ORIGINAL ARTICLE

Outcome Evaluation of Massive Transfusion Protocol in Emergency Departments, Hospital Putrajaya and Hospital Ampang: A 3-year Retrospective Study

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ABSTRACT

Introduction: Massive Transfusion Protocol (MTP) is a rapid administration of large amount of blood product at a fixed ratio of 1:1:1 of fresh frozen plasma (FFP), platelets (PLT) and a PRBC. The primary objective for this study was to evaluate the transfusion delivery time (TDT), mortality and length of hospital stay (LOS) between patients with and without MTP activation. **Materials and methods:** This is a retrospective cohort study of 253 trauma and non-trauma patients who underwent blood transfusion in the emergency departments (ED) of Hospital Putrajaya and Hospital Ampang from January 2017 until December 2019. Groups comparison was conducted between patients with the MTP and non-MTP groups, and trauma and non-trauma groups. Data was obtained from patient's electronic medical record. **Results:** MTP was activated in 49 patients. The prevalence of MTP was higher in trauma patients compared to non-trauma. MTP resulted in shorter TDT and reduced 24-hour mortality in all patients receiving blood transfusion in ED. There were no significant association between MTP activation and LOS, and mortality reduction in the trauma and non-trauma groups. No data on transfusion error was obtained. **Conclusion:** This study demonstrated a significant association between MTP and improved patient's outcome by reducing TDT and 24-hour mortality in all patients who received blood transfusion in ED. The findings of this study can be utilised for the development of national MTP clinical practice guideline (CPG).
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Keywords: Massive transfusion protocol, Emergency and trauma department, Outcome, Hospital Putrajaya, Hospital Ampang

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INTRODUCTION

Massive blood loss is encountered during various situations such as polytrauma, upper gastrointestinal bleed (UGIB), obstetric emergency such as postpartum haemorrhage (PPH) and placenta abruptio, or any tumour bleed in malignancy. In polytrauma, massive haemorrhage is a major preventable cause of death with adequate and optimized haemostatic control and blood transfusion (1).

Massive transfusion protocol (MTP) is designed to interrupt the lethal trial of acidosis, hypothermia and coagulopathy that developed with massive bleeding. Massive transfusion is defined as the delivery of ten or more units of packed red cell within 24 hours, replacement of 50% total blood volume within 3 hours or replacement of one entire blood volume within 24 hours (2). MTP is a transfusion of a large blood volume in a fixed ratio 1:1:1 of fresh frozen plasma (FFP), platelet (PLT) and packed red blood cell (PRBC). It provides specific guidelines in the management of blood transfusion that includes clinical, laboratory, blood bank and logistic response to ensure effective management of massive haemorrhage (3).

MTP were first established and developed in the trauma setting in military theatres to facilitate and coordinate large transfusion volumes (4). Subsequently it was adapted to the civilian trauma setting and involve multilevel work processes. Activation of MTP, which takes place at a discretion of a senior physician, can

be guided by scoring systems that predict the need for massive transfusion. Once activated, MTP set in motion a string of events to facilitate blood product release, decrease delays and allow timely delivery of blood products from the blood bank until the protocol ceases. MTP facilitates close adherence to ideal haemostatic resuscitation - a transfusion ratio of 1:1:1 of FFP, PLT and PRBC (5).

In a local setting, MTP was first introduced in Hospital Putrajaya in January 2017 (6). It was initiated even earlier in Hospital Ampang in 2009 (7). Activation of the MTP in the Emergency Department (ED) requires a discretion from an emergency physician based on the specific criteria. The indication for blood transfusion in the ED of both Hospital Putrajaya and Hospital Ampang are similar, which are active bleeding leading to haemodynamic instability or class III haemorrhagic shock. Not only that, the indication for MTP in both hospitals are also similar, which is rapid blood loss more than 150mls per min leading to haemodynamic instability and circulatory failure. Once a clinician (either the emergency physician or the specialist from a primary team) decided to activate the MTP, a call will be made and a blood product request form will be sent to the blood bank. Once notified, the blood bank will begin a continuous preparation of blood and blood product as per respective MTP package. The prepared blood product will be delivered to the ED, once arrived, they will be cross checked by the attending medical officers and staff nurses before transfusion started. A continuous blood transfusion monitoring shall be performed and documented on each patient. The deactivation of MTP will be decided by clinicians based on improving patients' clinical condition or change in medical direction of treatment, such as in the case of newly decided not for active resuscitation (NAR) status. Several studies had shown that MTP improved survival in trauma patients and the data are still lacking for the non-trauma group (8). Since MTP introduction in 2017 in Hospital Putrajaya and 2009 in Hospital Ampang, no publication of outcome has been done to verify the implementation of the protocol. The indication for the blood transfusion in the respective emergency departments are patients who are actively bleeding causing circulatory failure and haemodynamic instability, or class III shock. The objective of this study is to evaluate the association between MTP activation with the outcome of trauma and non-trauma patients receiving blood transfusion in ED.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study of patients in Hospital Putrajaya and Hospital Ampang who received blood transfusion in the respective emergency departments from January 2017 till December 2019. The inclusion criteria are all patients of all age who received blood transfusion in the emergency departments of the respective hospitals, either they are trauma or non-trauma presentations. Patients who had previous history of transfusion reaction and issued no-active-resuscitation (NAR) were excluded. Data was obtained from patient's electronic medical record (EMR) provided by the information technology department and the blood bank. The indication for blood transfusion in the ED are patients who are actively bleeding causing haemodynamic instability or in III haemorrhagic shock.

Data collection and analysis

The collected EMR data included demographic characteristics and causes of bleeding, either trauma or non-trauma cause. The prevalence of MTP in trauma and non-trauma patients were compared. They were divided into 2 major groups; the MTP and non-MTP groups. The outcomes were evaluated based on transfusion delivery time (TDT), which is the time of MTP activation to time of first blood received by patient in the MTP activated group, and the time of first blood request made to blood bank to time of first blood received by patient in the non-MTP group, the mortality rate (24-hour and 30-day mortality), the length of hospital stay (LOS) until discharge and the rate of transfusion error (9). All data were collected using a standardised form. Data were descriptively and categorically analysed using SPSS Version 27. Univariable and multivariable logistic regression models were used to estimate variables associated with outcome following MTP activation.

Ethical Clearance

Ethical approvals were obtained from the National Medical Research and Ethics Committee (NMRR-20-1644-55079) and Pusat Perubatan Universiti Kebangsaan Malaysia Ethics Committee (UKM/PPI/8/JEP-2020-509).

RESULTS

Baseline characteristics

A total of 253 patients were enrolled, of which 149 patients were from Hospital Putrajaya while the other 104 patients were from Hospital Ampang (Table I). All the patients who received blood transfusion in the respective emergency departments were those who were actively bleeding leading to haemodynamic instability or in class III shock. The mean age of patients receiving blood transfusion in emergency departments was 44 years old. The patients receiving MTP were generally younger in comparison to the non-MTP group (median age 32 vs 46, $p<0.001$). There was higher prevalence of MTP and blood transfusion overall for male patients compare to female (34 vs 15, 164 vs 69, $p<0.001$).

Table I: Demographic

Demographic Data				
Variables	**MTP**	**NON-MTP**	**All MTP and NON-MTP**	***p* value**
Total no of patients received blood transfusion in ED, n(%)	49 (19)	204 (81)	253 (100)	<0.001
Age (year-old)	32 (IQR 26-39)	46 (IQR 32-61)	44 ±17	<0.001
Sex, n(%)				
Male	34 (13)	130 (51)	164 (64)	<0.001
Female	15 (6)	74 (29)	69 (27)	
Causes of bleeding, n(%)				
Trauma	39 (15)	73 (29)	112 (44)	<0.001
Non-Trauma	10 (4)	131(52)	141 (56)	
ABC score, n(%)				
0	0 (0)	13 (5)	13 (5)	<0.001
1	0 (0)	54 (21)	54 (21)	
2	17 (7)	96 (38)	113 (45)	
3	22 (9)	33 (13)	55 (22)	
4	10 (4)	8 (3)	18 (7)	
Transfusion Delivery Time (TDT), min	35 (IQR 20-48)	55 (IQR 38-80)	56 ±32	<0.001
Mortality, n(%)				
Yes, within 24 hours	14 (5)	24 (9)	38 (15)	0.003
Yes, within 30 days	3 (1)	25 (10)	28 (11)	0.215
Total mortality	17 (7)	49 (19)	66 (26)	0.125
Survived	29 (11)	142 (56)	171 (67)	0.125
Lost to follow up	3 (1)	13 (5)	16 (6)	

They were categorised into trauma and non-trauma groups. In the trauma group, the causes of bleeding include head and neck trauma, isolated abdominal trauma, isolated chest trauma, long bone trauma or polytrauma. In the non-trauma group, the causes of bleeding were obstetrics and gynaecology (O&G) emergencies, upper gastro-intestinal bleeding (UGIB), lower gastro-intestinal bleeding (LGIB), tumour bleed, ruptured abdominal aortic aneurysm (AAA), dengue shock or haematological malignancy. O&G emergencies include ruptured ectopic pregnancy, PPH and miscarriages. The occurrence of blood transfusion in ED were almost similar in both trauma and non-trauma (112 (44%) vs 141 (56%), p<0.001).

Although the total number of patients receiving blood transfusion in ED of the respective hospitals were 253, MTP was activated in only 49 (19%) of cases. This was a small percentage considering that 186 (74) of them had ABC score of ≥2, which already fulfilled the criteria for MTP activation (Table 1). There was no significant difference between the number of MTP activated in Hospital Putrajaya and Hospital Ampang (25(17%) vs 24(23%), p=0.212).

The prevalence of MTP in trauma vs non-trauma patients Only 49 (19%) out of 253 patients who received blood transfusion in ED had the MTP activated, although 186 (74%) of them actually fulfilled the criteria for MTP activation, which is ABC score ≥2. Meanwhile, a total of 29 patients received massive transfusion throughout their hospital stay despite MTP not activated. 142 (56%) were non-trauma patients while the other 111 (44%) were trauma patients. The prevalence of MTP activation was higher in trauma group compare to non-trauma (34 (15%) vs 15 (6%,) p<0.001). In the non-trauma group, MTP was activated in only 10 (7%) of cases, whereas 39 (15%) of patients in the trauma group had the protocol activated (Figure 1).

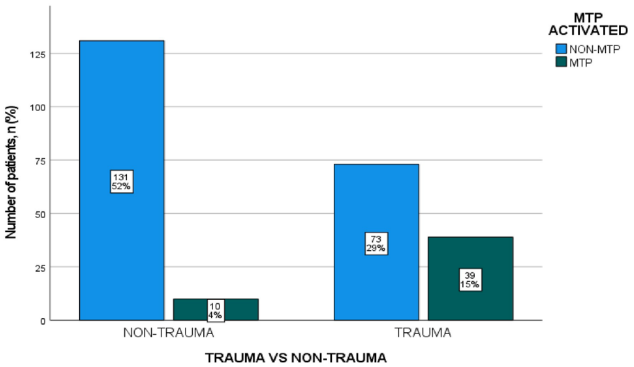

Figure 1: The prevalence of MTP activation in trauma and non-trauma groups in all patients receiving blood transfusion in ED. The prevalence of MTP is higher in trauma than non-trauma (p<0.001).

Transfusion delivery time (TDT)

Result showed that the TDT, which was the time interval between MTP activation or request for blood product to blood bank, to the time of first blood or blood product received by patients, was shorter in the MTP activated

group compared to the non-MTP activated group (median 35min vs 55min, p<0.001). Comparing between trauma and non-trauma patients, the median TDT is shorter at 45min vs 55min respectively. Meanwhile, the TDT for the MTP group were shorter for non-trauma group compared to trauma (median 32min vs 38min). In the both trauma and non-trauma groups, patients who had the MTP activated demonstrated a shorter TDT (median 38min vs 50min, p<0.001 and 32min vs 60min, p=0.001) (Table II).

Table II: Transfusion Delivery Time (TDT) in trauma, non-trauma and all patients

Transfusion Delivery Time (TDT)					
		MTP n=49	**NON-MTP n=204**	**All MTP and NON-MTP n=253**	***p* value**
TDT (min)	**All Trauma and Non-Trauma** n=253	35 (IQR 20-48)	55 (IQR 38-80)	57 ±32	<0.001
	Trauma n=112	38 (IQR 20-50)	50 (IQR 34-75)	45 (IQR 30-60)	<0.001
	Non-Trauma n=142	32 (IQR 14-46)	60 (IQR 40-80)	55 (IQR 38-80)	0.001

24-hour and 30-day mortality rate

Table III summarises the mortality among patients who received blood transfusion in ED. 171 (68%) out of 253 patients survived, while the other 66 (26%) died. Out of the 66, 38 (15%) patients succumbed to death within 24 hours while another 28 (11%) patients died within 30 days. The result showed a significant association between MTP activation and reduced 24-hour mortality in all trauma and non-trauma patients (14 (6%) vs 24 (10%), p=0.003). Logistic regression analysis supported this finding by showing activation of MTP may lead reduction in 24-hour mortality at odd ratio (OR) 0.33. Nevertheless, in the trauma patients, the 24-hour mortality rate was significantly higher in the MTP group compared to the non-MTP (13(12%) vs 11(10%), p=0.033).

Table III: Mortality for trauma, non-trauma and all patients

Mortality for Trauma, Non-Trauma and all patients						
			MTP	**NON-MTP**	**All MTP and NON-MTP**	***p* value**
Mortality	**All Trauma**	Within 24 hours, n(%)	14 (6)	24 (10)	38 (15)	0.003
	and Non-	Within 30 days, n(%)	3 (1)	25 (10)	28 (11)	0.215
	Trauma	Total mortality, n(%)	17 (7)	49 (19)	66 (26)	0.125
	n=253	Survived, n(%)	29 (12)	142 (56)	171 (68)	0.125
		Lost to follow up, n(%)	3 (1)	13 (5)	16 (6)	
	Trauma	Within 24 hours, n(%)	13 (12)	11 (10)	24 (21)	0.033
	n=112	Within 30 days, n(%)	3 (3)	7 (6)	10 (9)	0.677
		Total mortality, n(%)	16 (6)	18 (7)	34 (13)	0.098
		Survived, n(%)	20 (18)	46 (41)	66 (59)	0.098
		Lost to follow up, n(%)	3 (3)	9 (8)	12 (11)	
	Non-Trauma	Within 24 hours, n(%)	1 (0.7)	13 (9)	14 (10)	0.981
	n=141	Within 30 days, n(%)	0 (0)	18 (13)	18 (13)	0.201
		Total mortality, n(%)	1 (0.3)	31 (12)	32 (12)	0.300
		Survived, n(%)	9 (6)	96 (68)	105 (75)	0.300
		Lost to follow up, n(%)	0 (0)	4 (3)	4 (3)	

Table IV summarises the univariable and multivariable LR analysis to explore the association between MTP activation and mortality. In the univariable analysis, MTP activation was significantly associated with reduction of mortality within 24 hours with the OR 0.33 (95% CI 0.15-0.70, p=0.04). However, no significant association was observed with total and 30-day mortality. In the multivariable analysis, MTP activation remains a significant predictor for a reduction in 24-hour mortality even after the adjustment for age and sex, with the OR 0.31 (95% CI 0.13-0.72, p=0.006). Moreover, the model adjusted for age and sex improved the R2 from 5.5% to 15.2%.

Table IV: Logistic Regression (LR) analysis assessing the relationship between MTP activation and mortality

Univariate Logistic Regression				
Variables	**Odds Ratio (OR)**	**95% CI**	***p* value**	**R^2 (%)**
Mortality within 24 hours	0.33	0.15-0.70	0.04	5.5
Mortality within 30 days	2.159	0.62-7.49	0.225	1.4
Total mortality	0.59	0.30-1.16	0.127	1.4
Multivariate Logistic Regression				
Variable adjusted for Age and Sex				
Mortality within 24 hours	0.31	0.13-0.72	0.006	15.2

OR – Odds Ratio
CI – Confidence Interval

The MTP activation showed a significant reduction in the 24-hour mortality rate in all trauma and non-trauma patients in the MTP group compared to the non-MTP group. However, the result was not statistically significant for the 30-day mortality and for the total mortality. The remaining 16 (6%) patients were lost to follow up due to either transfer to the other hospitals for step-up care, or at own risk (AOR) discharge.

Length of hospital stay (LOS)
The result was not statistically significant for LOS in either the trauma, non-trauma or all patients. For the non-trauma patients, the LOS were increased in the MTP group compared to non-MTP group (7days vs 4days, p=0.28). In contrast, the LOS were shorter in the MTP compared to the non-MTP group for the trauma patients (6days vs 8days, p=0.32). In all trauma and non-trauma patients, the LOS was longer in the MTP activated group compared to non-MTP group (7days vs 5days, p=0.77).

Transfusion error
No data of transfusion error was obtained in this study. Therefore, we were unable to proceed with the statistical analysis.

DISCUSSION

Prevalence of MTP activation in trauma patients
The result showed that the prevalence of MTP is higher in trauma group compare to the non-trauma group. The outcome benefit of MTP has been proven in several studies involving trauma patients such as the renowned PROMMT and PROPPR trial (11, 12), however, there are still limited evidence of in non-trauma patients. A systematic review and meta-analyses by Somer et al. concluded that there is limited evidence that the implementation MTP may be associated with decreased mortality in-non trauma patient (8). Based on the current knowledge regarding the proven effectiveness of MTP, there is a lower threshold for MTP activation among emergency physicians for trauma cases compare to the non-trauma in emergency departments. A study by Wan Zulkipli et al. reported that the prevalence of MTP activation in Hospital Universiti Sains Malaysia (HUSM) was 0.07% out of total patients who were admitted. The MTP was activated in 56.3% trauma cases while the remaining 43.7% were non trauma (13). Wijaya et al also emphasized that a higher number of MTP was activated for trauma cases compare to non-trauma (69.9% vs 39.1%) in Changi General Hospital, Singapore (2). Similar to this study, both discussed studies supported the findings of the prevalence of MTP is higher in trauma compared to non-trauma.

Transfusion delivery time (TDT) in MTP group
In our study, MTP resulted in shorter TDT in all three categoriesof patients who received blood transfusion in ED This is supported by a sub-analysis of PROPPR trial, which showed that MTP was significantly associated with reduced time from activation of MTP to delivery of first MTP cooler (14, 15). ACS-QTIP Best Practices recommended initial massive transfusion cooler delivery within 15 minutes of protocol activation, with a goal of 10 minutes (14). Once MTP is activated, the blood bank will begin a continuous preparation and supply of blood and blood product according to the MTP package as shown in the workflow sheet. This will ensure an accurate and timely delivery of blood products to patients. The preparation for the second MTP package would be continuous right after the first MTP package was supplied to the requested department. This expedited process results in shorter transfusion delivery time in MTP. As haemorrhage is a reversible cause of death in trauma and non-trauma bleeding, early recognition and prompt blood transfusion is mandatory to allow rapid restoration of circulating red cells, plasma proteins and platelets, concurrent with definitive control of bleeding (16).

Mortality rates in MTP group
This study demonstrated a significant association between MTP activation and reduced 24-hour mortality in all trauma and non-trauma patients who were transfused in ED. However, our study also suggested an association between MTP activation and increased 24-hour mortality rate in trauma patients. This is contradictory to a meta-analysis by Consunji et al. which showed MTP significantly reduced the overall mortality for trauma patients (18). The possible confounding factors to our result was a concomitant severe traumatic brain injury in trauma patients which contributed to the mortality. In our study, there was no significant association between MTP and reduced 24-hour or 30-day mortality rate in the non-trauma patients. This is supported by a

retrospective study by Yoon et al. which concluded that MTP did not result in statistically significant death-rate reduction in non-trauma patients (19) While MTP had been proven to reduce mortality in trauma patients, there are still limited data of its efficacy in the non-trauma group (8). Haemorrhage is the number one preventable cause of death in trauma, thus the golden one hour of resuscitation is important to prevent mortality (20). The same concept can also be applied to the non-trauma bleeding such as UGIB, ruptured ectopic pregnancy or postpartum haemorrhage. The early and timely delivery of blood/blood product during resuscitation restores haemostasis and prevents further progression into the lethal triad (21).

Length of hospital stay

There was no association between MTP activation and shorter LOS in this study. This is comparable to a retrospective study by Van Der Meij et al which showed that there was no significant association between MTP and shorter LOS among trauma patients (22). In contrast, a retrospective study by Nunn et al showed that the LOS was shortened from 31 to 26 days after the MTP implementation compare to before the procedure was introduced (23). The patients who received MTP were more likely to survive, thus the likelihood of developing the complications of polytrauma (rhabdomylosis, fat embolism syndrome, trauma induced coagulopathy) and MTP (dilutional coagulopathy, electrolyte imbalances, immune haemolysis, air embolism) was higher, leading to prolonged hospital stay (24). Once the hospital stay was extended, there is greater likelihood of developing hospital acquired infections, deep vein thrombosis or pulmonary embolism, which causes even longer hospital admissions (25).

Limitations

Since this is a retrospective study, the data collection heavily relied on the documentations of the doctors, staff nurses and assistant medical officers in the electronic medical records (EMR). Some details such as time of MTP activation, time of blood product arrived to ED, and time of blood transfused to patients was not being written properly in the EMR. This resulted in less accurate transfusion delivery time as the documentation of event was always done retrospectively. Combining trauma and non-trauma cases can lead to numerous confounding factors that may influence the outcomes. Each case type has distinct characteristics that can affect the results differently.

Currently, there is no standardised protocol for MTP among the hospitals in Malaysia. All different hospitals have different activation criteria and workflows, as well as scoring system to guide the decision making to activate MTP. The MTP activation criteria for both Hospital Putrajaya and Hospital Ampang is similar, which are rapid blood loss of more than 150mls per min leading to circulatory failure and haemodynamic instability. One may appreciate that these criteria are neither specific nor objective in comparison to the more renowned existing MTP criteria such as the ABC score or Transfusion Associated Severe Haemorrhage (TASH) score. This, combined with possible lack of awareness among clinicians about the indication of MTP may lead to higher threshold to activate MTP, thus resulted in lower number of MTP activated when it was actually indicated. There were a lot of similarities in the criteria, workflow and monitoring of MTP in both Hospital Ampang and Putrajaya, thus enabling the data to be analysed together. It is also important to note that data was collected from two different hospitals, with similar activation protocol and only minimal different package. This minimal operation difference may exist that is not captured by data which may influence the result. In Hospital Putrajaya, the first MTP cycle include 6 units of cryoprecipitate, 4 units of PRBC and 4 units of FFP (24). On the other hand, the first MTP cycle in Hospital Ampang consisted of 4 units PRBC and 4 units FFP without the cryoprecipitate. Nevertheless, the 6 units cryoprecipitate will be given in the second MTP cycle (25). No data was obtained for rate of transfusion error, possibly due to limited number of samples in this study.

Recommendation

Since MTP is activated in a small number of patients who actually fulfilled the criteria, more training should be done to create awareness of the indication for MTP, such as bedside teaching or continuous medical education (CME) on MTP implementation. A CPG for MTP should be developed at a national level to standardize the process workflow among all tertiary hospitals in Malaysia. The CPG should outline simple and objective criteria for MTP activation using a pre-existing scoring system such as Assessment of Blood Consumption (ABC) score or Trauma Associated Severe Haemorrhage (TASH). Based on our study, one can appreciate that the TDT of 35 mins in the MTP group fell far from the recommended ACS-QTIPS time frame of 15 mins from the time of MTP activation to the time of first blood received by patients. This CPG should also recommend on an acceptable TDT which is more suitable for Malaysian hospital settings and outline a comprehensive process workflow to achieve the targeted TDT.

CONCLUSION

Activation of the MTP is significantly associated with improved outcomes notably in the aspect of time to definitive treatment (TDT) and 24-hour mortality among all patients receiving blood transfusions in the emergency eepartments. However, MTP activation was paradoxically linked to increased 24-hour mortality among trauma patients. Trauma and non-trauma cases have unique clinical characteristics and management pathways, which should be considered when evaluating the true impact of MTP activation on patient outcomes. The results emphasize the potential advantages of

implementing a standardized MTP, which could serve as the basis for developing a national clinical practice guideline to enhance transfusion management in emergency settings.

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