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Clinical impact of massive transfusion protocol implementation in non-traumatic patients

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ABSTRACT

Background: Massive transfusion protocol (MTP) has been used to provide plasma and packed red blood cells (pRBCs) rapidly. MTP also has been adapted for non-traumatic patients. The effects of hospital-wide MTP implementation on clinical outcomes were reviewed.
Methods: This was a retrospective study of patients who received massive transfusion before and after MTP implementation, between August 2010 and May 2018. Massive transfusion was defined as 10 or more units of pRBCs within 24 h. Recipients of massive transfusion were divided into periods before and after MTP implementation. The 24 -h death rate, thirty-day death rate and several laboratory findings were investigated.
Results: Eighty patients whose massive transfusion occurred before MTP implementation and 63 patients whose massive transfusion occurred after MTP implementation were compared. 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).
Conclusions: MTP implementation showed improved coagulation profiles, but did not show a statistically significant death-rate reduction in non-traumatic patients.

1. Introduction

Massive transfusion, which is the large-volume transfusion of blood products over a short period of time, can be a life-saving treatment for hemorrhagic patients. The most common definition of massive transfusion in adult patients is the transfusion of 10 or more units of packed red blood cells (pRBC) within 10 h [1–3]. This MTP includes minimizing the use of crystalloid fluids with early administration of blood components, especially plasma and platelets to mimic whole blood transfusion, and suggested improved coagulation profiles and death rates. On the other hand, uncorrected coagulopathy is associated with ongoing transfusion requirements and increased risk of death [3–8]. Transfusion of plasma with pRBC in a fixed ratio is a management practice derived from studies of traumatic hemorrhagic patients. There has been concern about the use of MTP on non-trauma patients, because several etiologies aside from traumatic injury may cause significant hemorrhage in hospitalized patients. MTP has been applied to patients with non-traumatic hemorrhagic shocks. However, non-trauma patients are heterogeneous and differ from trauma patients [9–13]. Previous studies showed different results: one study reported that 30-day survival was not significantly different after MTP implementation [12]. A study conducted with pediatric patients reported that mortality was not significantly different between MTP group and non-MTP group [14]. However, another study reported the opposite results, that increasing the plasma to pRBC ratio was associated with improved survival in non-trauma patients [13]. Since additional studies are necessary to refine

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MTP in non-trauma patients, we aimed to investigate the clinical effect of the implementation of massive transfusion protocol in non-trauma patients.

2. Methods

2.1. Study design and population

This was a retrospective before-and-after study of non-traumatic adult patients, who received massive transfusion at Samsung Medical Center, Seoul, South Korea. This study was conducted after the approval of the Institutional Review Board of Samsung Medical Center (approval no. 2018-08-036). We analyzed medical records between August 2010 and May 2018.

The inclusion criteria for this study were of patients who: (a) were adult patients, age 18 or older, (b) were admitted to the emergency department or were hospitalized, (c) had non-traumatic hemorrhage, and (d) received massive transfusion.

In this study, massive transfusion was defined as transfusion of 10 or more units of pRBC within 24 h. Hence, certain patients who died within a few hours after an initial event, before receiving 10 units of pRBC, are not included in the study population. Patients with operation-related hemorrhage were excluded from this study. Operation-related hemorrhage was defined as a transfusion which was chosen and initiated during surgical operations. When massive transfusion is required during operations, a cardiopulmonary bypass or intraoperative blood salvage are used, and these might affect the actual transfusion amount and the patient's coagulation status; hence we excluded operation-related hemorrhage from the study population to minimize bias.

The hospital's MTP was implemented on July 2014. Patients who received massive transfusion before and after this point were divided into the pre-MTP implementation group (from August 2010 to June 2014) and the post-MTP implementation group (from July 2014 to May 2018).

2.2. Massive transfusion protocol

The MTP calls for a ratio of 1:1:1 for pRBC to plasma to platelets: accordingly, six units of pRBC, six units of plasma, and six units of platelet or one unit of platelet pheresis are released without cross-matching (defined as package-1). For this MTP activation, a blood bank is notified by a phone call or electronic medical record (EMR) system. Subsequent packages contain the same ratio of pRBCs, plasma, and platelets. Additional transfusing of cryoprecipitate or separated units of the blood products are decided on by the clinician who initiated MTP. Target laboratory findings for additional transfusing of the blood products were a platelet count of more than $100 \times 10^3/\mu L$, INR (International normalized ratio for prothrombin time) less than 2.0, and fibrinogen more than 150 mg/dL.

During the transfusion, fluid warmers such as ANIMEC (AM-2S-5A, ELLTEC, Nagoya, Japan) or Level 1® (H-1000 Fast Flow Fluid Warmer, Smiths Medical, OH, USA) and a forced-air warming system (WarmTouch Patient Warming System, Nellcor [Medtronic], MN, USA) for patients were applied. Body temperature was measured every 30 min, and target body temperature was above 36 °C. Fluid resuscitation was carefully performed while avoiding use of excessive crystalloid to prevent dilution coagulopathy. The crystalloid fluid of choice was plasmalyte solution (Plasma Solution A Inj., CJ Pharma, Seoul, Korea). Normal saline was used when plasmalyte solution was not available. Synthetic colloid fluid, such as hydroxyethyl starch, was prohibited because its potential risk of coagulopathy and nephrotoxicity. Target systolic blood pressure was 80–100 mmHg; this permissive hypotension was adopted unless there was no sign of systemic hypoperfusion, until active bleeding was controlled. Serum ionized calcium level was checked every two hours, and supplemental calcium gluconate was given to maintain the ionized calcium level at more than 0.9 mmol/L. Anti-fibrinolytic agents, such as tranexamic acid, were routinely recommended and used with a loading dose of 1 g over 1 min and a maintenance dose 0.125 g per hour. Before implementation, there was no MTP, and all management was decided on by each clinician, case by case.

2.3. Outcomes and statistical analysis

The primary outcome was the death rate of massively bleeding patients who received massive transfusion before and after MTP implementation. The secondary outcomes included ratio of transfused plasma to pRBC, platelet to pRBCs ratio, the use of anti-fibrinolytic agents, and coagulation profiles. Evaluated variables were age, cause of bleeding, severity of illness (*via* the Sequential Organ Failure Assessment [SOFA] score), laboratory findings of pre-transfusion value, and worst value during the 24 -h periods. Laboratory findings included hemoglobin, platelet counts, INR, fibrinogen, *p*H, ionized calcium level, lactic acid level, and body temperature.

Data are described as median (interquartile range, IQR), mean ± standard deviation (SD), or percentage (%). Continuous variables were compared by using the Student's *t*-test or the Mann-Whitney test. Categorical variables were compared by using the chi-square test or Fisher's exact test, as appropriate. Statistical analyses were performed using SPSS software version 25 (IBM, Chicago, IL, United States), and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patients characteristics

In total, massive transfusion was performed in 684 patients during the study period. Non-adult patients (n = 41) and trauma-related hemorrhagic patients (n = 28) were excluded, as were 472 patients with operation-related hemorrhage. As mentioned before, we excluded operation-related hemorrhage from the study population to minimize bias from the effects of cardiopulmonary bypass or intraoperative blood salvage. Finally, 143 patients who met the inclusion criteria were enrolled. Of the 143 patients, 80 (55.9%) had massive transfusions before the MTP implementation period (between August 2010 and June 2014) and 63 (44.1%) had massive transfusions after the MTP implementation period (between July 2014 and May 2018) (Fig. 1).

The median age of the patients was 58 (40.5–65.0), and 90 (62.9%) were male. Of the 143 patients, vessel injury was the most common cause of massive bleeding (71 patients, 49.7%), including ruptured abdominal or thoracic aortic aneurysms, major vessel injuries after invasive procedures, pseudoaneurysm ruptures, or bleedings from malignant tumor invasion to a vascular structure. The second most common cause of massive bleeding was gastrointestinal bleedings, such as varix bleeding or ulcer bleeding (50 patients, 35.0%), followed by postpartum hemorrhages (21 patients, 14.7%) and one massive hemoptysis patient. The baseline use of antithrombotic medication was investigated. The use of antiplatelet agents was found in 22 (15.3%, 12 patients in the pre-MTP group and 10 patients in the post-MTP group). Among them, nine (6.3%, five in the pre-MTP group and four in the post-MTP group) of the patients were taking dual antiplatelet agents, such as aspirin and clopidogrel. Eleven (7.7%) patients were prescribed anticoagulation medication such as warfarin, including one patient who was receiving NOAC (Novel Oral Anticoagulants). Mean pre-transfusion SOFA scores were 10.4 in the pre-MTP implementation group and 10.6 in the post-MTP implementation group. There was no statistically significant difference between the two groups (p = 0.824) (Table 1).

3.2. 24-Hour and 30-Day death rate

When comparing the survival of patients who received massive

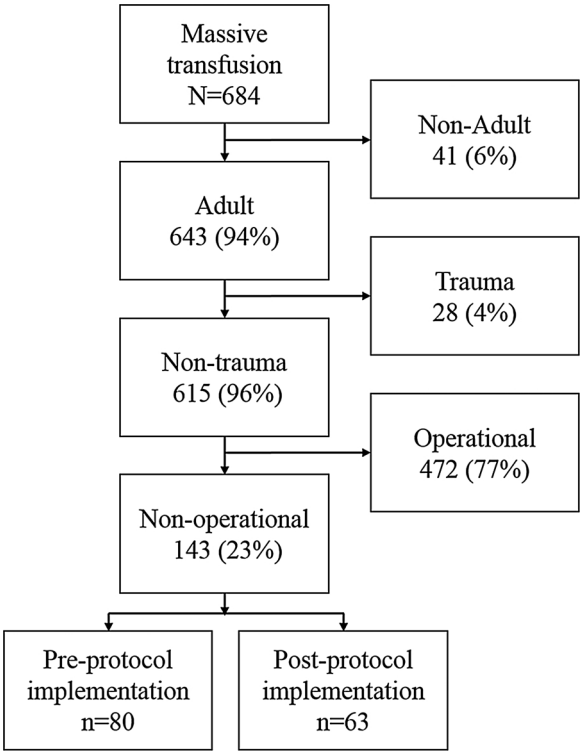

Fig. 1. Study population.

Table 1
Characteristics of the Pre- and Post-MTP implementation patients.

Characteristics	Pre-MTP (n = 80)	Post-MTP (n = 63)	p value
Age	52.0 ± 16.0	56.6 ± 14.1	0.070
Sex (male) (%)	51 (63.8)	39 (61.9)	0.821
SOFA score	10.4 ± 5.0	10.6 ± 4.3	0.824
Previous use of antithrombotic agents			
Antiplatelet agents	12 (15.0)	10 (15.9)	0.886
Warfarin or NOAC	6 (7.5)	5 (7.9)	0.906
Cause of bleeding			0.205
Vessel injury	35 (43.8)	36 (57.1)	0.131
Gastrointestinal bleeding	31 (38.8)	19 (30.2)	0.296
Postpartum hemorrhage	14 (17.5)	7 (11.1)	0.346
Hemoptysis	0 (0)	1 (1.6)	0.441

Values are presented as mean ± standard deviation or number (%).
MTP = massive transfusion protocol; SOFA = sequential organ failure assessment; NOAC = novel oral anticoagulants.

transfusion, no statistically significant difference was found for the 24-h death rate (15.0% *vs* 23.8%%, p = 0.181) or the 30-day death rate (43.8% *vs* 36.5%%, p = 0.381) between before and after MTP implementation.

The study population was classified into three different subgroups according to their causes of bleeding: vessel injury, gastrointestinal bleeding, and postpartum hemorrhage. When comparing the survival of patients in these subgroups, there was no statistically significant difference in 24-h or 30-day mortalities (Table 2).

3.3. Coagulation profiles and use of blood products

Table 3 lists the characteristics of coagulation profiles comparing the pre-MTP implementation group and the post-MTP implementation group. Pre-transfusion INR, fibrinogen, pH, and lactic acid level were worse in the pre-MTP implementation group than in the post-MTP implementation group. No statistically significant difference was observed in the pre-transfusion platelet level between the two groups.

Table 2
24-Hour and 30-Days death rates.

Mortality	n	Pre-MTP	n	Post-MTP	p value
24-h (%)					
Total	80	12 (15.0)	63	15 (23.8)	0.181
Vessel injury	35	7 (20.0)	36	9 (25.0)	0.614
Gastrointestinal	31	4 (12.9)	19	5 (26.3)	0.273
Postpartum	14	1 (7.1)	7	1 (14.3)	1
30-day (%)					
Total	80	35 (43.8)	63	23 (36.5)	0.381
Vessel injury	35	20 (57.1)	36	22 (61.1)	0.124
Gastrointestinal	31	14 (45.2)	19	8 (42.1)	0.833
Postpartum	14	1 (7.1)	7	1 (14.3)	1

Values are presented as number (%).
MTP = massive transfusion protocol.

Table 3
Laboratory profiles of the Pre- and Post-MTP implementation patients.

Characteristics	Pre-MTP (n = 80)	Post-MTP (n = 63)	p value
Hemoglobin (g/dL)			
Pre-transfusion value	8.40 ± 2.55	8.65 ± 2.12	0.562
Worst value during the 24-h	7.11 ± 2.21	8.62 ± 8.80	0.143
Platelet ($x10^3/\mu L$)			
Pre-transfusion value	138.81 ± 85.13	169.81 ± 96.61	0.057
Worst value during the 24-h	49.09 ± 26.85	68.05 ± 32.90	< 0.001
INR			
Pre-transfusion value	1.51 (1.18–2.18)	1.26 (1.11–1.72)	0.035
Worst value during the 24-h	2.25 (1.63–3.74)	1.89 (1.59–2.74)	0.062
Fibrinogen (mg/dL)			
Pre-transfusion value	180.26 ± 121.07	278.04 ± 159.02	0.016
Worst value during the 24-h	114.56 ± 81.11	135.76 ± 56.16	0.115
pH			
Pre-transfusion value	7.37 (7.19–7.45)	7.41 (7.33–7.47)	0.074
Worst value during the 24-h	7.12 (6.90–7.32)	7.17 (7.04–7.33)	0.101
Ionized Ca^{2+} (mmol/L)			
Pre-transfusion value	1.09 ± 0.14	1.04 ± 0.14	0.153
Worst value during the 24-h	0.75 ± 0.24	0.82 ± 0.23	0.115
Lactic acid (mmol/L)			
Pre-transfusion value	5.90 (2.73–12.01)	3.66 (1.74–5.11)	0.011
Worst value during the 24-h	10.49 ± 6.52	8.71 ± 6.58	0.140
Use of anti-fibrinolytic agents (%)	25 (31.3)	35 (55.6)	0.003
Worst Body temperature (°C)	34.7 ± 1.50	35.6 ± 0.88	< 0.001

Values are presented as mean ± standard deviation, median (range) or number (%).
MTP = massive transfusion protocol; INR = international normalized ratio for prothrombin time; pRBC = packed red blood cell.

However, the worst level of the platelets during the 24-h period was significantly improved in the post-MTP implementation group. The other parameters, such as the worst level of INR, fibrinogen, pH, ionized calcium, and lactic acid showed no significant difference between the two groups during the 24-h period. Anti-fibrinolytic agents were used significantly more frequently by patients who received transfusion after the MTP implementation (31.3% *vs* 55.6%, p = 0.003). The lowest body temperature was higher in the post-MTP implementation group than in the pre-MTP implementation group during a 24-h period (34.7 °C *vs* 35.6 °C, p < 0.001). Table 4 shows the blood products and their ratio during the 24-h periods. The post-MTP implementation group showed more units of plasma use than did the pre-MTP implementation group (12.41 *vs* 14.29, p = 0.270). But no statistically significant differences in the number of transfused blood products were

Table 4
Use of blood products.

	Pre-MTP (n = 80)	Post-MTP (n = 63)	p value
24 -h period			
pRBC	22.35 ± 13.27	22.24 ± 13.51	0.960
Plasma	12.41 ± 9.68	14.29 ± 10.51	0.270
PLT	18.95 ± 14.04	19.30 ± 16.69	0.891
Ratio			
Plasma:pRBC ratio	1: 1.91	1:1.58	0.173
PLT:pRBC ratio	1:1.16	1:1.35	0.604
Time			
Time to initiate the first pRBC (min)	51 (30–121)	40 (17–85)	0.042
Time to initiate the first Plasma (min)	69 (46–118)	65 (40–103)	0.339

Values are presented as mean ± standard deviation or median (range).
MTP = massive transfusion protocol; pRBC = packed red blood cell; PLT = platelet.

found between the two groups. Similarly, plasma to pRBC ratio was numerically higher in the post-MTP group (1:1.91 *vs* 1:1.58, p = 0.173) but failed to show statistical significance. We calculated time (in minutes) between ordering pRBC through the EMR system and actual initiation of transfusing the first pRBC. There was earlier initiation of pRBC transfusion after the implementation of MTP and the median time for preparing transfusion was shortened from 51 min before implementation to 40 min after implementation. However, this improvement was not achieved in initiation of plasma transfusion.

4. Discussion

MTP has been implemented to deliver blood products rapidly and effectively to patients with severe hemorrhagic shock. Previous studies have shown that the death rate was reduced in trauma patients who received massive transfusion in accordance with a pre-determined protocol. Several studies suggested that higher plasma to pRBC and platelet to pRBC ratios provide a survival benefit in massively transfused traumatic patients [2–8]. Existing studies also demonstrated benefits of MTP implementation in non-trauma patient population. However, a high ratio of plasma to pRBC is not associated with an improved death rate in certain studies [9–13,15]. In our retrospective review of hospital-wide MTP implementation involving non-trauma patients with severe hemorrhage, we tried to investigate the effect of implementation by comparing patients of the pre-MTP implementation period and the post-MTP implementation period.

Despite several improvements of transfusion-related management, such as earlier initiation of transfusion, a higher ratio of plasma to pRBC and maintaining appropriate body temperature, our implementation of MTP did not improve the 24 -h or 30-day death rate in the post-MTP implementation group over those in the pre-MTP implementation group. The lack of improved survival outcomes might have resulted from insufficient compliance with the protocol, which was designed to have a 1:1 ratio of plasma to pRBC transfusion, but the actual plasma to pRBC ratio given was 1:1.58 even after MTP implementation. This transfusion ratio may be affected by unbalanced pRBC transfusion prior to the activation of the MTP. Numerical improvement of the plasma to pRBC ratio from 1:1.91 to 1:1.58 was probably not sufficient to generate statistically significant improvement of the death rate in non-trauma patients. Mesar [12] and their colleagues reported that survival was not significantly different between patients who received a high plasma to pRBC ratio and patients who received a low ratio. They also mentioned that certain categories of non-traumatic hemorrhagic patients might have improved or worsened survival when transfused with a high ratio of plasma to pRBC. Their subgroup analysis showed a beneficial effect for patients who received massive transfusion during vascular surgeries, but a contrary result was found for patients in general surgery. This result suggests that one should not assume that the transfusion of a high plasma to pRBC ratio will always benefit all patient groups. Recent meta-analysis [16] reported that the non-significant effect of MTP on death rate and delayed MTP activation in non-trauma patients may have affected the result. This delay might result from the unclear actual onset of bleeding in patients with non-traumatic massive hemorrhage.

The worst value of the platelets during the 24 -h period was significantly improved in the post-MTP implementation group, although there was no statistically significant difference in pre-transfusion platelet level between the two groups. This improvement might be achieved by more aggressive administration of platelet components after protocol implementation. On the other hand, coagulation profiles of our results showed several numerically or statistically better pre-transfusion values in the post-MTP implementation group than in the pre-MTP implementation group. Because the SOFA score was similar between the two groups, we could assume that there was no difference in the severity of illness. This difference of pre-transfusion coagulation profiles could be explained by improvement in the timeliness of initial laboratory tests after protocol implementation.

Our result showed a significant improvement in the timeliness of the first unit of pRBC transfusion after implementation of MTP. The speed of delivery of blood products was increased by removing the cross-matching process from the first package of blood products in a massive hemorrhagic situation. During the transfusion of the first package, the blood bank performs a preemptive cross-matching process for the next packages. Protocol-based communication between the clinical team and the laboratory medicine team was essential to improve the efficiency of the overall process. McDaniel et al. [11] also showed the benefit of MTP implementation in non-trauma patients by shortening of blood product release time. They commented that the use of a protocol is related to consistent rapid release of blood products. The time to initiate the first plasma was shortened, but this was not significant, probably because of our practice, we usually transfuse pRBC prior to plasma when the route of administration is limited thus causing more delay of plasma than of pRBC. This limitation could be improved by preparing thawed plasma at the blood bank, but, in our institute, thawed plasma is not available yet.

Hypothermia is associated with impairment of coagulation factor activity and platelet function [1,17]. Considering the vicious cycle of acidosis, hypothermia, and coagulopathy [18], our protocol was developed to maintain body temperature above 36 °C. Implementation of MTP successfully elevated mean body temperature from 34.7 °C to 35.6 °C with statistical significance. This might prevent reducing of coagulation system activity and platelet function, but neither showed an improvement of the actual measured coagulation profiles or of the death rate.

Tranexamic acid was demonstrated to positively reduce death rate in multiple or head trauma patients [19,20] and postpartum hemorrhage when administrated within three hours [21]. In our protocol, use of tranexamic acid was routinely recommended during the resuscitation of patients with hemorrhage. After MTP implementation, there was a statistically significant increase of use of tranexamic acid from 31% to more than 55%. However, this improvement was not connected to survival benefit after implementation of MTP in our study, perhaps because too little tranexamic acid was used or because of other confounding factors mentioned previously. Nevertheless, tranexamic acid is recommended and should be used during resuscitation [1].

The limitations of this study are as follows. First, it was retrospective. Second, we did not investigate clinical sequelae of massive transfusion, such as transfusion-related acute lung injury or abdominal compartment syndrome from the perspective of morbidity and death rate. Such undiscovered confounding factors might have influenced our results. Third, there were difference in laboratory sampling frequencies. Investigating the worst value of coagulation profiles was possible, but this value may not reflect the actual worst moment of the coagulation

profile of each patient. Fourth, the study population was highly heterogeneous, even though we excluded a large portion of the patients (n = 472) because massive transfusion was decided on and initiated during the operation. And the use of anticoagulation medications should be considered. Finally, we did not investigate clinical management of hemorrhage other than by massive transfusion, such as crystalloid fluid resuscitation or use of vasopressor agents, which can affect the final result of resuscitation from hemorrhagic shock.

5. Conclusions

MTP implementation did not show a statistically significant death rate reduction in patients who received massive transfusion because of hemorrhage. However, laboratory profiles and clinical practice were improved after implementation. Development and implementation of an evidence-based protocol for massive transfusion is also critical in non-traumatic patients. Investigation of this non-traumatic patient population is challenging because of its heterogeneity, so further large-scale research is needed to evaluate confounding severity and co-morbidity.

Authorship contributions

K.W.Y., D.C., D.S.L., E.G., K.Y., K.J.C. and C.P. designed the study. K.W.Y. and C.P. acquired and analyzed the data. K.W.Y., D.C., D.S.L., and C.P. participated in drafting the article and critically revising it. All authors approved the final version of the manuscript.

Disclosure

- The authors declare no conflicts of interest.
- This manuscript is based on master's degree thesis of the first author (Kyoung Won Yoon)
- The abstract of this manuscript has been presented at the 70th annual congress of KSS (the Korean Surgical Society), November 1, 2018, Grand Hilton Seoul, Seoul, Korea, and the 39th annual congress and acute critical care conference of KSCCM (the Korean society of critical care medicine), April 26, 2019, The-K Hotel, Seoul, Korea.

Declaration of Competing Interest

No potential conflict of interest relevant to this article was reported and no funding was used for this work.

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