type O fresh whole blood compared to those who did not (38). Also in 2013, Cotton et al. performed a randomized controlled trial that looked at modified whole blood transfusion vs component therapy with 1 unit of PRBC and 1 unit of plasma (39). The patients receiving whole blood did not have a reduction in transfusion volumes, but in subset analysis of severe brain injury, the whole blood group received less 24-hour RBC, plasma, platelets, and total products. A more recent study by Willams et al. found low-titer group O whole blood to be associated with a 53% reduction in post-ED blood product transfusion and a two-fold increase in likelihood of survival (40). Gallaher found that primarily using large volumes of whole blood in the civilian trauma population is a safe and effective addition to component therapy when retrospectively analyzing trauma patients who were resuscitated with component therapy versus component therapy plus whole blood (41).

Timing of delivery of blood products

In a study by Meyer et al. an increase in time to call an MTP activation and increased time to arrival of first cooler were associated with prolonged time to achieving hemostasis (14). In a study by Hess et al. their MTP protocol that made blood components readily available in a portable refrigerator with a blood bank technician at the trauma activations was found to be associated with low rates of total component usage and low mortality for trauma patients, and was not associated with overuse (42). Lim et al. in 2018 showed that MTP patients receive blood products more expeditiously with secondary outcomes associated with a trend ($p = 0.08$) in decreased hospital length of stay (43). In a study by Riskin et al. expeditious product availability decreased the mortality in trauma patients when the same FFP:PRBC ratio was still provided (44). This is further supported by Cotton et al. who found in their single institution there was a decreased risk of organ failure and complication rates when blood products are delivered early in the resuscitation through a predefined MTP (45). Pneumonia, pulmonary failure, open abdomens, abdominal compartment syndrome, severe sepsis, septic shock, and multi-organ failure were all lower in the patients who received MTP. This shows that as soon as MTP is activated by the provider, products should be administered which will result in improved outcomes.

Savage et al. used critical administration thresholds of more than 3 units PRBC per hour to identify hemorrhaging patients and to study the effect of concurrent administration of PRBC/FFP during the course of the MTP on patient survival. They found that patients that spent more time during their MTP with a 1:1 ratio had a decreased risk in mortality than those who spent less time at this ratio (46) and recommended concurrent administration of FFP with PRBCs during the course of the MTP. Nascimento et al. found a fixed-ratio MTP was feasible, however this was associated with increased plasma wastage once thawed (47).

Adjuncts in Massive Transfusion Protocols

There are several adjuncts available for massive transfusion as outlined by TQIP. These include antifibrinolytic medications such as TXA, recombinant activated factor VIIa, and prothrombin complex concentrate (5).

The CRASH-2 trial showed that early administration of TXA safely reduced the death in bleeding trauma patients and is highly cost-effective. Treatment beyond 3 hours of injury is unlikely to be effective (48). In 2019, El-Menyar et al. retrospectively found that prehospital TXA administration is associated with less in-hospital blood transfusion and massive transfusion protocol without significant increase in thromboembolic events and mortality while numerically lower with TXA was not statistically significant (49). In contrast, Dixon et al. in 2019 retrospectively found no benefit in TXA administration in their patients when used within 24 hours (50). In 2020, Neeki et al. found a statistically significant reduction in mortality in the civilian adult trauma population after blunt or penetrating trauma who received TXA. The reduction was seen at 28 days in those patients who received TXA, but no reduction was seen at 24 and 48 hours (51).

Recombinant activated factor VIIa has an unclear role in MTP due to a lack of long-term mortality benefit and potential increases in morbidity (5). The CONTROL trial evaluated the efficacy and safety of rFVIIa as an adjunct for hemostasis in major trauma. There was reduced blood product use but no effect on mortality compared with placebo. In addition, enrollment was terminated at 573 of 1,502 planned patients due to unexpected low mortality prompted by futility analysis and difficulties consenting and enrolling sicker patients (52).

In Sellers et al., 188 trauma and acute care surgery patients required reversal of anticoagulation with 98 receiving FFP and 90 receiving PCC. The patients who received PCC had a greater decrease in INR, however also had worse outcomes than those who received FFP which may have been due to baseline differences between the patients receiving FFP versus PCC. More studies still need to be completed to further elucidate the role of PCC in the trauma patient (53).

TEG and ROTEM provides a real time assessment of viscoelastic clot strength under low shear stress. Components of the studies inspect the interaction of platelets with the coagulation cascade and can be used to specifically recommend what type of blood product should be given based off of the deficiency seen in these real time studies. In a study by Gregory et al. in 2015, recommended point of care testing methods such as thromboelastography should be used to guide resuscitation instead of reflexively jumping to a 1:1:1 transfusion strategy for MTP keeping in mind that there are pitfalls with these methods as well, as these tests are affected by in vivo environmental conditions such as hematocrit, platelet count, and plasma levels (54). In contrast, Unruh et. al in 2019 saw conserved blood product utilization with similar outcomes using TEG compared to traditional coagulation tests (55). The ongoing randomized controlled trial iTACTIC is exploring Viscoelastic Hemostatic Assays in the trauma setting (56).

Blunt vs. Penetrating Trauma

In Dente et al. a subset analysis showed a reduction in 30 day mortality after blunt trauma compared with penetrating trauma for pre-MTP and post-MTP initiation (29). They showed that in penetrating trauma, there was a decrease in 24-hour mortality noted, however it was much more modest than in patients with blunt trauma. In addition, unlike the patients with blunt trauma, the mortality difference was not sustained to the point of discharge. This is supported by Sperry et al. that showed patients requiring ≥ 8 units of blood after serious blunt injury, an FFP:PRBC transfusion ratio ≥ 1:1.5 was associated with a significantly lower risk of mortality but a higher risk of acute respiratory distress syndrome (57). In 2018 Givergis et al. compared MTP activation between blunt and penetrating trauma patients and found that differences existed. Penetrating trauma patients were younger, had higher probability of survival, and decreased mortality compared to blunt trauma patients. These penetrating trauma patients also received higher plasma content therapy, defined as RBC:FFP ratio <2, relative to blunt trauma patients (67% vs. 59%) (58).

Discussion

Optimal Ratio of Blood Products

Multiple studies have shown that having an MTP in place is beneficial in decreasing mortality of the acutely hemorrhaging trauma patient. A balanced transfusion ratio among the 3 main component (PRBC:FFP:platelets) should be between 1:1 or 1:2. The most rigorous trial advocating this is the PROPPR trial, plus other prospective and retrospective studies lend additional weight. This balanced transfusion provides an adequate replacement in patients who are losing whole blood. Additionally, other studies should explore the utilization of fresh whole blood compared to separate component therapy as this may provide further individualized treatment and better outcomes for trauma patients who are rapidly losing whole blood.

Timing of Delivery of Blood Products

Time to MTP activation and delivery of blood products is critical for trauma patients who are foreseen to require greater than 10 or more packed red cells in a 24 hour period. Having blood products readily available in the trauma bay leads to better resuscitation of these patients. The faster the replacement of shed whole blood, the better the outcomes.

Adjuncts in Massive Transfusion Protocols

TXA, recombinant activated factor VIIa, prothrombin complex concentrate, and the use of TEG and ROTEM are potentially useful adjuncts in treating patients who require MTP. TXA used within the 3 hours of injury may improve mortality in bleeding trauma patients. Further studies are needed to outline the proper use of factor VIIa and PCC, if it exists, in a patient who requires MTP as the risks may outweigh the benefits in current studies. The use of TEG and ROTEM in the resuscitation of the massively hemorrhaging trauma patient is still controversial. While pitfalls do exist, these adjuncts may prove to be useful to provide the optimal answer in how to resuscitate trauma patients on an individual basis. However, more studies, including a randomized controlled trial, are currently underway and will provide further information on this matter.

Blunt vs. Penetrating Trauma

Blunt trauma patients tend to have lower probability of survival, more multi-organ and multisystem injuries and therefore increased mortality compared to penetrating trauma patients due to mechanism of injury alone. In addition, the patient demographics of blunt versus penetrating trauma patients are vastly different. This is seen in the reduction in 30 day morality that was seen only in blunt trauma patients when compared with penetrating patients (52) when using a balanced transfusion approach.

Limitations

The value of a literature review is dependent on the level of evidence of the studies included and there is a high risk of bias in many of the studies included in our review. We were only able to identify 4 RCTs which each evaluated several aspects of this literature review: optimal transfusion ratio, time to delivery of blood products, the emerging use of thromboelastography. This did not allow direct comparison between results of RCTs for the same topic within this review. In addition, there was no standardized approach to evaluating outcomes across the studies; some studies looked at survival within 24 hours while others looked at 30-day mortality. Furthermore, many studies explored optimal resuscitation ratios with blood products using partial component ratios (i.e. PRBC:FFP:platelets, PRBC:FFP, PRBC:platelets or FFP:platelets).

Conclusion

The use of a Massive Transfusion Protocol in the hemorrhaging trauma patient is critical to their survival and emergency physicians are the first line providers available to these patients as soon as they enter the hospital. A balanced transfusion of FFP:platelet:PRBC ranging between 1:1:1 and 1:1:2 has been associated with a decreased mortality as well as other complications. Early initiation of an MTP and faster timing of product delivery is also associated with less organ failure. TXA use if done within 3 hours of injury is associated with lower mortality. A more individualized approach to the massively hemorrhaging

patient can be obtained through the use of adjuncts such as TEG and ROTEM, however further studies are needed in order to elucidate the outcomes of these patients as well as the cost-effectiveness of these adjuncts. In addition, the use of fresh whole blood combined is promising but further research is needed. Attempts at replacing massive blood loss and maintaining hemodynamics until definitive care is the hallmark of a Massive Transfusion Protocol. This is important for emergency room physicians as they are the first line hospital provider to take care of these patients who require individualized time specific care.

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Table 1: Studies Investigating Outcomes for Balanced MTP

Author	Year	Balanced MTP Better Outcomes?	Ratio(s) with Better Outcomes	Study Design
Holcomb et al	2015	Yes	PRBC:FFP:PLT = 1:1:1	Prospective
Duchesne et al	2008	Yes	FFP:PRBC = 1:1	Retrospective
Teixeria et al	2009	Yes	FFP:PRBC = 1:1	Retrospective
Kashuk et al	2008	No		Retrospective
Scalea et al	2008	No		Prospective
Shaz et al	2010	Yes	PLT:PRBC > 1:1 and FFP:PRBC ≥ 1:2	Retrospective
Dente et al	2009	Yes	PRBC:PLT = 1:1	Prospective
Borgman et al	2007	Yes	FFP:PRBC = 1:1.4	Retrospective
Sperry et al	2008	Yes	FFP:PRBC ≥ 1:1.5	Retrospective
Holcomb et al	2008	Yes	PLT:PRBC = 1:1	Retrospective
Maegele et al	2008	Yes	PRBC:FFP < 1:1	Retrospective

Figure 1. Flow diagram of MTP studies, MTP studies looking at timing and delivery of blood products to trauma bay and MTP pre-hospital treatment and adjuncts included in the literature review.