STUDY ON PRACTICE OF MASSIVE TRANSFUSION PROTOCOL ACTIVATION IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Abstract
Massive transfusion protocol (MTP) was designed to improve the outcome of patients at risk of massive haemorrhage. This study focused on the prevalence, indications, factors associated with indication of MTP activation cases and twenty-four-hour mortality among those who received MTP in Hospital Universiti Sains Malaysia (USM). A retrospective cross-sectional study was performed on 110 patients for whom MTP was activated in Hospital USM. Data were extracted from the medical records and blood bank system (MyTransfusi). Descriptive statistics and logistic regression were used for statistical analysis. A total of 273,087 patients were admitted to Hospital USM and 193 patients required MTP activation during the study period. The prevalence of MTP activation was only 0.07%. This study included 110 MTP activation cases which consisted of 62 (56.3%) trauma and 48 (43.7%) non-trauma patients. The overall mean age of patients was 40.0 years old, and majority were male (66.4%). The two most common MTP activation indications were motor vehicle accidents (93.5%) and gastrointestinal bleeding (50%). Female and presence of comorbidity significantly associated with MTP activation indication. Meanwhile, no emergency procedure and non-compliance to activated MTP were significantly associated with high mortality within twenty-four-hour post MTP activation. The prevalence of MTP was low. Our result suggested that early emergency procedures and compliance towards MTP improved patient outcomes.

Keywords: Compliance, Indications, Massive Transfusion Protocol (MTP), Mortality.

Introduction

Massive blood loss has a significant impact on the survival and prognosis of many patients. About 40% of trauma-related mortality is due to uncontrolled bleeding, and approximately 25% of trauma patients arriving in the emergency department develop early coagulopathy due to massive haemorrhage (1, 2). Furthermore, a major cause of maternal mortality and morbidity is due to massive bleeding (3). In the operating theatre, haemorrhagic shock accounts for 80% of deaths, and up to 50% of mortality was in the first twenty-four hours following injury (4). In order to maintain adequate circulation and haemostasis, patients with severe haemorrhage require massive transfusion.

Effective coordination and communication between the transfusion team, other laboratory services, and the clinical team are crucial to ensure optimal management of massively bleeding patients. Thus, a proactive

standardised protocol, MTP, is designed to facilitate communication between different services (clinician, laboratory, and blood bank personnel), avoid delay in critical care, laboratory testing, and blood transfusion for patients at risk of massive bleeding (5). The goal of MTP is to ensure that a pre-defined ratio of blood products id delivered quickly and efficiently to critically ill patients. (6). Furthermore, the protocol enables the release of blood for initial resuscitation at a standardised pre-defined ratio of blood products regardless of the patient's laboratory result. The effectiveness of MTP requires full cooperation and involvement from the treating clinician and blood bank team (6). Good communication between both teams is essential to prevent poor clinical outcomes, suboptimal or inappropriate transfusion practice, and component wastage.

Previously in the inexistence of the MTP era, transfusion of large amounts and the improper ratio of blood products has caused higher mortality in severely bleeding patients since the condition quickly entered the lethal triad of hypothermia, metabolic acidosis, and coagulopathy (7). Moreover, the complication of massive bleeding had been exacerbated due to excessive fluid resuscitation (8, 9). A well-established MTP is pivotal to intervene in the severe bleeding and break the triad (10). Therefore, MTP is an important approach to prevent the complication of massive transfusion, particularly dilutional coagulopathy, which may aggravate the patient's condition.

MTP has received a lot of attention and was implemented more frequently for the past two decades, especially in trauma-related massive haemorrhage, gastrointestinal (GI) or obstetric haemorrhage, and bleeding intra-operatively (1, 11). However, many literatures previously only focused on patients' outcomes between pre-MTP and post-MTP periods in specific trauma or obstetric centres. There is no study on the indication of MTP and compliance towards the established MTP in Malaysia. Therefore, this study focused on the prevalence, indications, associated factors toward the indication of activated MTP cases and twenty-four-hour mortality among those who received MTP in Hospital USM.

Methodology

Hospital USM is a tertiary referral centre for the east coast of Peninsular Malaysia, and MTP has been implemented in Hospital USM since 2014 (Figure 1). A total of 193 MTP have been activated since the introduction of the protocol in Hospital USM. However, only 110 cases have been traced to fulfil the sample size to analyse the practice of MTP activation. This study was a retrospective cross-sectional study involving 110 patients who received MTP activation in Hospital USM in Kelantan, Malaysia, from January 2014 until May 2020. This study was approved by the Human Research Ethics committee (HREC) of USM (USM/JEPeM/19120951). The inclusion criteria were patients above 18 years old and received transfusion after MTP activation. Those below 18 years old, did not receive blood transfusion even though MTP was activated, or missing data of more than 30% were excluded from the study.

Data were extracted from the medical records and blood bank information system (MyTransfusi). All data comprised of patients' demographic, underlying medical illness, the person who activated MTP, indication of MTP activation, total number of blood cycles released, total numbers of blood products transfused, use of haemostatic agents, any emergency procedures done, twenty-four-hour mortality and compliance towards the criteria assessed were analysed. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 27.0 for window-software (SPSS, Chicago, Illinois, USA).

The prevalence and indications of MTP activation, blood product usage, cycle of MTP released, ratio of blood product transfused, and twenty-four-hour mortality were analysed and presented descriptively. The categorical data were expressed as frequency (percentage) and numerical data as mean (SD). The associated factors toward the indication of MTP activation and twenty-four-hour mortality were determined using simple and multiple logistic regression analysis. A p-value of < 0.05 was considered statistically significant

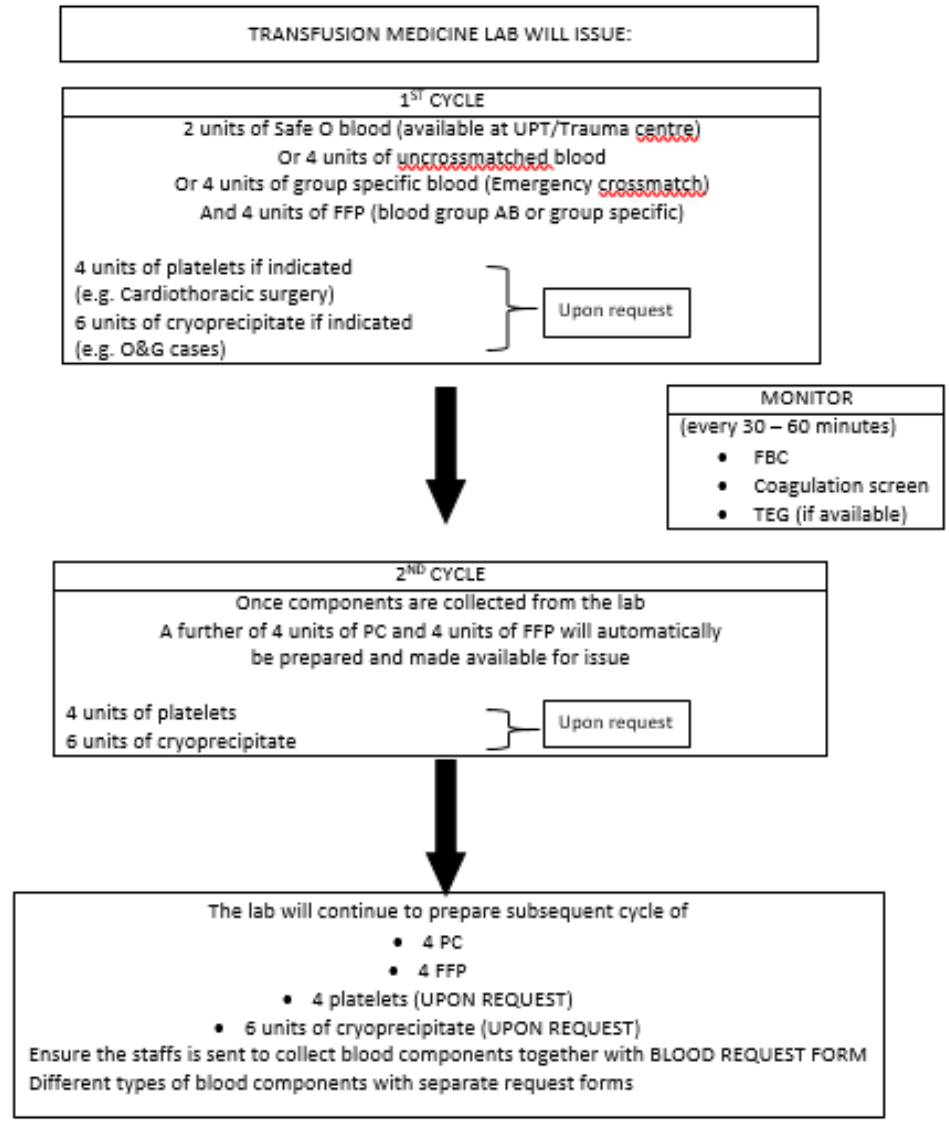

Figure 1: MTP flow diagram in Hospital USM (39); UPT = Unit Perubatan Transfusi; PC = packed cells; FFP = fresh frozen plasma; FBC = full blood count; TEG = thromboelastography

Results

Prevalence of massive transfusion protocol activation

A total of 273,087 patients were admitted to Hospital USM, and 193 patients from all disciplines required MTP activation during the study period from 1st January 2014 until 30th May 2020. The prevalence of MTP activation was only 0.07%. We had traced 118 patients' data in this study and eventually included 110 cases. The remaining 8 cases were excluded because of age below 18 years old or more than 30% missing data.

Demographic and descriptive analysis of patients' variables and the indication of MTP activation

The details of patients' descriptive based on MTP activation indication were summarised in Table I. Indication of MTP activation was divided into trauma and non-traumatic causes. The mean age of patients was 40.0 ± 18.26 years old. The mean age for the trauma group was 35.5 ± 17.25 years old while the non-trauma group was 45.5 ± 18.05 years old. A total of 66.4% cases were male. The majority of the trauma patients were male (87.1%), while in non-trauma, the patients were mostly female (60.4%). About 66.4% of all the patients had no comorbid. Comorbidity effects only 24.2% of trauma patients, whereas it affects more than half of non-trauma patients. (66.7%). Most of the patients required only one cycle of MTP in both trauma (62.9%) and non-trauma cases (72.9%). The ratio of the packed cell (PC) to the plasma unit administered appeared to be no difference between trauma and no-trauma cases. The majority of patients were transfused between the ratio of 1:1 to 1:2 (85.5% vs 70.8%) (Table I).

Table 1. Demographics and descriptive analysis of patients who indicated for MTP activation

Variable	All (n = 110) n (%)	MTP indication	
		Trauma (n = 62) n (%)	Non-trauma (n = 48) n (%)
Age (years)[a]	40.0 ± 18.26	35.5 ± 17.25	45.5 ± 18.05
Gender			
• Male	73 (66.4)	54 (87.1)	19 (39.6)
• Female	37 (33.6	8 (12.9)	29 (60.4)
Comorbidity			
• No	73 (66.4)	47 (75.4)	15 (31.3)
• Yes	37 (33.6	15 (24.2)	33 (68.8)
MTP activated by			
• Medical officer	81 (73.6)	49 (79.0)	32 (66.7)
• Specialist	29 (26.4)	13 (21.0)	16 (33.3)
Number of MTP cycle(s) released			
• 1 cycle	74 (67.3)	39 (62.9)	35 (72.9)
• 2 cycles	24 (21.8)	18 (29.0)	6 (12.5)
• 3 cycles or more	12 (10.9)	5 (8.1)	7 (14.6)
Ratio of PC : FFP unit			
• <1:2 (<0.5)	9 (8.2)	2 (3.2)	7 (14.6)
• 1:1 – 1:2 (0.5 – 1.0)	87 (79.1)	53 (85.5)	34 (70.8)
• > 1:1 (> 1.0)	14 (12.7)	7 (11.3)	7 (14.6)
Number of PC transfused (unit)[a]	5.8 ± 4.09	5.8 ± 3.55	5.7 ± 4.73
Number of FFP transfused (unit)[a]	6.0 ± 3.74	6.2 ± 3.75	5.7 ± 3.77
Number of platelets transfused (unit)[a]	3.9 ± 3.21	3.7 ± 2.95	4.2 ± 3.52
Number of cryoprecipitates transfused (unit)[a]	6.0 ± 5.11	5.7 ± 4.81	6.4 ± 5.48
Emergency procedure			
• No	34 (30.9)	20 (32.3)	14 (29.2)
• Yes	76 (69.1)	42 (67.7)	34 (70.8)
Haemostatic agent given			
• No	36 (32.7)	12 (19.4)	24 (50.0)
• Yes	74 (67.3)	50 (80.6)	24 (50.0)
Haemostatic agent*			
• Tranexamic acid	71 (92.2)	49 (96.1)	22 (84.6)
• FVII concentrate	4 (5.2)	1 (2.0)	3 (11.5)
• Vitamin K	1 (1.3)	0 (0.0)	1 (3.9)
• Gelfoam	1 (1.3)	1 (2.0)	0 (0.0)
twenty-four-hour mortality			
• Yes	25 (22.7)	14 (22.6)	11 (22.9)
• No	85 (77.3)	48 (77.4)	37 (77.1)

FFP = fresh frozen plasma; MTP = massive transfusion protocol; PC = packed cell

[a] mean ± SD

*Among patients who received haemostatic agent (n = 74) and 3 patients received more than 1 agent

The emergency procedure was done for the majority of the patients (67.3%) from both groups. In trauma cases, most of the patients were given haemostatic agents (80.6%), while 50% of the non-trauma group patients received the same medication. Overall, tranexamic acid was used most frequently as a haemostatic agent in MTP activation cases (92.2%). Within twenty- four hours of MTP activation, 22.7% of patients died, including 22.6% from trauma and 22.9% from non-trauma cases.

The main indication of MTP activation was trauma cases (56.4%), in which the majority of the cases were activated due to motor vehicle accidents (MVA) (93.5%), followed by vascular injury (4.8%) and assault (1.6%). GI bleeding cases accounted for most non-trauma cases (50.0%), followed by Obstetrics and Gynaecology (O&G) bleeding (33.3%), vascular rupture (8.3%) and intra-operative bleeding (8.3%).

Factors associated with the indication of MTP activation (trauma and non-trauma)

Simple logistic regression (SLR) was performed to determine factors associated with the indication of MTP activation which includes age, gender, presence of comorbidity, the person who activated MTP, number of MTP cycle(s) released, number of PC, fresh frozen plasma (FFP), platelet and cryoprecipitate transfused, ratio of PC to FFP transfused, haemostatic agent given and presence of emergency procedure. Significant associations were found between age, gender, presence of comorbidity, and haemostatic agent with the indication of MTP activation. One year increment of patient age had 1.03 times (crude OR = 1.03, 95% CI 1.01 – 1.06, p = 0.004), female patients had 10.3 times (crude OR = 10.30, 95% CI 4.02 – 24.41, p <0.001) and presence of comorbidity had 6.89 times (crude OR = 6.89, 95% CI 2.97 – 16.01, p <0.001) higher odd of MTP activation due to non-trauma compared to trauma. Meanwhile, patients who received haemostatic agents had a lower chance of MTP activation due to non-trauma compared to trauma (crude OR = 0.24, 95% CI 0.10 – 0.56, p = 0.007).

Multiple logistic regression (MLR) was performed, controlling for all the variables with a p-value of less than 0.25 (7 variables). Only gender and the presence of comorbidity remained significantly associated with the indication of MTP activation. Female patients had 20.08 times (adjusted OR = 20.08, 95% CI 5.76 – 70.00, p <0.001), and those patients with comorbidity had 13.66 times (adjusted OR = 13.66, 95% CI 4.21 – 44.39, p<0.001) higher odds of MTP activation due to non-trauma compared to trauma. The detail of the results are summarised in Table II.

Table 2. Factors associated with the indication of MTP activation (trauma and non-trauma) (n = 110)

Variables	**Simple logistic regression**		**Multiple logistic regression**	
	Crude OR (95% CI)	**p value**	**Adjusted OR (95% CI)** [a]	**p value**
Age (years)*	1.03 (1.01 – 1.06)	0.004	-	-
Gender*				
• Male	1		1	
• Female	10.30 (4.02 – 26.41)	<0.001	20.08 (5.76 – 70.00)	<0.001
Co-morbidity*				
• No	1		1	
• Yes	6.89 (2.97 – 16.01)	<0.001	13.66 (4.21 – 44.39)	<0.001
MTP activated by*				
• Medical officer	1			
• Specialist	1.89 (0.80 – 4.44)	0.147	-	-
Number of MTP cycle(s) released*				
• 1 cycle	1			
• 2 cycles	0.37 (0.13 – 1.04)	0.06	-	-
• ≥ 3 cycles	1.56 (0.45 – 5.36)	0.48	-	-
Number of PC transfused (unit)	0.99 (.090 – 1.09)	0.842	-	-
Number FFP transfused (unit)	0.96 (0.87 – 1.07)	0.492	-	-
Number platelets transfused (unit)	1.05 (0.94 – 1.19)	0.397	-	-
Number cryoprecipitate transfused (unit)	1.03 (0.96 – 1.11)	0.461	-	-
Ratio of FFP: PC unit*				
• <1:2 (<0.5)	3.50 (0.53 – 23.14)	0.194	-	-
• 1:1 – 1:2 (0.5 – 1.0)	0.64 (0.21 – 1.99)	0.442	-	-
• > 1:1 (>1.0)	1			
Haemostatic agent given*				
• No	1			
• Yes	0.24 (0.10 – 0.56)	0.001	-	-

Emergency procedure				
• No	1			
• Yes	1.16 (0.51 – 2.62)	0.728	-	-
twenty-four-hour mortality				
• Yes	1.02 (0.42 – 2.50)	0.967	-	-
• No	1			

FFP = fresh frozen plasma; MTP = massive transfusion protocol; PC = packed cell
*7 variables with p-value <0.25 were included for multivariable analysis. At multivariable analysis, only 2 remained significant
[a] Variable selection using forward (LR) method
Multicollinearity and interaction terms were checked and not found
Hosmer-Lemeshow test (p-value = 0.215), classification table (overall correctly classified percentage = 79.1%) and area under the ROC curve (86.2%) were applied to check model fitness

MTP activation compliance

Table III summarises the compliance criteria and the percentage of compliance for each criterion. All MTP cases (100%) in this study were activated by authorised personnel who were medical officers or specialists, as stated in the protocol. According to the protocol, laboratory investigation which consists of full blood count (FBC) and coagulation profile should be monitored every 30 – 60 minutes. Only 69.1% of cases were compliant with this criterion. For criteria of MTP-based product administration, 54.4% of patients were transfused based on pre-determined blood products in the MTP.

Table 3. MTP compliance criteria

Compliance criteria	Yes n (%)	No n (%)
Activated by authorized personnel	100 (0.0)	0 (0.0)
MTP-based administration blood product	60 (54.4)	50 (45.5)
FBC and coagulation profile sent*	76 (69.1)	34 (30.9)
Overall compliance	48 (43.6)	62 (56.4)

FBC = full blood count
*Sent during activation and monitoring

Twenty -four- hour mortality rate and factor associated with the twenty- four -hour mortality after MTP activation

We found that the mortality within twenty-four-hour after MTP activation was 22.7%. Majority of patients who had mortality within twenty-four-hour after MTP activation were male (72%), with underlying comorbidity (64%), received one MTP cycle (68.2%), transfused with PC to FFP ratio of 1:1 – 1:2 (72%), with no emergency procedure performed (76%), did not fulfil the MTP activation compliance criteria (84%) and received haemostatic agents (76%).

SLR analysis was performed to determine the factor associated with twenty-four-hour mortality (age, gender, presence of comorbidity, indication of MTP activation, the person who activated MTP, number of MTP cycle released, number of PC, FFP, platelet and cryoprecipitate units transfused, the ratio of PC to FFP transfused, haemostatic agent given, any emergency procedure done, and compliance of selected activated MTP criteria). In order to assess factors that were significantly associated with twenty-four-hour mortality, patients who survived within twenty-four-hour after MTP activated were set as the reference group.

The SLR analysis revealed a significant association between the presence of comorbidity, emergency procedure, and compliance criteria with mortality within twenty-four-hour of MTP activation. We found that patients who had underlying comorbidity were 2.94 times (Crude OR = 2.94, 95% CI 1.17 – 7.44, p = 0.022) at higher odd of twenty-four-hour mortality, and those with no emergency procedure done had 14.78 times higher chance of mortality within twenty-four-hour after MTP activation (Crude OR = 14.78, 95% CI 5.05 – 43.25, p <0.001). Without fulfilling compliance criteria, there were 5.63 times (Crude OR = 5.63, 95% CI 1.78 – 17.81, p = 0.003) higher odds of mortality within twenty-four-hour of MTP activation.

MLR was performed to control for all the variables with a p-value of less than 0.25 at SLR. Only emergency procedures and compliance with MTP remained significantly associated with twenty-four-hour mortality after MTP activation. Without an emergency procedure done, there were 12.77 times higher odds of mortality within twenty-four-hour after MTP activation (adjusted OR = 12.77, 95% CI 4.22 – 38.61, p <0.001). Meanwhile, non-compliance to any one of the compliance criteria caused 4.3 times higher risk of death within twenty-four-hour of MTP activation (adjusted OR = 4.30, 95% CI 1.21 – 15.38, p = 0.024). The detailed results on the associated factors of twenty-four-hour mortality after MTP activation are shown in Table IV.

Table 4. Factors associated with twenty-four-hour mortality after MTP activation (n = 110)

Variables	twenty-four-hour mortality		Simple logistic regression		Multiple logistic regression	
	No (n=85) n (%)	Yes (n=25) n (%)	Crude OR (95% CI)	p value	Adjusted OR (95 % CI) [b]	p value
Age	39.0 ± 17.28[a]	43.3 ± 21.32[a]	1.01 (1.00 – 1.04)	0.295	-	-
Gender						
• Male	55 (64.7)	18 (72.0)	1	1		
• Female	30 (35.3)	7 (28.0)	0.71 (0.27 – 1.90)	0.499	-	-
Comorbidity						
• No	53 (62.4)	9 (36.0)	1	1		
• Yes	32 (37.6)	16 (64.0)	2.94 (1.17 – 7.44)	0.022*	-	-
MTP activated by						
• Medical officer	63 (74.1)	18 (72.0)	1	1		
• Specialist	22 (25.9)	7 (28.0)	0.34 (0.13 – 0.86)	0.833	-	-
Number of MTP cycle(s) released	58 (68.2)	16 (64.0)	1	1		
• 1 cycle	18 (21.2)	6 (24.0)	1.21 (0.41 – 3.55)	0.731	-	-
• 2 cycles	9 (10.6)	3 (12.0)	1.21 (0.29 – 4.99)	0.794	-	-
• ≥ 3 cycles						
Ratio of PC: FFP unit						
• < 1:2 (< 0.5)	6 (7.1)	3 (12.0)	1	1		
• 1:2 – 1:1 (0.5 – 1.0)	69 (81.2)	18 (72.0)	1.21 (0.41 – 3.55)	0.731	-	-
• > 1:1 (> 1.0)	10 (11.8)	4 (16.0)	1.21 (0.29 – 4.99)	0.794	-	-
Number of PC transfused (unit) [a]	5.7 ± 3.86[a]	6.1 ± 4.86[a]	1.03 (0.93 – 1.14)	0.610	-	-
Number of FFP transfused (unit) [a]	5.9 ± 3.59[a]	6.2 ± 4.32[a]	1.02 (0.91 – 1.15)	0.698	-	-
Number of platelets transfused (unit) [a]	4.0 ± 3.19[a]	3.4 ± 3.29[a]	0.93 (0.81 – 1.08)	0.363	-	-
Number of Cryoprecipitates transfused (unit)[a]	6.4 ± 5.34[a]	4.6 ± 4.03[a]	0.92 (0.83 – 1.02)	0.130*	-	-
Haemostatic agent given						
• No	27 (31.8)	6 (24.0)	1	1		
• Yes	58 (68.2)	19 (76.0)	1.33 (0.50 – 3.55)	0.567	-	-
Emergency procedure						
• Yes	70 (82.4)	6 (24.0)	1	1	1	1
• No	15 (17.6)	19 (76.0)	14.78 (5.05 – 43.25)	<0.001*	12.77 (4.22 – 38.61)	<0.001
Compliance to MTP [#]						
• Yes	44 (51.8)	4 (16.0)	1	1	1	1
• No	41 (48.2)	21 (84.0)	5.63 (1.78 – 17.81)	0.003*	4.30 (1.21 – 15.38)	0.024

FFP = fresh frozen plasma; MTP = massive transfusion protocol; PC = packed cell

[a] mean ± SD

*4 variables with P-value <0.25 were included for multivariable analysis. At multivariable analysis, only 2 remained significant

[#] Not compliance to any 3 criteria is considered not compliance

[b] Variable selection using forward (LR) method

Multicollinearity and interaction terms were checked and not found

Hosmer-Lemeshow test (p-value = 0.977), classification table (overall correctly classified percentage = 84.5%) and area under the ROC curve (85.2%) were applied to check model fitness

Discussion

Since 2014, MTP has been placed for activation by all departments in the Hospital USM. Our findings showed that the prevalence of MTP activation was very low, only 0.07% among patients admitted to Hospital USM. The very low prevalence of MTP activation in our study can be explained by the larger number of denominators (total admission within the study period) since MTP activation in Hospital USM is applied for all departments. Currently, there is limited data on MTP activation prevalence which cover all disciplines in one centre to compare with our finding. However, MTP activation prevalence ranging from 0.26% - 1.6% was reported previously in trauma and O&G centres in other countries (12–14).

MTP has a significant role in the management of massive bleeding secondary to both trauma and non-trauma indications. The main indication for trauma cases in our studies was polytrauma due to MVA, which is consistent with previous study findings (15). Haemorrhage in trauma accounts for 30% of all death in trauma (16). Controlling haemorrhage promptly in these patients is one of the crucial elements in trauma management to avoid mortality (17). Our findings also showed that GI bleeding was the leading cause of MTP activation in non-trauma cases. It was comparable to the studies by *Wijaya et al*., which found that more than half of the non-trauma patients in their research bleed in the GI tract (66.7%) and eventually caused MTP activation (18). The massive GI bleed should be managed promptly and MTP activation has become part of the strategy to manage this scenario in Hospital USM.

According to our findings, female patients were statistically significantly more likely than males to have MTP activation due to non-traumatic causes ($p < 0.001$). This is because massive bleeding secondary to obstetric causes was the second most common indication in non-trauma cases. In contrast, other studies did not find any significant association between gender and the indication of MTP activation because obstetric bleeding cases account for only less than 10% of these studies (15, 19).

The non-trauma patients who had MTP activation in our study were older and most had underlying comorbidities, which were statistically significant factors of MTP activation compared to trauma patients ($p < 0.001$). This was consistent with the other studies because comorbidities that cause bleeding were usually present in old-age patients (15, 20). Underlying diseases such as liver failure, renal failure, and cardiovascular disease are found frequently in non-trauma MTP activation cases (15). It was similar to our studies in which MTP activation for patients of non-trauma mostly had the underlying disease, for example, liver disease was at risk for massive bleeding. The low level of coagulation factors due to liver diseases, such as factors II, V, VII, IX, and X, impaired the haemostasis and caused bleeding (21).

The main goal of blood transfusion in MTP is to provide the patients with blood products in a 1:1 (PC to FFP) ratio because it improves the patient's outcome in cases of massive bleeding (22). Moreover, previous study has concluded that higher plasma doses are significantly associated with a better prognosis (23). The MTP in Hospital USM is based on the ratio of 1:1- 1:2. Our study discovered that most patients received a PC to FFP ratio of 1:1 to 1:2 in both trauma and non-trauma cases, implying that the treating clinician followed the protocol as it was recommended. This correlates with the previous study's finding, where most patients received the blood component ratio based on their protocol as intended (15).

The competence of clinicians in managing severe bleeding, aetiology of the massive bleeding, and clinicians' knowledge of MTP are the main contributing factors of the MTP cycle released (24). Early blood product administration in MTP cases can reduce the total number of blood products transfused, resulting in fewer MTP cycles being required since the patients with early blood resuscitation obtained better haemostasis than those with delayed blood resuscitation (22, 25). Our result showed that most of the cases in trauma and non-trauma only required one cycle of MTP. Similarly, *Chay et al.* discovered that 66% of MTP cases activated in non-level one trauma centres were terminated before the second cycle of MTP was initiated (24). Apart from that, we found that the high proportions of MTP activation that did not continue beyond one cycle of MTP were attributed to the patients who did not survive before the second cycle was initiated. As reflected in our study, 64% of patients having twenty-four-hour mortality after MTP activation received only one cycle of blood products. Some of the patients in our study did not proceed more than one cycle because of inappropriate MTP activation. Such "overactivations" for the patients who did not fulfil the massive transfusion criteria will lead to early termination of MTP during the first cycle. According to the literature, hospitals and medical centres that implemented hospital-wide MTPs covering both trauma and non-trauma cases revealed a higher proportion of MTP overactivation (15, 24, 26, 27). This emphasises the importance of improving MTP triaging and activation criteria for each diagnostic category.

Non-surgical haemostasis adjuncts such as tranexamic acid and factor VII concentrates may be added besides blood products to help with haemostasis in bleeding patients. Due to these reasons, many hospitals and medical centres incorporated tranexamic acid as a part of MTP (18, 24, 28). Thus, tranexamic acid was recommended for a better prognosis in the early stage of resuscitation in bleeding patients (29, 30). Even though the haemostatic agent is not included in Hospital USM protocol, tranexamic acid remained the most common drug given to patients of both trauma and non-trauma cases in our study.

We discovered no significant difference between twenty-four-hour mortality and the indication (trauma and non-trauma) of MTP activation. This finding was similar to a study that found no correlation in twenty-four-hour mortality between trauma and non-trauma groups (30% vs 41%; p = 0.20) (11). Other than that, the overall twenty-four-hour mortality rate was low in our study. *DeSimone et al*. reported that 22.8% of all patients in their research did not survive within twenty-four hours, which was comparable to our result (31). Regardless of the aetiology of massive bleeding, the implementation of MTP aims to improve the overall mortality for massively bleeding patients. It allowed the treating clinician to begin the resuscitation with blood products earlier, and blood products were delivered faster to the massively bleeding patients and thus achieved better outcomes (32, 33).

Our research discovered an association between emergency procedures and twenty-four-hour mortality ($p < 0.001$). An emergency procedure is when a patient requires an urgent procedure for life-saving purposes (34). Exploratory laparotomy, esophagogastroduodenoscopy (OGDS), wound debridement, chest tube insertion, craniectomy, dilatation and curettage (D&C), internal and external bone fixation were the most common procedures done among patients in our study. Blood transfusion was not the only measure to treat massive bleeding patients. The main source of bleeding needs to be secured in order to avoid massive blood loss and further derangement in coagulopathy. Many overseas studies had shown that apart from blood transfusion, the emergency procedure was one of the first-line treatments in massively bleeding patients secondary to trauma or non-trauma causes (35–37). In patients with massive upper GI bleeding, according to *Cheung et al*., endoscope improves patients' outcomes in reducing the risk of recurrent bleeding, emergency surgery, and mortality (35). *Haumonté et al*. also found that emergency surgical procedure has 70% effectiveness in stopping haemorrhage secondary to postpartum haemorrhage, and it was associated with low morbidity when medical treatment failed (37).

As for the overall compliance rate to MTP criteria, we found that more than half of the cases did not fulfil one or more of the criteria. MTP activation by authorised personnel was the only criterion that all the cases in our analysis met 100% of the time. *Cotton et al.* found that their study showed that 92% of MTP cases were activated by proper medical personnel and complied with this criterion (38). The difference might be due to the fact that in our centre, the MTP can be activated by an attending medical officer or specialist. However, only trauma physicians were authorised to activate the MTP in their study since they were in the level-one trauma centre. Nevertheless, MTP should be activated by an experienced doctor to avoid suboptimal activation and overactivation.

The non-compliance rate for the criteria of MTP-based blood product administration was 45.5% which was less than half of the total cases. It was consistent with the finding by *Bawazeer et al*., who reported a 47% non-compliance rate to the similar criteria (28). This non-compliance might be due to the fact that the decision of choice and amount of blood products transfused was based on the patient's clinical assessment by the attending clinician and the blood investigation result available at that point of time. Since there was no consensus that all the blood products provided must be transfused completely based on MTP in the centre, the clinician might deviate from the protocol based on the patient's clinical condition and the blood investigation result. *Cotton et al*. found that this compliance criterion significantly affects the survival of the patient (38). However, as mentioned in the literature, there is currently insufficient evidence on the best practice of blood product administration in massive bleeding patients (28). According to the Pragmatic, Randomised, Optimal Platelet and Plasma Ratios (PROPPR) study, having a high ratio of plasma to PC leads to better haemostasis status. However, there was no significant effect on the rate of mortality (22).

For the last criteria we assessed in this study, 30.9% of the cases failed to send routine laboratory tests as recommended in the local protocol. *Bawazeer et al.* discovered the same significant non-compliance criteria in which up to 89% of the cases failed to do it (28). The high percentage of failure to comply with this criterion might be due to a lack of understanding as well as the awareness of the need for continuous patient monitoring during resuscitation. Besides, this might be due to the blood investigation assessed in this previous study consisting of more investigations (arterial blood gas, serum electrolytes, FBC, coagulation profile, and fibrinogen) following their local MTP compared to our study. Currently, a new practice of guiding blood transfusion using point-of- care coagulation testing is rapidly growing and gaining attention. It would be ideal if the centre could gradually include a thromboelastography (TEG) in managing all MTP cases to ensure a better prognosis of the patients.

In our study, we discovered a significant association between twenty-four-hour mortality and compliance criteria ($p = 0.024$). When the MTP criteria were not compliant, the patient had a higher risk of twenty-four-hour mortality than the compliant group. This finding was consistent with *Cotton et al.,* where 38.5% of twenty-four-hour mortality was in the non-compliance group compared to 11.8% in the compliance group ($p = 0.004$) (38). By complying with the MTP, early transfusion with the optimal blood product ratio and proper laboratory monitoring can be achieved to improve overall mortality. To improve the compliance rate in teaching hospitals or medical centres with a high turnover of medical officers and registrars, previous literature recommended giving intensive, regular, and comprehensive continuous

medical education on compliance to the protocol (28, 38). In addition to circulating the MTP flowchart in the emergency department, intensive care unit (ICU), or in the wards, the development of MTP pocket cards or mobile applications to serve as reminders may also be taken into consideration (28).

The ratio of blood products transfused to massive bleeding patients is important since it could impact the patients' haemostatic status, either improving or worsening their condition (11, 22). The ratio of blood products near to whole blood was said to be the most ideal ratio for patients to have a better prognosis (22). In terms of twenty-four-hour mortality, however, our study also found no significant difference between the different ratios of blood products with the patients' twenty-four-hour mortality. Similarly, according to a large multicentre randomised trial (PPROPPR) done by *Holcomb et al.,* there was no significant difference in overall mortality at twenty-four hours or thirty days among 680 patients transfused with a 1:1:1 or 1:1:2 ratio (22).

There were limitations in our study. It was a study that represented only one centre. Therefore, the finding might not reflect the practice of the whole country. It would be better in our study if we could include a multicentre for a larger sample, as shown by the wide 95% confidence interval. Hence, for a more accurate estimation of the odd ratio, a larger sample size is needed.

Conclusion

The prevalence of MTP activation was very low in Hospital USM. The two most common indications of MTP activation in our study were MVA and GI bleeding. Females and the presence of comorbidity were significantly associated with the indication (non-trauma) of MTP activation. Our result suggested that early emergency procedures and compliance towards MTP improved patient outcomes.

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