단일 3차 병원에서 외상환자와 비-외상환자의 대량수혈 분석

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Analysis of Massive Transfusion for Trauma Patients and Non-Trauma Patients in a Tertiary Hospital

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Background: Management of patients with massive hemorrhage often requires the massive blood transfusions. However, few studies have investigated the effects of massive transfusions on non-traumatic patients. Therefore, this study analyzed mortality and descriptive data for patients receiving massive transfusion, including non-trauma patients and trauma patients.

Methods: We reviewed a retrospective audit of massive transfusions to investigate the major causes, patient characteristics, ratio of the blood components, and the mortality of massively transfused patients. The analysis was performed using electronic medical records collected from January 2010 to December 2013. Patients who had received a massive transfusion (≥ 10 units of RBCs within 24-hours) were categorized into trauma and non-trauma patients. We calculated the ratio of blood components and investigated the relationship between ratio and mortality. Descriptive statistics were used to characterize the patients and the indications.

Results: A total of 532 massive transfusions were performed, including 187 trauma and 345 non-trauma patients. The overall mortality rate was 32.0%, encompassing 36.4% of the trauma patients and 29.6% of the non-trauma patients. The mortality in trauma patients was significantly reduced ($P < 0.001$) within the first 48-hours compared with that in non-trauma patients, which was due to the high FFP: RBC ratio transfusion. The annual FFP: RBC ratio in trauma patients showed an increasing trend. Non-trauma patients showed no relationship between mortality and procedure indication/blood component ratio.

Conclusion: We report clinical data pertaining to massive transfusions. Annual increasing FFP: RBC ratio in trauma patients was associated with a decreasing mortality. Non-trauma patients showed heterogeneous characteristics and a lower FFP: RBC ratio than trauma patients. (Korean J Blood Transfus 2016;27:237-246)

Key words: Massive hemorrhage, Massive transfusion, Trauma, Non-trauma, Mortality

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Introduction

Massive hemorrhage is a significant challenge for all clinicians, and interdisciplinary therapeutic approaches to their treatment must be decided within a limited time frame. Massive transfusion, which has historically been defined as the replacement of blood by the transfusion of 10 units of red blood cells (RBC) in 24 hours, had been conducted in cases of massive and uncontrolled hemorrhage.

In the 1970s, massive transfusion was associated with mortality rates of more than 90%, but advances in care have led to a dramatic decrease in mortality to 30%~70%.¹⁾ Massive hemorrhage is a common complication in some clinical settings. In traumatic injury, hemorrhage is one of the leading causes of morbidity, and it is responsible for almost 50% and up to 80% of deaths occurring within 24 hours of injury and deaths during operation, respectively. Moreover, cardiovascular procedures frequently results in massive bleeding,²⁾ and postpartum hemorrhage events could occur after delivery.³⁾ In these situations, supporting blood components while controlling massive hemorrhage is critical. However, the majority of literature has focused on massive transfusion due to traumatic hemorrhage, while there is little information available regarding massive transfusion in other situations.

There has been recent concern regarding the excessive application of massive transfusion in non-trauma patients who do not ultimately require massive transfusion.⁴⁾ However, there are virtually lack data available on massively transfused non-trauma patients. To address the paucity of data regarding massive transfusion for non-trauma patients, we reviewed all

cases of massive transfusion, regardless of trauma relation. Specifically, we collected massive transfusion data regarding both trauma and non-trauma cases and evaluated the clinical characteristics of patients in both groups. In addition, associations between in-hospital mortality and baseline risk factors, procedural risk factors, and transfused blood component ratio were assessed.

Materials and Methods

1. Study design

This retrospective study was based on data acquired from a tertiary referral hospital that has 1,104 beds and used over 20,000 RBC units per year, from January 2010 to December 2013. Over 500 patients who were given ≥ 10 red blood cell units within 24 hours, including all massively transfused patients categorized as both trauma and non-trauma. We identified trauma patients as those with a potentially severe physical injury caused by an external source (falling, automobile crash, knife wound, etc.) that required emergency medical intervention to prevent loss of life or limb or substantial, permanent physical impairment. Non-trauma patients were identified as those who suffered moderate or minor injuries, as well as heart attacks, strokes, other internal conditions such as chronic infectious diseases or surgical procedures.

2. TASH scoring system

The Trauma-Associated Severe Hemorrhage (TASH) score is recognized as an easy-to-calculate and valid scoring system to predict an individual's probability

for massive transfusion and thus ongoing life-threatening hemorrhage at a very early stage after severe injury. The TASH scoring system uses seven independent variables to identify patients who will require a massive transfusion.⁵⁾ These include blood pressure, gender, hemoglobin, focused abdominal sonography for trauma, pulse, base excess, and extremity or pelvic fractures and are weighted. Overall, 16 scores need to be summed to calculate the total score with a possible range of scores from 0 to 23. Recently, a threshold of 18 points as cut off, which corresponded to a 50% probability of massive transfusion in trauma patients.⁶⁾

3. Ratio of transfused blood components

Each transfusion requirement for fresh frozen plasma (FFP), platelets (PLT) and RBCs in the massive transfusion were used to determine the FFP: RBC or PLT: RBC ratio. As this was a continuous variable, a specific cut point was required to categorize patients into the comparison groups. Those patients who received at least a ratio of 1:1.0 were categorized as the high ratio group. Patients who received a transfusion ratio of 1:1.0 or less were categorized as the low ratio group.

4. Surgical procedure categorization

The surgical procedure is a reliable predictor of massive transfusion and mortality; thus, it was important to adjust for this variable when assessing the relationship between massive transfusion and outcome. We categorized patient procedures based on 231 clinically meaningful categories by using the clinical classification software (CCS) procedures for

ICD-9-CM developed by the Agency for Healthcare Research and Quality.⁷⁾ We then aggregated the identified CCS categories into one of the following 16 procedure categories: nervous, endocrine, eye, ear, nose, respiratory, cardiovascular, hemic and lymphatic, digestive, urinary, male genital, female genital, obstetrical, musculoskeletal, integumentary, and miscellaneous procedures. Since some of the 16 procedure categories of the patients had low frequencies ($n < 8$), we combined them into a single group in this study to simplify the table.

5. Statistical methods

For each of the outcomes, the proportion of patients

Fig. 1. The number of patients for each trauma or FFP: RBC ratio subgroup. The patients who received at least a ratio of 1:1.0 were categorized as the high ratio group and other patients who received a transfusion ratio of 1:1.0 or less were categorized as a low ratio group.

Abbreviations: RBC, red blood cells; FFP, fresh frozen plasma.

experiencing the outcome and its associated 95% binomial exact confidence interval (CI) were estimated. A two-sided P value of <0.05 was considered to be statistically significant. Continuous, normally distributed data were reported as the means (standard deviation [SD]). The univariate association between RBC usage, FFP or PLT to RBC ratio and mortality was performed using the chi-square test, while the Mann-Whitney U or ANOVA was used to identify differences between ranked ordinal data. Statistical analysis was performed using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

From 2010 to 2013, 499 patients received a total of 532 episodes of massive transfusion totaling 23,741 blood components. The mean age was 53.5 years, and the study population consisted of 322 men and 177 women. The overall in-hospital mortality was 32.0% and the 48 hr-mortality was 11.9%. Cases were divided into several subgroups, including trauma, death, and FFP: RBC ratio (Fig. 1). Each graph is divided into death and survivor patients, and each cell shows the number of patients.

Table 1. Characteristics in massively transfused episodes (n=532)

	Trauma (n=187)	Non-trauma (n=345)	P value
Age (years), mean (SD)	47.7 (17.7)	56.6 (16.9)	$<0.001^*$
< 18, N (%)	3 (1.6)	7 (2.0)	
18 ~ 39, N (%)	57 (30.5)	56 (16.2)	
40 ~ 64, N (%)	96 (51.3)	138 (40.0)	
65 ~ 79, N (%)	22 (11.8)	129 (37.4)	
≥ 80 , N (%)	9 (4.8)	15 (4.3)	
Male, N (%)	132 (70.6)	195 (56.5)	<0.001
ASA classification, N (%)	142 (75.9)	268 (77.7)	$<0.001^{\dagger}$
1	4	15	
2	20	51	
3	46	84	
4	62	107	
5	10	11	
Emergency operation, N (%)	127 (67.9)	171 (49.6)	<0.001
TASH score, mean (SD)	13.2 (6.4)	7.8 (5.3)	<0.001
Initial Hb, mean (SD)	9.5 (2.6)	9.8 (3.0)	0.43

* P values based on the Mann-Whitney test; † P values based on one way ANOVA.

Abbreviations: SD, standard deviation; ASA, american society of anesthesiologists; TASH, trauma-associated severe hemorrhage score; Hb, hemoglobin.

1. Demographics of massively transfused patients

Among 532 massive transfusion cases, 187 (35.2%) were due to traumatic injuries and 345 (64.8%) were due to non-traumatic indications. Baseline demographic data comparing trauma with non-trauma in the massive transfusion group are presented in Table 1. Statistical analysis of age, gender, anesthesia level, elective or emergency operation, TASH score, and initial hemoglobin (Hb) level was conducted. There were differences between groups, with the trauma group having a relatively younger age, higher male portion, more frequent emergent operations, and higher TASH score. A total 409 operations were conducted, 298 of which were conducted as emergencies. Based on the American Society of Anesthesiologists (ASA) physical status, 50.7% (72 of 142) of the trauma and 44.0% (118 of 268) in non-trauma for whom general anesthesia was implicated were greater than class four. General anesthesia was performed more frequently in the trauma group ($P < 0.001$), possibly because more patients in the non-trauma group were too sick to undergo surgery.

2. Mortality and blood usage between trauma and non-trauma groups

There was no difference in overall mortality between the trauma and non-trauma groups; however, a difference in early mortality existed between the two groups. Specifically, the mortality within 12 hours in trauma patients (17.8%) was higher than that in non-trauma patients (9.2%), which was similar to the 2 day mortality of massively transfused patients ($P < 0.001$). The number of RBC transfu-

Table 2. Mean units and ratios of transfused products and mortality in trauma and non-trauma patients

	Mortality		RBC (units)		FFP/RBC ratio		PLT/RBC ratio	
	Trauma N (%)	Non-trauma N (%)	Trauma	Non-trauma	Trauma	Non-trauma	Trauma	Non-trauma
Total	187	345	20.2	16.7	0.74	0.59	0.61	0.77
Survivor	119	243	17.7	16.1	0.75	0.58	0.67	0.81
12 hr mortality	34 (17.8)	32 (9.2)	23.7	19.3	0.75	0.58	0.31	0.32
48 hr mortality	47 (24.6)	64 (18.5)	26.6	19.0	0.74	0.6	0.4	0.44
In-hospital mortality*	68 (36.4)	102 (29.6)	24.4	18.1	0.71	0.63	0.51	0.67
2010	21/57 (36.8)	21/115 (18.3)	18.1	16.2	0.62	0.49	0.47	0.58
2011	20/44 (45.5)	19/73 (26.0)	20.9	18.8	0.72	0.57	0.77	0.77
2012	15/37 (40.5)	30/86 (34.9)	22.8	16.9	0.83	0.70	0.65	0.94
2013	12/39 (24.5)	32/71 (45.1)	19.9	15.2	0.82	0.64	0.60	0.87
P value			0.234 [†]	0.262 [†]	0.172 [†]	0.054 [†]	0.556 [†]	0.724 [†]

*Mortality indicates number of expired patients/number of massively transfused patients (%); [†]P value determined by a chi-squared test of mortality between trauma and non-trauma patients; [‡]P value based on chi-squared tests of survivor and non-survivor between trauma subgroups using trauma-weight cases. Abbreviations: RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelet; hr, hour.

sions in patients who expired in admission (20.6 [12.9]) was univariably greater than in patients who survived (16.7 [8.5], $P < 0.001$).

Comparison of trauma patients and non-trauma patients revealed a difference in transfused RBC units, with an average of 20.2 units being observed in trauma- and 16.7 units in non-trauma patients (Table 2). Massively transfused trauma patients received FFP: RBC and PLT: RBC at 0.74:1 and 0.61:1, respectively. Although the appropriate product ratio for non-trauma patients is unclear, our transfusion ratio is similar to the protocol goal of 1:1:1 (FFP: RBC: PLT), which was developed based on data pertaining to trauma patients.⁸⁾ We didn't faithfully carry out the guidance, even though better ratio was shown in trauma patients.

3. Mortality with FFP: RBC ratio in trauma patients

The trend of early mortality in trauma patients has decreased since 2012; however, the FFP: RBC ratio has increased with time (Fig. 2). There were no differences in the annual mean TASH score in the trauma and non-trauma groups (9.29 [6.4], $P > 0.05$). According to the blood component ratio, two groups, a low and high ratio, were similar in age, gender, and overall mortality, but trauma sustained, mean TASH score, and average RBC usage was different (data not shown). Although no statistical differences in mortality were observed between those who received a high FFP: RBC ratio versus those who had a low FFP: RBC ratio, the group with the high FFP:

Fig. 2. Annual mortality (A) and FFP: RBC ratio (B) for early (within 2 days) mortality. (A) Mortality of trauma patients was higher than that of non-traumatic patient, except for 2013. (B) Annual FFP:RBC ratio in trauma patients showed an increasing trend.

Abbreviations: See Fig. 1 for FFP, RBC and T_12h_M, 12 hours-mortality of trauma; N_12h_M, 12 hours-mortality of non-trauma; T_48h_M, 48 hours-mortality of trauma; N_48h_M, 48 hours-mortality of non-trauma; T_12h_FR, FFP:RBC ratio of trauma patients who died within 12 hours; N_12h_FR, FFP:RBC ratio of non-trauma patients who died within 12 hours; T_48h_FR, FFP:RBC ratio of trauma patients who died within 48 hours; N_48h_FR, FFP:RBC ratio of non-trauma patients who died within 48 hours.

RBC ratio had a reduced blood transfusion requirement ($P < 0.001$). Moreover, the high FFP: RBC ratio group had low average RBC usage instead of a high mean TASH score.

4. Blood transfusion requirement according to surgical procedure categories

According to CCS categories, the individual diagnostic categories were 42.1% of cardiovascular procedures, 17.7% of musculoskeletal operations, 11.8% of gastrointestinal operations, and 5.8% of obstetrical complications. The cardiovascular procedural category included many non-trauma cases (84.8%) and the mean age was older than that of trauma patients. The significant high mortality in several categories disappeared after a partial correlation controlling for age. The categories with a lower proportion (below 50%) of traumatic patients showed higher mortality than traumatic patients, except for the non-procedure category (Table 3). These results

could be explained by a large proportion of the categories showing high mortality.

Discussion

As massive hemorrhage is a highly emergent situation that can be life-threatening, many patients who received massive transfusion sustained an overall mortality rate of 32.0%. Mortality rate ranged was lowest (3.2%) for the obstetrical procedure and highest (69.0%) for patients with severe illnesses that could not undergo surgery. Previous studies of massive blood transfusions have mostly been based on trauma patients. For example, there are several clinical scoring systems that can predict the implications of receiving a massive blood transfusion in trauma patients, or known risk factors for prognosis such as the FFP:RBC ratio or sex.^{1,5,8)} However, other large numbers of massively transfused patients are admitted due to massive non-traumatic hemorrhage.^{3,9)} Therefore, there are clinical limitations to

Table 3. Blood transfusion requirements according to disease categories (n=532)

Procedure	Total patients		Trauma patients		RBC	FFP/RBC ratio	PLT/RBC ratio
	N	Mortality (%)	N	Mortality (%)	Mean units		
Cardiovascular	224	32.1	34	29.4	17.3	0.57	0.87
Musculoskeletal	94	10.6	53	13.2	16.5	0.62	0.57
Digestive	63	41.3	33	45.5	23.6	0.74	0.65
Obstetrical	31	3.2	3	0.0	21.0	0.78	0.74
Thoracic	23	43.5	16	50.0	22.6	0.78	0.58
Nervous	21	47.6	19	52.6	15.0	0.70	0.58
Others*	18	5.6	7	0.0	17.2	0.73	0.52
Non-procedure	58	69.0	22	81.8	14.3	0.68	0.58

*A group of orthopedics, neurosurgery, urology, otolaryngology, plastics, and gynecology.
Abbreviations: RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelet.

applying massive transfusion scoring systems such as the TASH score to non-trauma patients. In this study, the results showed a surprisingly low TASH score in both trauma and non-trauma patients, with a mean (SD) 13.2 (6.4) in trauma patients and 7.8 (5.3) in non-trauma patients. These discrepancies indicate that the predictive scoring system could not be utilized in our clinical situation. According to the TASH score definition, our patients may have received over-activation of massive transfusion, especially non-trauma patients. TASH score is selectively studied in some trauma cases, and the above definition may not reflect the acute resuscitative phase of treatment or non-trauma cases appropriately.^{5,6)} The relationship between blood loss and administered blood volume will be most direct for a large number of RBC units. Use of the blood component during massive transfusion in the expired group was significantly higher than in the survivor group. This might be explained by survivors sustaining relatively mild blood loss relative to expired patients (data not shown, $P < 0.001$).

Although most patients were massively transfused with a low FFP: RBC ratio and low PLT: RBC ratio, there was no significant difference between blood component ratio and mortality, which is contrary to the results of previous studies.¹⁰⁾ Unexpectedly, non-trauma patients showed low FFP: RBC ratio and an even higher mean age than trauma patients. Overall usage of blood components during massive transfusion in the high FFP: RBC ratio group was significantly lower than in the low FFP: RBC ratio group. The hospital blood bank and physician hypothesized that a fixed blood component ratio would help reduce utilization of the overall blood com-

ponent. For our trauma department, education regarding the implications of using a 1:1:1 ratio in massive transfusion started to improve the mortality of massively transfused patients from 2011.⁸⁾ Thereby, we report a trend of decreasing mortality in trauma patients although non-trauma patients do not have company with inconstant policies on FFP: RBC ratio for non-trauma patients. These findings are supported by those of previous clinical studies that have provided evidence that a higher ratio of FFP: RBC is associated with an improved outcome.¹¹⁾

The results of this study demonstrate the importance of education regarding a high ratio of FFP: RBC in the case of massive transfusion. Furthermore, efficient massive transfusion protocols must be established to control problems that occur in massive transfusions such as inconstant blood usage or component ratio, regardless of disease categories or trauma. Some known massive transfusion protocols have confirmed that the use of massive transfusion protocol is directly correlated with improved mortality and reduced number of complications in clinically injured patients who receive Rh-O pack RBC and subsequent laboratory tests.¹²⁻¹⁴⁾ The first goal of the protocol is to improve mortality and reduce blood usage by establishing appropriate implication timing of massive transfusion.

In future studies, we will evaluate the implications of a standardized massive transfusion protocol in our hospital. After several years, we hope to report the appropriations and usefulness of a massive transfusion protocol in a tertiary referral hospital.¹⁵⁾

요 약

배경: 대량출혈 환자의 처치시 대량수혈을 필요로 하는 경우가 종종 있다. 하지만 외상환자에 비해 비-외상환자의 대량수혈 연구는 드물게 보고되어 있다. 본 연구에서는 대량수혈을 받은 비-외상환자와 외상환자를 포함하여 사망률과 설명적 데이터를 분석하였다.

방법: 대량수혈을 받은 환자들의 주요 원인, 환자 특성, 혈액제제비 및 사망률 등을 살펴보기 위해 후향적으로 대량수혈 사례를 검토했다. 2010년 1월부터 2013년 12월까지의 전자의무기록을 이용하였다. 대량수혈(24시간 내에 ≥ 10 단위 적혈구제제 수혈) 환자를 외상환자와 비-외상환자로 분류하였다. 혈액제제비를 구하고, 비와 사망률의 상관관계를 확인하였다. 환자 특성과 대량수혈의 적응증에 대해서는 기술적 통계를 사용하였다.

결과: 총 532건의 대량수혈을 수행하였고, 이는 187건의 외상환자와 345건의 비-외상환자로 구분되었다. 전체 사망률은 32.0%였고, 외상환자군은 36.4%, 비-외상환자에서는 29.6%의 사망률을 보였다. 외상환자군에서 높은 신선동결혈장:적혈구 비로 수혈 받은 환자의 48시간 이내 사망률이 유의하게 낮았으며, 연간 신선동결혈장:적혈구 비는 증가하는 경향을 보였다. 비-외상환자군은 혈액제제비나 적응증이 사망률과 상관관계를 보이지 않았다.

결론: 외상환자군에서 연간 경향을 보면 신선동결혈장:적혈구 비가 증가하면서 외상환자의 사망률이 감소하는 경향을 보였다. 비-외상환자군은 이질성을 보이며 외상환자군에 비해 낮은 신선동결혈장:적혈구 비를 보였다.

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