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# Massive transfusion practice in non-trauma related hemorrhagic shock

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ABSTRACT

*Purpose:* Evidence suggests that trauma patients with hemorrhagic shock requiring massive transfusion have improved outcomes if resuscitated with a prescribed massive transfusion protocol (MTP). However, there is limited data regarding the efficacy of MTP in non-trauma patients.
*Methods:* This was a retrospective observational study of all patients who received a massive transfusion protocol for non-traumatic hemorrhagic shock over a four-year period. The primary outcome was in-patient hospital survival. We dichotomized recipients of MTP into survivors versus non-survivors, comparing outcomes of interest within the categories by nonparametric testing. Summary statistics expressed as median (interquartile range).
*Results:* Fifty-nine patients were reviewed, with the median age of 59.0 (35.0–71.0) years old. Thirty-three (56%) patients survived. Survivors were younger, 57.0 (30.0–67.0) versus 64.0 (53.5–71.5) years old ($p = 0.047$), and had lower Sequential Organ Failure Assessment scores (6.0 (3.0–8.0) versus11.5 (9.5–13.0); $p = 0.008$). Patients on the medical service receiving MTP had an increased risk of mortality (odds ratio 4.26; $p = 0.02$).
*Conclusion:* Over half of the patients receiving massive transfusion protocols for their non-trauma related hemorrhagic shock survived. Survivors were younger, were less acutely ill, and on non-medical services. Further research is needed to investigate best practice for transfusion in non-trauma related hemorrhagic shock.
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## 1. Introduction

Transfusion of large amounts of platelets and plasma to red blood cells in a fixed ratio is a practice derived from trauma patients, with significant focus on hemostatic resuscitation with the use of massive transfusion protocol (MTP) [1-10]. These protocols incorporate limiting the use of crystalloids and colloids with early transfusion of fresh frozen plasma (FFP) and platelets in balanced ratio to mimic whole blood replacement [2,3]. The desired effect of massive transfusions is to prolong survival in the acute setting, allowing time to perform directed interventions to control the site of bleeding [8-14]. The threshold for activating a massive transfusion protocol has been emphasized to occur when a patient has received ≥10 units of blood products within 24-h [1,2,15]. There exist other thresholds for initiation, such as the critical administration threshold, which is defined as the transfusion of 3 units of packed red blood cells (RBC) within any 1 h after arrival to the hospital, in the hope of earlier recognition of life-threatening bleeding [16-17]. Regardless of when to activate large volumes of blood products for transfusion, massive transfusion protocols have resulted in a standardized transfusion intervention [18-22].

This standardization of MTP also applies to patients with non-trauma hemorrhagic shock [17-19]. However, the acceptance of such transfusion practices for non-trauma patients has drawn criticism recently, highlighting that non-trauma patients differ as a population from trauma patients: from source of bleeding to having more co-morbidities than trauma patients [21,22]. Further, non-trauma patients themselves are greatly heterogeneous as a population [22]. Finally, there is a paucity of data regarding the clinical outcomes of non-trauma patients receiving a massive transfusion protocol, especially in non-trauma centers [21].

This study intended to review the transfusion practice and outcomes of a massive transfusion protocol in a non-trauma population, evaluating the differences between in-hospital survivors and non-survivors. This retrospective analysis hypothesizes that non-trauma patients who received our massive transfusion protocol had no difference in transfusion amount and ratio between in-hospital survivors and non-survivors. Further, we evaluated patient survival based on care (obstetric, medical, and surgical) in order to further address the heterogeneity of non-trauma patients and their outcomes from a massive transfusion protocol.

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## 2. Methods

### 2.1. Study design

This was a retrospective observational study of adult non-trauma patients for whom massive transfusion protocol (MTP) was activated between 2012 and 2016 at a single urban, non-trauma center hospital. The study was conducted after protocol approval by the St. Agnes Hospital Institutional Review Board.

### 2.2. Study population and massive transfusion protocol

Study population included all adult (age 18 or older), non-traumatic patients who were admitted and had MTP activated. Massive transfusion was defined as (a) transfusion of 10 units of packed red blood cells (RBC) within 24 h after initiation of MTP or (b) transfusion of three or more units of RBC within any one hour in the first 24 h after admission (critical administration threshold, CAT) [23].

The hospital's massive transfusion protocol calls for a ratio of 2:1 for packed red blood cells (RBC) to fresh frozen plasma (FFP). For every MTP activation, the blood bank is notified and a designated person is in charge of obtaining and delivering the blood products. Initially, two units of RBC are released. This is followed by 4 units of RBC and 2 units of FFP (known as batch-1). Subsequent batches contain the same ratio of blood RBC and FFP. For every 10 units of RBC, one packed unit of platelet (average of 6 pooled units) is issued and for every 20 units of RBC, 10 units of cryoprecipitate are issued. Initiation and termination of the MTP, subsequent laboratory data and defining the endpoint of resuscitation is at the discretion of the attending who initiated the MTP.

### 2.3. Outcome measures

The primary exposure variable was completion of a massive transfusion protocol. The etiology of hemorrhage was identified by review of electronic medical records, which included the patient's history, clinical notes, laboratory investigations and diagnostic imaging reports.

The primary outcome was in-hospital survival of non-traumatic, massively bleeding patients who received the MTP. Secondary outcomes included evaluating survival differences in regards to blood products received and survival among the in-patient subgroups: surgery, medicine and obstetrics. Variables that were evaluated to assess impact on the primary and secondary outcomes included age, severity of illness on admission to the intensive care unit (ICU) admission (via the Sequential Organ Failure Assessment (SOFA score)), length of stay in the ICU, length of stay in the hospital, laboratory data (specifically lactic acidosis), Charlson Comorbid Index, presence or absence of cirrhosis and model for end stage liver disease (MELD score) for cirrhotic patients. The total unit of blood products transfused represents the number of blood products given as part of MTP. Lactic acid levels represented the worst value within 24 h of initiation massive transfusion.

### 2.4. Statistical analysis

Patient characteristics are reported as median (interquartile range, IQR). Non-parametric testing was conducted using Mann Whitney *U* test for continuous variables and Fisher's exact tests for categorical variables. Kruskal–Wallis test was conducted to compare statistically significant differences between independent patient groupings. Logistic regression models were evaluated for best-fit modeling for the primary outcome of in-hospital survival. Both univariable and multivariable regression models were conducted for best fit modeling. Odds ratios are reported with 95% confidence intervals. Statistical analyses were conducted with SigmaPlot 11.0 (San Jose, CA) and R software (Version 0.99.903) with alpha set at $<0.05$.

## 3. Results

### 3.1. Patient characteristics

There were 102 patients who were ordered massive transfusion protocol (MTP) between 2012 and 2016. Of the 102 patients, 59 (57.8%) patients met the criteria warranting MTP, as described in the methods section, and constituted our study population. The median age of the patients was 59.0 (35.0–71.0) and 38 (64.4%) were female. In regards to transfusion ratios, 15 (25.4%) patients received a FFP:RBC at a ratio > 1:2, while 31 (52.5%) received platelets:RBC at a ratio > 1:2. Thirty-three (55.9%) of the 59 patients who received MTP survived their in-hospital admission. Table 1 summarizes the characteristic of the patients who received MTP.

The 59 patients who met MTP criteria were divided based on their in-patient team: obstetrics (14 patients), medicine (28 patients), and surgery (17 patients). The majority of obstetric patients (10 of the 14) had post-partum hemorrhage; the rest had vaginal bleeding, uterine bleeding, or post-Cesarean section bleeding. Regarding medicine patients, three had bleeding due to procedural vascular complications, one patient had an intra-abdominal hematoma, and the remaining (24 patients) had gastrointestinal bleeding. The majority of the surgery patients [11] had bleeding due to vascular morbidities (e.g. abdominal aortic aneurysm rupture). The remaining surgical patients had an intraoperative bleed (two patients), a post-operative bleed, a splenic bleed, a spontaneous thigh hematoma, and one gastrointestinal bleed.

### 3.2. Massive transfusion protocol survivor characteristics

Survivors of hemorrhagic shock who received the massive transfusion protocol were younger (57.0 (30.0–67.0) years old) than non-survivors (64.0 (53.5–71.5) years old) ($p = 0.047$) and had a lower Charlson co-morbidity index (1.0 (0.0–4.0) versus 3.5 (3.0–4.8); $p = 0.004$). In regards to the severity of their presentation at the time of their hemorrhagic shock, survivors had lower SOFA scores (6.0 (3.0–8.0) versus 11.5 (9.5–13.0); $p = 0.005$) and lactic acid levels (2.5

**Table 1**
Baseline characteristics of patients who received massive transfusion protocol. Variables are expressed as median (interquartile range) where appropriate.

| | Patients ($N = 59$) |
|---|---|
| Age (years) | 59.0 (35.0–71.0) |
| Female (%) | 38 (64.4) |
| Charlson co-morbidity index | 3.0 (0.0–4.5) |
| Cirrhotic (%) | 8 (13.6) |
| MELD score | 23 (15.5–27.0) |
| End Stage Renal Disease on Hemodialysis (%) | 1 (1.7) |
| Medications | |
| VKA (%)[a] | 3 (5.1) |
| Antiplatelet Agents (%) | 14 (23.7) |
| SOFA score (first 24 h) | 7.0 (3.0–11.0) |
| In-hospital service (%) | |
| Obstetric | 14 (23.7) |
| Surgery | 17 (28.8) |
| Medicine | 28 (47.5) |
| Total RBC Transfusion (units) | 8.0 (5.0–11.0) |
| Total FFP Transfusion (units) | 4.0 (2.0–7.0) |
| Total Platelet Transfusion (units) | 6.0 (0.0–12.0) |
| Ratio of Blood Products | |
| FFP:RBC >1:2 (%) | 15 (25.4) |
| Platelet:RBC >1:2 (%) | 31 (52.5) |
| Lactic acid (mg/dL) | 5.1 (2.1–9.6) |
| Length of stay (days) | |
| Intensive Care Unit | 3.0 (1.0–5.5) |
| Hospital | 5.0 (2.0–12.0) |
| Expired (%) | 26 (44.1) |

Abbreviations: SOFA = sequential Organ Failure Assessment; RBC = red blood cells; FFP = fresh frozen plasma; MELD = model for end stage liver disease; INR = international normalized ratio; VKA = vitamin K antagonist.

[a] Note that all three patients on vitamin K antagonists survived.