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Review Article

Protocol of Massive Transfusion (MTP) — A Systematic Review

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ABSTRACT

Introduction: *MTP has been widely adopted for the care of bleeding trauma patients but its actual effectiveness is uncertain even today. MTP is an efficient way of ensuring of blood components to rapidly exsanguinating patients. For effective management of severely injured patients, regardless of etiology (trauma, obstetrical, surgical), effective preparation of MPT is needed.* ***Methods and Materials:*** *This review included 9 original studies that reported the effect of the implementation of an MTP on trauma patients. It shows that MTP implementation improves overall survival, with a statistically significant reduction in the overall mortality. The total study population was 4245.* ***Results:*** *MTP significantly reduced the overall mortality for trauma patients (OR 0.71 [0.56-0.90]). No significant reduction was seen in either the 24-hour mortality (OR 0.81 [0.57-1.14]) or the 30-day mortality (OR 0.73 [0.46-1.16]). In GMS MTP patients, there was a statistically significant increase in the percentage of platelet units wasted (MTP 12.8% vs non-MTP 8.1%; p ¼ 0.046). This increase was also seen in trauma MTP patients (MTP 12.2% vs non-MTP 4.0%; p < 0.001). No statistically significant difference was found in 24 -h death rate (15.0% vs. 23.8%, p = 0.181). The ABC scoring system used for trauma patients had a sensitivity and specificity of 81.8% and 41.2%, respectively.* ***Conclusion:*** *MTP may be used for both trauma and non-trauma patients to improve the outcomes of patients.*

Keywords: *Massive transfusion; massive transfusion protocol; ABC scoring, Hemorrhage.*

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INTRODUCTION

Massive Transfusion Protocol or MTP is a strategic way of blood component delivery which is simple to follow and the probable outcome of this process are predictable in most of the time. It is an effective way to deal with the situation when the patients are critically injured. A dramatic reduction in many of the complications including organ failure has been observed in receiving massive transfusions in that cases [1-4]. MTP is the management of 10 or more units of packed red blood cells (RBC) in less than 24 hours and it can be a lifesaving therapy in the treatment of severe bleeding due to injury. As per the volume of blood transfused during 24 hours equals to one blood volume (5liters), it is generally being considered as a massive transfusion. Besides, MTP can be also defined as 50% of the volume replaced within 3 hours, or when the rate of replacement is > 150 ml/ min [5,6]. However, the MTP is basically a treatment method which is commonly used in trauma cases. Trauma is considered to be a leading cause of hemorrhagic shock and subsequent mortality across the world [7]. Moreover, the availability of blood and blood products was a major challenge in treatment process which often hampers effective management of polytrauma patients [8]. But with the development of trauma centers and increasing awareness among the common people, MTP can now be initiated faster and especially in patients who are suffer with profound hypotension as a result of the trauma [9]. Although the accessibility of measures for stimulation of MTP in required cases but the preferences regarding when to administer blood and in what quantity often tends to prevail from the doctor who are in charge of treatment of the patients. Hence a simple score to assess the need for MTP was developed and now it is seen to be increasingly practice in most of the cases [10]. Although the MTP is to some extent algorithmic, but for this process a complex medical scenario is required, and the considerations for MTP initiation are often controlled by limited time and information [11,12]. As an alternative to existing scores like the Trauma Associated Severe Hemorrhage (TASH) and McLaughlin scores, the Assessment of Blood Consumption (ABC) score was developed in 2008-09 as a simple, reproducible tool for the early recognition of need for MTP [13]. However, some studies have also inspected the use of these protocols outside of the trauma cases. In gastrointestinal hemorrhage, the implementation of an MTP has been associated with decreased PRBC transfusion without increased incidence of adverse outcomes [14]. MTP has been applied to patients with non-traumatic hemorrhagic shocks. However, non-trauma patients are heterogeneous and differ from trauma patients [15-19].

Objective of the Study

The objective of this systematic review was as follows:

- To investigate whether rapid and efficient administration of blood products was achieved
- To assess the clinical outcomes of applying a massive transfusion protocol (MTP).
- To investigate whether an MTP could be used effectively in GMS patients without detrimentally impacting resource allocation.

METHODS & MATERIALS

This review included 9 original studies that reported the effect of the implementation of an MTP on trauma patients. It shows that MTP implementation improves overall survival, with a statistically significant reduction in the overall mortality. The key findings from the systematic review of 9 studies are the marked inconsistency and/or opaqueness in the reporting of mortality outcomes and implementing MPT. To date, this meta-analysis has the distinction of having the largest study population; it analysed data on the effect of an MTP on 4245 patients, from the most recent studies. It has focused on 3 clinically pertinent mortality outcomes, ABC score, reduction of blood products wastage and produced an analysis of studies on a critically injured and homogenous trauma population.

Inclusion Criteria:

- The studies which are already published and focused on implementing MPT in Trauma and non-trauma cases.
- The studies which focused on effectiveness of MPT use.

Exclusion Criteria:

- The studies which were not focused on MPT use were excluded from this systematic review.

RESULT

Table I: The authors, number of cases, publishing year and objective of the study:

Author	Case	Year	Objective of study
Hyun Woo Sun, M.D., Sang Bong Lee, M.D., Sung Jin Park, M.D., Chan Ik Park, M.D., Jae Hun Kim, M.D.	139	2020	To investigate whether rapid and efficient administration of blood products was achieved and whether clinical outcomes were improved by applying a massive transfusion protocol (MTP).
Rafael Consunji, Alaa Elseed, Ayman El-Menyar, Brijesh Sathian , Sandro Rizoli, Hassan Al-Thani , Ruben Peralta	3201	2020	The effect of massive transfusion protocol implementation on the survival of trauma patients
Chris Bell et. al.	45	2018	Optimum Accuracy of Massive Transfusion Protocol Activation
Lauren M McDaniel, BS, Matthew D Neal, MD, Jason L Sperry, MD, FACS, Louis H Alarcon, MD, FACS, Raquel M Forsythe, MD, FACS, Darrell Triulzi, MD, Andrew B Peitzman, MD, FACS, Jay S Raval, MD	64	2013	To investigate whether an MTP could be used effectively in GMS patients without detrimentally impacting resource allocation.

Dr Santoshkumar G Thakur, Dr Vishal C Bhatt, Dr Vernica Kala	20	2019	To understand the role of a simple scoring system to predict an early activation of Massive Transfusion Protocols (MTP)in polytrauma patients.
Terence O'Keeffe, MB, ChB, MSPH; Majed Refaai, MD; Kathryn Tchorz, MD; John E. Forestner, MD; Ravi Sarode, MD	132	2008	To Decrease Blood Component Use and Costs
Kyoung Won Yoon, Duck Cho, Dae-Sang Lee, Eunmi Gila, Keesang Yoo , Kyoung Jin Choi, Chi-Min Park	143	2018	Clinical impact of massive transfusion protocol implementation in non-traumatic patient
Lauren M. McDaniel, Darrell J. Triulzi, James Cramer, Brian S. Zuckerbraun, Jason L. Sperry, Andrew B. Peitzman,4 Jay S. Raval, and Matthew D. Neal4	483	2014	Massive Transfusion Protocol Activation Does Not Result in Preferential Use of Older Red Blood Cells
Ramesh Wijaya, et. al	18	2016	The use of massive transfusion protocol for trauma and non-trauma patients in a civilian setting: what can be done better.

Hyun Woo Sun, M.D et.al. in their study showed whether rapid and efficient administration of blood products was achieved and whether clinical outcomes were improved by applying a massive transfusion protocol (MTP). The sample size was 139 patients who received massive transfusions. Among them the non-MTP was 84 and MTP was 55. No significant differences were found in the units of PRBC (23.2 vs. 25.3, respectively; p=0.46), fresh frozen plasma (FFP) (21.1 vs. 24.4, respectively; p=0.40), and platelets (PLT) (15.4 vs. 17.0, respectively; p=0.54) administered in the first 24 hours [20]. Rafael Consunji et. al. in their report include14 studies which met the inclusion criteria and analyze outcomes of 3,201 trauma patients. In that study a wide range of outcomes, study population, and process indicators were utilized by the several authors. MTP significantly reduced the overall mortality for trauma patients (OR 0.71 [0.56-0.90]). No significant reduction was seen in either the 24-hour mortality (OR 0.81 [0.57-1.14]) or the 30-day mortality (OR 0.73 [0.46-1.16]). However, as mortality timing was not fixed, mortality was statistically reduced (OR 0.69 [0.55-0.86]) [21]. Chris Bell et.al. in their study received responses from 35 clinicians in the TACS group and 10 clinicians in the CLMS group. 45.7% of respondents in the TACS group had an MTP overactivation rate of 5% - 10% (vs. 60% of the CLMS group; not significant (NS)). 34.2% of the respondents in the TACS group had an MTP under-activation rate of less than 5%, and 60% of respondents in the CLMS group had an

under-activation rate of less than 5% (NS). A significantly greater proportion of respondents in the TACS group felt that an anticipated need for > 20 units of packed red blood cells within the next 24 hours was an acceptable criterion for MTP activation. Respondents in the CLMS group were more likely to consider "poor communication" because of blood component wastage [22]. In the study of Lauren M McDaniel, BS, et. al. the protocol was showed overactivated in 53.8% of GMS patients. In GMS MTP patients, fresh frozen plasma units were issued a median of 7 minutes earlier than in GMS non-MTP patients (MTP: median 1.0 minute; interquartile range [IQR] 0.0 to 2.0 minutes vs non-MTP: median 8.0 minutes; IQR 0.0 to 37.5 minutes; p ¼ 0.009), and platelet units were issued 17 minutes earlier (MTP: median 7.0 minutes; IQR 0.0 to 15.0 minutes vs non-MTP: median 24.0 minutes; IQR 9.0 to 96.0 minutes; p ¼ 0.010). In GMS MTP patients, there was a statistically significant increase in the percentage of platelet units wasted (MTP 12.8% vs non-MTP 8.1%; p ¼ 0.046). This increase was also seen in trauma MTP patients (MTP 12.2% vs non-MTP 4.0%; p < 0.001) [23]. Dr. Santoshkumar G Thakur, et. al. showed 20 patients received blood products in the form of MTP. 80% patients had orthopedic injuries with long bone fractures with 40% were suffering with polytrauma. MTP was activated within 1 hour in most of the cases [24]. Terence O'Keeffe, MB, ChB, MSPH, et. al. in their study showed the activation of the MTP and a significant decrease in packed red blood cells, plasma, and platelet use. The improvement time for the first shipment was <10 minutes, and the duration between the 1st and 2nd shipments was reduced from 42 to 18 minutes, compared to the previous record. The study also showed the decreased use of blood products and saved $2270 per patient or an annual savings of $200 000, despite increased costs for recombinant facts. There was no difference in mortality in either group and it was around 50%. Also, the thromboembolic complications did not increase, despite a significant increase in the use of recombinant factor VII [25]. Kyoung Won Yoon, Duck Cho, et. al. in their study found that 80 patients' massive transfusion occurred before MTP implementation and 63 patients' massive transfusion occurred after MTP implementation. No statistically significant difference was found in 24 -h death rate (15.0% vs. 23.8%, p = 0.181), or 30-day death rate (43.8% vs. 36.5%, p = 0.381). Use of an anti-fibrinolytic agent was more frequent in patients after the MTP implementation (31.3% vs. 55.6%, p = 0.003). A statistically significant difference was found in the lowest body temperature of the two groups during the 24 -h period (34.7 °C vs. 35.6 °C, p < 0.001). Transfusion ratio of plasma to pRBC was numerically improved after the MTP implementation (1:1.91 vs. 1:1.58, p = 0.173). Earlier initiation of pRBC transfusion was achieved after implementation (51 min vs. 40 min, p = 0.042) [26]. Lauren M. McDaniel, Darrell J. et. al. in their study identified 176 patients transfused with ≥10 RBC units in a routine manner over 24 hours signified the nonemergency release (nER) cohort. Though the median age of ER RBCs was 5 days older than nER RBCs (ER 20, nER 15 days, *P* < 0.001), both fell within the third week of storage. Regardless of MTP

activation, transfused ER RBCs had the same median age (MTP 20, no-MTP 20 days, P = 0.069). In the ER cohort, transition to type-specific blood components increased the median age of transfused RBC units from 17 to 36 days (P < 0.001) [27]. In the study of Ramesh Wijaya, Hui Min Gloria Cheng and Chee Keong Chong, only 39.1% of all cases with MTP activation received MTs; 39.8% of the MTs were for non-trauma patients. Mean fresh frozen plasma to packed red blood cells (pRBC) ratio achieved with MTP was 0.741, while mean platelet to pRBC ratio was 0.213. The 24-hour mortality rate for all patients who received an MT upon MTP activation was 33.3% (45.5% vs. 14.3%). The ABC scoring system used for trauma patients had a sensitivity and specificity of 81.8% and 41.2%, respectively [28].

DISCUSSION

Massive transfusion protocol or MTP is a common practice throughout the world. After thoroughly go through several previous studies his systematic review found that the transfusions for obstetric bleeding, the amount of administered FFP increase the amount of RBC utilized. Those studies had found that the mortality rate from massive obstetric bleeding is significantly reduced relative to traumatic bleeding [29-34]. In a study there was a mention of two major guidelines which were available for MT: the European guidelines by the Task Force for Advanced Bleeding Care in Trauma (updated in 2013) and the Trauma Quality Improvement Program (TQIP), recommended by the American College of Surgeons [35]. The study of Rafael Consunji et. al. found a significant reduction in mortality due to MTP implementation and they emphasis that, it should be recommended to all institutions to manage acutely injured patients [21]. Besides, several steps had been taken to increase public awareness regarding the blood donation in order to advance the blood procurement, blood bank storage methods and faster availability of blood products for patients in case of emergency and ensure the reduction of the mortality rate because of the unavailability of blood [36]. Luckily, several studies had found an increased survival rate through use of massive transfusions in trauma patients [37,38]. It is a pleasure that, the hospitals having trauma centers also had their own robust blood bank services to activate MTP in time of emergency [38]. However, most of the retrospective studies basically focused on transfusions for obstetric bleeding and found that there should be a necessary direction for the implementation of MTP in the case of obstetrics. However, MTPs can include preparation and administration of blood products based on laboratory test results, predetermined transfusion packages of adult MTPs and pediatric MTPs or integration of both [39]. The number and schedule of blood component delivery, laboratory testing algorithms, and other factors of the MTPs varies between institutions but recently most of the time MTPs use pre-determined transfusion packages [39]. Though the MTPs may vary in their pre-determined transfusion packages the platelet and plasma units had consistence with RBC units [40-45]. In the study of Ramesh Wijaya, Hui Min Gloria Cheng and Chee Keong Chong, only 39.1% of all cases with MTP activation received MTs and among them 39.8% were the non-trauma patients [28].

Hyun Woo Sun, M.D et.al. in their study showed whether rapid and efficient administration of blood products was achieved and whether clinical outcomes were improved by applying a massive transfusion protocol (MTP). They claimed hemorrhage as the main cause of death in patients with severe trauma and has a high mortality rate (39–54%) [26]. In that study, the total count of PRBC, FFP, and PLT units which were administered before and after MTP implementation was not significantly different. But the study found that after the implementation of the MTP, the average time to transfusion decreased from 41.1 minutes to 14.9 minutes (p=0.003). Rafael Consunji et. al. in their study discussed 14 studies which met the inclusion criteria and analyze outcomes of 3,201 trauma patients. The study found a significant reduction in mortality implementing the MTP and recommended MPT to manage severely injured patients. The study emphasis the use of standard nomenclature, indicators, protocols and patient populations in all future MTP studies to get better result. Chris Bell et. al. in their study received responses from 35 clinicians in the TACS group and 10 clinicians in the CLMS group which was consistent with the findings of a University of Pittsburgh study which showed the benefits of MTP implementation in non-trauma patients despite an over-activation rate of 53.8% [22]. For trauma patients every minute was counted as each minute of delay in receiving blood increased patient morbidity and mortality [22]. They emphasized a more liberal implementation of MTP to reduce blood component wastage, as 25% of acutely injured patients were coagulopathic and early aggressive resuscitation may reduce the overall blood need [22]. In the study of Lauren M McDaniel, BS, et. al. the protocol was showed overactivated in 53.8% of GMS patients which was similar with the study of Morse and colleagues, as GMS patients were transfused with similar ratios as trauma patients and that these ratios approached their protocol goal [17]. The protocol stated a ratio of 1:1:0.5 for the initial release of products. No statistically significant differences found between MTP and non-MTP cohorts which suggested that clinicians at that institution could practice hemostatic resuscitation, though the protocol was not formally initiated. Higher FFP: PRBC and PLT:PRBC ratios was found in GMS MTP patients compared with GMS non-MTP patients [23]. This study also agreed with Morse and colleagues on overactivation the rate of overactivation in GMS patients was much higher (53.8%) than that for trauma patients (19.2%) [17]. Dr. Santoshkumar G Thakur, et. al. showed 20 patients received blood products in the form of MTP [18-20]. The ABC score was used extensively in the ED to recognize the need for MTP. Increase in the time to achieve homeostasis and increase in mortality with any delay in activation and initiation of MTP was also found. The study suggested the use of the ABC score as a simple and highly consistent predictor and must be mandated in all Eds and control of hemorrhagic shock has a direct impact on the mortality of polytrauma patients [24]. Terence O'Keeffe, MB, ChB, MSPH, et. al. in their study showed the activation of the MTP and a significant decrease in packed red blood cells, plasma, and platelet use and a significant decrease in the number of blood components transfused. The coagulation testing

turnaround time was 30-40 minutes but coagulation tests do not truly represent the current hemostatic profile of a patient who is exsanguinating but represents the state of hemostasis 30-40 minutes earlier. In that study the authors tend to avoid treatment decisions depending on inaccurate data, and preferred to transfuse blood and components in predefined ratios. This concept was the evidence that more plasma should be given earlier to prevent the early coagulopathy in trauma cases. Although the blood transfusions reduced but no improvement was found in mortality. However, the authors here claimed that blood transfusion and blood components wasn't risk free, and hence a protocol should be welcome so that unnecessary transfusions can be avoid and issues regarding transfusion-related acute lung injury and unknown blood-borne diseases can be controlled [25]. Kyoung Won Yoon, Duck Cho, et. al. in their study found that massive transfusion occurred before MTP implementation in 80 cases and after MTP implementation in 63 cases. No statistically significant difference was found in 24 -h death rate and no significant effect of MTP on death rate and delayed MTP activation in non-trauma patients was found as well. The use of tranexamic acid was timely recommended during the recovery of patients with hemorrhage [16]. A statistically significant increase of use of tranexamic acid from 31% to more than 55% was found after MPT. The study also found that the majority of the studies focused on MTP use and trauma cases exclusively. However, some studies also examined the benefits of MPT implementation in non-trauma patient. No association was found between a high ratio of plasma to pRBC with reduced death rate in some studies which suggests that one should not assume that the transfusion of a high plasma to pRBC ratio will always benefit all patient [26]. Lauren M. McDaniel, Darrell J. et. al. in their study showed that massive transfusion protocol activation does not result in preferential use of older red blood cells. RBC units issued to massively transfused patients in either an emergency or nonemergency cases. After MPT, the ABO type influenced the age of RBCs in patients. However, the clinical guidelines of storage age needed to be determined in ongoing randomized trials [27]. The greatest limitation of this systematic review is all study was performed as a retrospective analysis. Besides, no articles make specific mention of platelet ratios when discussing an MTP. Massive resuscitation makes the lungs susceptible to the spectrum of lung injury via volume or immune mediated mechanisms. Further studies are needed in this field to clarify the optimal ratios of blood products, treatment based on underlying clinical disorder, use of alternative therapies, and integration of laboratory testing results in the management of massively bleeding patients.

CONCLUSION

MTP has been designed to facilitate delivery of large volumes of blood and blood products to a patient who requires them to prevent exsanguination. Although no significant differences were found in the clinical outcomes of patients who had undergone severe trauma and non-trauma patients in most of the studies after implementing the MTP but the clinicians are claimed that MPT reduce the mortality rate to some extent. The implementation of

a hospital-specific MTP protocol to improve the supply and utilization of blood products to physicians managing major obstetric hemorrhage is also needed. Collaboration between involved parties is necessary for MTP protocol development to improve patient outcomes and reduce blood wastage. Throughout the recovery, the patient should be closely monitored and both metabolic and coagulation abnormalities corrected. Prompt use of the ABC score for trauma patients is highly predictive of the need for transfusion in hemorrhagic shock.

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