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Manuscript Title: Any changes in recent massive transfusion practices in a tertiary level institution?

Short Title: Recent massive transfusion practices

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This work should be attributed to Department of Haematology and Genetic Pathology, Flinders University
Background & Objectives: A previous review of transfusion practices in our institution between 1998 and 2008 showed a trend of high ratios of red cells (RC) to plasma (FFP) and platelets to RC towards the later years of review period. The aim of the study was to further evaluate transfusion practices in the form of blood product usage and outcomes following massive transfusion (MT).

Methods: All adult patients with critical bleeding who received a MT (defined as ≥10 units of RC in 24 hrs) in 2008 and between January 2010 and December 2014 were identified. Blood and blood products transfused, in-hospital mortality, 24 hour and 90-day mortality were analysed for the period 2010 to 2014. Blood and blood product usage, Massive Transfusion Protocol (MTP) activation and use of ROTEM between 2008 and 2014 were compared.

Results: A total of 190 MT including surgical (52.1%), gastro-intestinal bleeding (25.3%), trauma (11.6%) and obstetric haemorrhage (5.8%) episodes were identified between 2010 and 2014. The overall in-hospital mortality was 26.7% with a significant difference in 24 hour (p=0.04) and 90-day mortality (p=0.02) between diagnostic groups. Comparing 2008 (n=33) and 2014 (n=23), there was no significant difference in median RC, FFP and platelet units, cryoprecipitate doses and RC:FFP ratio; however there was an increase in number of patients who used cryoprecipitate (54.5% vs 87%, p=0.01).

Conclusion: Aligned with haemostatic resuscitation, the trend continues in the form of increased use of plasma and higher RC:FFP transfusion ratios including an increase in number of patients receiving cryoprecipitate.

Introduction

Massive haemorrhage remains a major cause of mortality in massively bleeding patients. Anticipating haemorrhage, managing coagulopathy and guiding transfusion is critical to managing massive haemorrhage. Advances in resuscitation using the concept of damage control, use of scoring systems to predict MT, early replacement of coagulation factors and improved laboratory testing have improved outcomes.

The key findings from the initial review of massive transfusion practices in our institution between 1998 and 2006 were (a) one third of the patients were coagulopathic at the start of MT episode (b) significant differences in laboratory parameters and transfusion practices between pre-Intensive Care (ICU) and ICU phase of MT episode (c) MT patients with early deaths were coagulopathic at the start and on ICU admission and did not correct coagulopathy[1]. This led to the implementation of MTP in our institution in 2008. When transfusion practices were reviewed between 1998 and 2008, there was a trend towards early and aggressive resuscitation to correct coagulopathy based on the use of high ratios of plasma to RC (1:1 or 1:1.2) and platelets to RC (1:1 or 1:2) including the use of haemostatic agents (recombinant factor VIIa), thawed plasma and prothrombinex-VF during the latter part of the review period[2].

Haemostatic resuscitation consists of early delivery of coagulation therapy (plasma and platelet transfusion) as a part of a massive haemorrhage protocol combined with permissive hypotension and early haemostatic control[3]. Haemostatic resuscitation of patients with massive haemorrhage has shifted towards earlier administration of higher ratios of plasma and platelets to RCs [4, 5]. In addition to the ratios of blood products, fibrinogen containing products in the form of fibrinogen concentrate and cryoprecipitate and anti-fibrinolytic agents such as tranexamic acid are being used increasingly in trauma and non-trauma resuscitation. A recent study found that a high platelet or plasma to RC ratio, and use of tranexamic acid were associated with a decreased need for MT and increased survival in injured patients with bleeding[6].
The objective of this study was to further evaluate recent transfusion practices in the form of blood and blood product usage and outcomes following MT in our institution after 2008. We hypothesised that the use of MTP and ROTEM would lead to changes in blood product use in MT patients.

Methods:

A retrospective study of patients from Flinders Medical Centre, a 560 bed tertiary care hospital and trauma and liver transplant centre was undertaken. All adult patients with critical bleeding who received a MT (defined as ≥10 units of RC in 24hrs) in 2008 and between January 2010 and December 2014 were identified. Blood and blood products transfused, in-hospital mortality, 24 hour and 90-day mortality were analysed for the period 2010 to 2014. Blood and blood product usage, MTP activation and use of ROTEM between 2008 and 2014 were compared.

Transfusion Practice

Issue of blood products by the transfusion laboratory was performed through locally implemented MTP. Upon activation of the massive transfusion response, and if the patient’s blood group were not known, 5 units of blood O Rh negative RC, 4 units of blood group AB thawed FFP and 1 unit of apheresis or pooled platelets were sent to the patient’s location in an appropriate transport shipper. The transfusion laboratory continued to prepare pre-designed massive transfusion packs with addition of cryoprecipitate in the second pack. All blood components met Australian specifications including leucodepletion. Plasma was thawed and issued to order. In cases where plasma was not used it was returned to stock and stored at 4°C for 5 days from thawing. Emergency group A plasma was not used during the review period for non-group A patients. A standard dose of cryoprecipitate was defined as 10 units of whole blood cryoprecipitate or five units of apheresis cryoprecipitate.

Coagulation management was guided by laboratory tests including haemoglobin level, platelet count, international normalised ratio (INR), partial thromboplastin time (APTT), fibrinogen and ROTEM. ROTEM when implemented in 2010 in our institution was used for monitoring coagulation and transfusion of blood products mainly for patients undergoing liver transplantation. Over time ROTEM was used in other clinical groups. Transfusion of FFP, platelets or cryoprecipitate based on a pre-defined ROTEM algorithm was not a part of MTP rather replacement was based on the ROTEM results and at the clinician’s discretion.

In the initial years of review period where only MTP was used, RC, plasma and platelets were transfused empirically during the MT episode. In the latter years, with the use of MTP and ROTEM it was a combination of empirical transfusion and ROTEM based transfusion. The transfusion threshold for blood products using ROTEM was: If EXTEM CT was >100, FFP was transfused. If EXTEM MCF >20 -<45 and FIBTEM MCF >8, platelets were transfused. If EXTEM MCF >20 -<45 and FIBTEM MCF <8 cryoprecipitate was transfused. If EXTEM MCF was <20 and FIBTEM MCF < 8, both cryoprecipitate and platelets were transfused.

Data Collection

Data collected included blood and blood product use, patient demographics, in-hospital mortality, and ICU and hospital length of stay (LOS). Blood and blood products transfused, in-hospital mortality, 24-hour and 90-day mortality were analysed for the period 2010 to 2014. Since the previous review of MT included the year 2008 we compared blood and blood product usage, MTP activation and use of ROTEM between 2008 and 2014 were compared.
Statistics

Continuous data were presented as medians and interquartile ranges (IQRs). Continuous variables between the groups were compared with the Mann-Whitney test and categorical variables were compared with Pearson’s Chi-square. P values <0.05 were considered statistically significant. All statistical analyses were undertaken using the Statistical Package for Social Sciences 20.0.

Results: A total of 190 MT episodes were identified during 2010-2014. The main causes of MT included gastro-intestinal haemorrhage (GIB) (48/190, 25.3%), trauma (22/190, 11.6%), cardiothoracic surgery (29/190, 15.3%) followed by other surgery (29/190, 15.3%), liver transplant/surgery (23/190, 12.1%), vascular surgery (18/190, 9.5%), obstetric haemorrhage (11/190, 5.8%), medical/other (10/190, 5.3%). Patients had a median age of 60 (IQR 45-73) and 62% were males. Eighty five per cent of patients were admitted into ICU with a median LOS of 82 (IQR 19-262) hours. The median length of hospital stay and intensive care stay was 18 (7-35) days and 99 (38-325) hours respectively.

Overall, patients received a median of 13 (IQR 11-18) units of RC, 10 (IQR 7-14) units of FFP, 3 (IQR 2-4) units of platelets, 1 (IQR 0-3) dose of cryoprecipitate during 24 hours of MT and 1:1.4 (IQR 1:1.6-1:1.8) FFP: RC ratio. A small proportion of patients also received Prothrombinex VF (11%) and recombinant factor VIIa (4.2%). There was no difference in blood and blood product usage between the different clinical groups except the use of platelets (p=0.01) as summarised in Table 1. There was a trend towards higher use of cryoprecipitate (p=0.05) mainly in the liver surgery and vascular surgery patients.

Table 2 summarise the blood and blood product transfused including the use of MTP and ROTEM through the 4-year period. Comparing 2008 and 2014, there was no a significant difference in the amount of RC, FFP and platelet use; however there was an increase in number of patients who used cryoprecipitate (Fig 2a). There was an increase in MTP activation and use of ROTEM over the study period (Fig 2b & 2c).

The overall in-hospital mortality was 26.7% (51/190) and ranged from 50% in medical group to none in obstetric haemorrhage (p=0.04) (Table 1). The overall 24-hour and 90-day mortality was 7.4% (14/190) and 30.5% (58/190) respectively. Figures 1 and 2 show the cumulative survival rate at 24 hours after admission and 90 days for all diagnostic groups including cardiothoracic, trauma, GIB, vascular surgery and medical/other group. There was no difference in overall in-hospital mortality between 2008 and 2014 (Table 3) including mortality within the different groups (data not shown).

Discussion

Our study confirmed ongoing massive transfusion practices such as early start of empirical plasma, higher plasma based RC: FFP transfusion and a trend towards increased use of cryoprecipitate in our institution. The majority (54%) of the MT episodes were for surgical indications including cardiac, vascular, liver and other surgery with a small percentage (12%) was being trauma patients. This is comparable to the large-scale study based on nationwide data from Sweden and Denmark that showed that massive transfusion for obstetrical care and trauma account for small proportion of all massive transfusion[7].

The median plasma to RC ratio was 1:1.5 at our institution with no difference in plasma to RC ratio across the diagnostic groups. The PROPPR trial [8], showed no difference in mortality at 24 hours or at 30 days in MT patients due to trauma patients who receive 1:1:1 or 1:1:2 ratio. However, the optimum ratios for non-trauma patient remain elusive. In addition to the optimum ratios of blood products, fine-tuning the timely communication, processing and delivering elements of MTP may be
just as essential [9]. Trying to refine the MTP processes at the participating centres was one of the key changes for PROPPR trial where after much effort; the median delivery time of the first round of products was reduced to 8 minutes[8].

There are little data regarding MT in non-trauma settings. In our study, the 90–day mortality differed considerably between diagnostic groups with the lowest mortality among patients with obstetrical haemorrhage and highest mortality in the medical group. The medical group in our study included patients with non-haematological malignancy and gastroenterological diseases. The epidemiology study from Denmark and Sweden[7] found an overall 5-year mortality rate of 54.6% in patients who received a massive transfusion with a 5-year mortality rate of 91.1% in patients with a malignant disease with no surgery and 1.7% among patients transfused for obstetrical bleeding[7]. According to the study by Turan et al, non–cardiac surgery patients who died within 30 days of a massive transfusion were generally older, more likely to have had a vascular surgical procedure, abnormal international normalised ratio, higher ASA status, preoperative coma and sepsis and higher postoperative bleeding requiring transfusion[10]. Kreuziger et al. [11] and Morse et al.[12] did not find any difference in in-hospital and 30-day mortality between trauma and non-trauma patients respectively including transfusion ratio whereas Martinez et al found a reduction in 24 hour and 30-day mortality after implementation of goal-directed MBP for prompt and aggressive management of non-trauma massive bleeding patients [11-13].

Massive Transfusion Protocols

There was an increase in MTP use between 2010 and 2014 with a higher proportion of patients (77.8%) using MTP in 2014 compared to 29% in 2008 when it was first implemented. Availability of MTP has led to its utilisation in patients with major bleeding from non-traumatic causes such as aneurysm rupture, post-partum haemorrhage and gastro-intestinal bleeding. Recent studies have evaluated the impact of MTP activation on blood product utilisation and patient mortality [11, 13, 14]. We previously reported that MTP use between 2008 and 2011 increased plasma, platelet and cryoprecipitate per patient but the median number of RCs transfused or hospital mortality did not change[15]. Kreuziger et al [11] in their study showed that transfusion ratios and mortality were not different between trauma and non-trauma patients with MTP implementation.

Viscoelastic assays

Similar to the use of MTP, ROTEM use has increased considerably in our institution from 46% in 2010 when it was implemented to 85.1% in 2014. The current practice in our institution is to run ROTEM as soon as an MTP is activated which then helps in guiding transfusion. A major challenge in treating severe bleeding patients, whether in trauma or obstetric haemorrhage, gastro-intestinal bleeding or cardiothoracic surgery, is to determine the cause of blood loss due to surgical causes or coagulopathy. More and more evidence suggests that whole blood viscoelastic assays such as thromboelastography and rotational thromboelastometry may have a role in identifying patients requiring supplementation and guiding the dose and timing of fibrinogen administration in trauma [16, 17]. A recent study has shown that utilisation of a goal directed, TEG-guided MTP to resuscitate severely injured patients improves survival compared with an MTP guided by conventional coagulation assays and uses less plasma and platelet transfusion during the early phase of resuscitation[18]. The role of these assays has also been extended to identification of target values for coagulation parameters in trauma haemorrhage as haemostatic resuscitation has been shown not to achieve correction of hypoperfusion and coagulopathy during the acute phase of trauma haemorrhage [19].
Cryoprecipitate

Our study highlighted an increase in number of patients receiving cryoprecipitate. Cryoprecipitate use was seen across all the clinical groups; patients undergoing liver surgery, which included liver transplant, had the highest use of cryoprecipitate. An association with increased use of cryoprecipitate and ROTEM can be speculated, although the data were not analysed to validate this finding. Our earlier review of transfusion practices for MT patients showed a negligible use of cryoprecipitate between 1998 and 2005[2]. In the initial years of the review period (2009-11), like most MTPs, transfusion of fibrinogen in the form of cryoprecipitate was late in the protocol. However, with increased use of viscoelastic assays; early use of cryoprecipitate has been observed in our institution. Rourke et al have shown that standard protocol driven transfusion ratios were ineffective in maintaining fibrinogen levels[16]. It is proposed that early cryoprecipitate administration could improve clinical outcomes during trauma haemorrhage. Khan et al have shown that high dose plasma transfusion does not correct trauma induced coagulopathy and coagulopathy parameters only improve with plasma, cryoprecipitate and platelet transfusion with a combined high fibrinogen load[20]. Early fibrinogen supplementation using cryoprecipitate is feasible in trauma patients and has been demonstrated by Curry et al [21].

There is increasing evidence supporting the role of fibrinogen during active bleeding and the use of Fibrinogen concentrate in clinical situations with severe haemorrhage such as trauma, cardiac surgery, obstetric haemorrhage and general surgery. Fibrinogen concentrate is only licensed in Australia for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenema.

Other Products

Transfusion practices in massive haemorrhage have continually changed as blood products administered to massively bleeding patients have changed. Other than improved laboratory testing and haemodynamic monitoring, pharmacological adjuncts in the form of tranexamic acid; products such as prothrombin complex concentrate have been advocated in the recent times.

The Clinical Randomisation of an Antifibrinolytic in Significant haemorrhage (CRASH-2) RCT showed that tranexamic acid significantly reduced the risk of death resulting from bleeding. Though tranexamic acid is not a part of our massive transfusion protocol, it may be given by the clinicians when required. One of the many clinical trials studying the effect of tranexamic acid in pre-hospital trauma care, is the PATCH study, an international multi-centre, randomised, double-blind, placebo-controlled trial of pre-hospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy[22]. It is possible that some of the trauma patients may have participated in the PATCH trial but it was beyond the scope of the study to collect these data.

In conclusion, this is a retrospective study from a single centre. Blood and blood product use based on the institutional transfusion practice may be different from other centres in Australia and worldwide. This study did not investigate the impact of RC:FFP ratios on mortality in trauma and non-trauma patients.

Haemostatic resuscitation in the form of plasma based RC: FFP transfusion continues in both trauma and non-trauma patients with massive bleeding with an increased use of cryoprecipitate. Optimum identification of target values for coagulation parameters is required to manage coagulopathy in these patients depending on the aetiology.
Acknowledgements

RS collected, analysed and interpreted the data; DR interpreted and critically evaluated the paper. The authors have no conflict of interest to disclose.

References


Fig 1a & b. Kaplan Meier cumulative incidence of survival over days (90 days & 24 hours) by clinical groups

CTS: Cardiothoracic Surgery
CTS: Cardiothoracic Surgery
GIB: Gastro-intestinal Bleeding
Fig 2 a& b & c. Yearly comparisons of cryoprecipitate use, MTP activations and ROTEM use for coagulation monitoring
Table 1 Summary of blood and blood product requirements for patients by clinical groups

<table>
<thead>
<tr>
<th></th>
<th>Gastrointestinal haemorrhage (n=48)</th>
<th>Other surgery (n=33)</th>
<th>Cardiotoracic Surgery (n=29)</th>
<th>Trauma (n=22)</th>
<th>Liver Surgery (n=23)</th>
<th>Obstetric haemorrhage (n=11)</th>
<th>Medical/Other (n=10)</th>
<th>Vascular Surgery (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>12 (10-20)</td>
<td>12 (10.5-17)</td>
<td>12 (11-15.5)</td>
<td>12.5 (11.3-18.5)</td>
<td>13 (10.8-20.3)</td>
<td>14 (11-15)</td>
<td>13 (10.8-20.3)</td>
<td>17 (13.5-26.5)</td>
</tr>
<tr>
<td>FFP</td>
<td>10 (6-16)</td>
<td>9.5 (7-13.5)</td>
<td>9 (8-15.5)</td>
<td>10 (7-14.5)</td>
<td>11.5 (7.3-18.8)</td>
<td>8 (6-10)</td>
<td>11 (6-15)</td>
<td>10 (7.5-19)</td>
</tr>
<tr>
<td>Platelets</td>
<td>2 (2-4)</td>
<td>3 (2-4)</td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
<td>4 (2.3-5.8)</td>
<td>2 (1-2)</td>
<td>3 (1.8-5.3)</td>
<td>3 (1.5-5)</td>
</tr>
<tr>
<td>Cryoprecipitate (doses)</td>
<td>1 (0-2.8)</td>
<td>1.5 (0-4)</td>
<td>1 (1-2.5)</td>
<td>1 (0-4)</td>
<td>4 (2.3-6.8)</td>
<td>1 (1-2)</td>
<td></td>
<td>0.5 (0-4.5)</td>
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<tr>
<td>Cryoprecipitate (n, %)</td>
<td>35 (72.9%)</td>
<td>20 (69%)</td>
<td>23 (79.3%)</td>
<td>15 (68.2%)</td>
<td>14 (87.5%)</td>
<td>9 (81.8%)</td>
<td>5 (50%)</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>Plasma to RBC ratio</td>
<td>1:1.4</td>
<td>1:1.4</td>
<td>1:1.4</td>
<td>1:1.4</td>
<td>1:1.2</td>
<td>1:1.6</td>
<td>1:1.4</td>
<td>1:1.6</td>
</tr>
<tr>
<td>Mortality</td>
<td>18 (37.5%)</td>
<td>7 (24.1%)</td>
<td>11 (34.4%)</td>
<td>5 (22.7%)</td>
<td>2 (8.7%)</td>
<td>0 (0%)</td>
<td>5 (50%)</td>
<td>7 (38.9%)</td>
</tr>
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</table>
Table 2  Summary of blood and blood product requirements, mortality, MTP and ROTEM use for patients – yearly comparison

<table>
<thead>
<tr>
<th></th>
<th>2008 (n=34)</th>
<th>2010 (n=50)</th>
<th>2011 (n=43)</th>
<th>2012 (n=39)</th>
<th>2013 (n=31)</th>
<th>2014 (n=27)</th>
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</thead>
<tbody>
<tr>
<td>RBC</td>
<td>12.5 (12-16)</td>
<td>12 (11-20.5)</td>
<td>14 (11-16)</td>
<td>12 (10-15)</td>
<td>14 (10-19)</td>
<td>14.5 (12-18.8)</td>
</tr>
<tr>
<td>FFP</td>
<td>10 (6-16)</td>
<td>9 (7-15)</td>
<td>9 (7-12)</td>
<td>9 (7-12)</td>
<td>9.5 (6-16.5)</td>
<td>10 (7-14.5)</td>
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<tr>
<td>Platelets</td>
<td>2 (1.8-3)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>3 (2-4.3)</td>
<td>3 (2-4.8)</td>
</tr>
<tr>
<td>Cryoprecipitate (doses)</td>
<td>1 (0-3)</td>
<td>1 (0-2.5)</td>
<td>1 (0-3)</td>
<td>2 (1-4)</td>
<td>1.5 (0-3.0)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Plasma to RBC ratio</td>
<td>1:1.4</td>
<td>1:1.5</td>
<td>1:1.4</td>
<td>1:1.4</td>
<td>1:1.4</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Mortality</td>
<td>11 (32.4%)</td>
<td>12 (24%)</td>
<td>14 (32.6%)</td>
<td>6 (15.4%)</td>
<td>7 (22.6%)</td>
<td>14 (51.9%)</td>
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