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Ten-year evolution of a massive transfusion protocol in a level 1 trauma centre: have outcomes improved?

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Abstract

Background: We aimed to evaluate the evolution and implementation of the massive transfusion protocol (MTP) in an urban level 1 trauma centre. Most data on this topic comes from trauma centres with high exposure to life-threatening haemorrhage. This study examines the effect of the introduction of an MTP in an Australian level 1 trauma centre.

Methods: A retrospective study of prospectively collected data was performed over a 14-year period. Three groups of trauma patients, who received more than 10 units of packed red blood cells (PRBC), were compared: a pre-MTP group (2002–2006), an MTP-I group (2006–2010) and an MTP-II group (2010–2016) when the protocol was updated. Key outcomes were mortality, complications and number of blood products transfused.

Results: A total of 168 patients were included: 54 pre-MTP patients were compared to 47 MTP-I and 67 MTP-II patients. In the MTP-II group, fewer units of PRBC and platelets were administered within the first 24 h: 17 versus 14 ($P = 0.01$) and 12 versus 8 ($P < 0.001$), respectively. Less infections were noted in the MTP-I group: 51.9% versus 31.9% ($P = 0.04$). No significant differences were found regarding mortality, ventilator days, intensive care unit and total hospital lengths of stay.

Conclusion: Introduction of an MTP-II in our level 1 civilian trauma centre significantly reduced the amount of PRBC and platelets used during damage control resuscitation. Introduction of the MTP did not directly impact survival or the incidence of complications. Nevertheless, this study reflects the complexity of real-life medical care in a level 1 civilian trauma centre.

Introduction

Haemorrhagic shock is consistently the second-leading cause of early deaths in trauma, second only to central nervous system injury.[1,2] In trauma patients, priority lies with early haemorrhage control and restoration of blood volume and coagulation. Bleeding patients that do not or barely respond to fluid therapy have exsanguinating injuries.[2] In these patients, a massive transfusion can be life-saving. Massive transfusion is usually defined as transfusion of more than 10 packed red blood cells (PRBC) within 24 h.[3]

Massively transfused patients often present with early and profound coagulopathy. Up to 25% of these patients have significant coagulopathy upon arrival to hospital.[4] In the hectic clinical situation of exsanguination, massive transfusion is often performed

empirically, not guided by blood tests.[2] Contemporary evidence suggests that outcomes are improved when PRBC, fresh frozen plasma (FFP) and platelets (PLTs) are transfused in predefined ratios.[4–6] These predefined transfusion ratios and timing for laboratory tests are described in a massive transfusion protocol (MTP). Once the protocol is activated, the blood bank provides rapid and timely delivery of all blood products to facilitate resuscitation.

Over time, MTPs have become standard practice for level 1 trauma centres, even though these protocols vary significantly and have not always been associated with improved mortality in before-and-after studies.[6–8] Nunez *et al*.[9] noted that only 3–5% of all trauma admissions will require massive transfusion. Consequently, in the busiest trauma centres, with 2000 trauma admissions annually, exposure is unlikely to exceed 100 patients per year. This study examines the effect of an MTP in an Australian level 1 trauma centre with 300 major trauma admissions (Injury Severity Score (ISS) >15) and approximately 12 massively transfused patients per year. The aim was to evaluate the evolution of the MTP in an urban level 1 trauma centre with lower exposure to life-threatening traumatic haemorrhage than the larger international trauma centres reflected in the current literature.

Methods

An observational study was performed in Liverpool Hospital, Sydney, Australia, a level 1 trauma centre. Three groups of trauma patients who underwent massive transfusion were compared: a pre-MTP group (2002–2006), a group treated according to MTP-I (2006–2010) and a group treated according to MTP-II (2010–2016) (Fig. S1).

Trauma patients who were massively transfused were identified through the Liverpool Hospital Trauma Registry and the Blood Bank Registry. Data collection was undertaken prospectively by a limited group of three specially trained nurses. The Sydney South West Area Health Service Human Research Ethics Committee approved the research design.

Massive transfusion protocol

The first MTP for trauma at Liverpool Hospital became active on 1 February 2006. This MTP-I could be activated by a doctor calling the blood bank or by the blood bank staff when noticing dispatch of the fifth unit of PRBC in a 2-h period. The MTP provided for empiric administration of FFP and PLTs (one pooled bag consists of four single donor PLT units) after the first 6 units of PRBC. Criteria for the use of recombinant activated factor VII (rFVIIa) and other management options were embedded (Appendix S1).

Before 2010 a transfusion ratio of PRBC : FFP : PLTs = 6:4:1 was used, based on the literature available at the time (Appendix S1). In 2010 the MTP was reviewed and updated to a ratio of PRBC : FFP = 1:1 because of a survival advantage identified in the literature.[10,11] With activation of the updated MTP-II in 2010, four pre-thawed units of FFP were dispatched with 4 units of PRBC. Then every subsequent shipment contained 4 units of red cells and 4 units of FFP, and alternating one pooled PLTs pack and 5 units of cryoprecipitate or only 5 units of cryoprecipitate (Appendix S2).

Patients and characteristics

Included were all trauma patients who received massive transfusion between January 2002 and July 2016. Massive transfusion was defined as having received 10 or more units of PRBC within 24 h of admission and the first blood product within 6 h of admission.

Trauma patients where MTP was activated because of another cause not directly related to trauma were excluded.

Clinical, laboratory and outcome parameters were extracted as well as time-interval and transfusion data by using the mentioned registries, individual patient notes and electronic patient files. Characteristics included age, gender, trauma mechanism, systolic blood pressure, heart rate, pH, haemoglobin level, PLT count and pre-hospital fluid volume.

Compliance

The average transfusion ratio was calculated, as was the percentage in which protocol target ratios were reached. In addition, the percentage of PRBC : FFP ratios of 3:1 or higher were scored as these appear to be associated with a worse outcome.[12]

Outcomes

Mortality at 24 h hospital discharge, ventilator and intensive care unit (ICU) days and complications were analysed. Abdominal compartment syndrome (ACS) was defined as sustained intra-abdominal pressure of more than 20 mmHg associated with new organ dysfunction or organ failure. Multiple organ dysfunction syndrome (MODS) as the development of progressive and potentially reversible physiological dysfunction in three or more organs.[13] Infection as a clinically relevant and/or culture positive diagnosis identified by the treating doctor. The number of blood products that were administered within the first 24 h through to the end of ICU stay was scored. Interval times were measured from time of arrival in the emergency department through to the administration of the first blood product. Data sets were checked for completeness before statistical analysis.

Statistical analyses

Parametric data were presented as mean ± standard deviation, whereas non-parametric data were presented as median plus range. For normally distributed data the Student's *t*-test was used to compare groups. Comparisons for categorical data were performed using chi-squared analysis. In case of skewed distribution of data, the Mann–Whitney *U*-test was used. Analyses of variance and Kruskal–Wallis test were used to compare all three groups (SPSS 16, Chicago, IL, USA). Statistical significance was set to P-values <0.05.

Results

Patients and characteristics

During the period of 1 January 2002 until 31 July 2016 a total of 4432 major trauma patients (ISS >15) were admitted. Of these, 168 patients met the study inclusion criteria for massive transfusion.

All groups were comparable regarding age, gender, mechanism of injury, ISS, systolic blood pressure, pH, PLT count and the administered volume of pre-hospital fluids upon emergency department arrival, except for haemoglobin level which was higher in the MTP-II group (114 versus 113 versus 123 mmoL/L, $P = 0.04$; Table S1).

Compliance

The average PRBC : FFP ratio in the 47 patients in the MTP-I group was 1.92:1; for the 67 patients in the MTP-II group this was 1.94:1. Fourteen (29.8%) patients of the MTP-I group met the PRBC : FFP transfusion ratio of 6:4, and one (2.1%) patient met the PRBC : FFP : PLTs ratio of 6:4:1. Fifty-two (77.6%) patients of the MTP-II group met a PRBC : FFP transfusion ratio of 1:1, and 39 (58.2%) patients met a PRBC : FFP : PLTs ratio of 1:1:1. In the pre-MTP group 19 (35.2%) patients had PRBC : FFP transfusion ratios higher than 3:1. In the MTP-I and MTP-II groups, six (12.8%) patients and 13 (19.4%) patients had transfusion ratios higher than 3:1 ($P = 0.35$; Table S2).

Outcomes

Mortality 24 h following admission did not differ between pre-MTP and MTP-I groups: 29.6% versus 29.8% ($P = 0.99$). No differences were found regarding the number of days patients were in ICU and the total number of ventilator days and hospital length of stay. Although the incidence of ACS and MODS was comparable between groups, the incidence of infections was significantly lower in the MTP-I group when compared to the pre-MTP group (51.9% versus 31.9%, $P = 0.04$).

Mortality 24 h following admission did not significantly differ between the MTP-I and MTP-II groups: 29.8% versus 38.8% ($P = 0.32$). Mortality through to hospital discharge was similar: 42.6% versus 49.3% ($P = 0.48$). Furthermore, no differences were found regarding ICU lengths of stay, ventilator days and hospital lengths of stay between groups: 21 versus 7 hospital days ($P = 0.37$). Moreover, the incidence of ACS, MODS and infections did not differ between the groups (Table S3).

Amount of blood products

The number of blood products administered within 24 h of admission and during the ICU stay did not differ between the pre-MTP group and the MTP-I group (Table S4). However, significantly fewer units of PRBC were administered within the first 24 h of admission and throughout the ICU stay, in the MTP-II group compared to the MTP-I group: 14 versus 17 ($P = 0.01$) and 16 versus 21 ($P > 0.001$), respectively. The number of administered units of PLTs within the first 24 h and in total was significantly lower in the MTP-II group compared to the MTP-I group: 8 versus 12 ($P < 0.001$) and 8 versus 12 ($P = 0.01$), respectively.

Regarding the administration of rFVIIa, it was significantly less frequently administered in the MTP-II group compared to the MTP-I group: 9.0% versus 27.7% ($P = 0.01$). There was no difference between groups regarding the administration of FFP within 24 h and in total until the end of ICU stay (Table S4).

The time interval between admission and administration of the first blood product seemed to improve in the MTP-II group, although the difference was not significant: MTP-I versus MTP-II; 19 versus 14 min ($P = 0.08$; Table S5). No difference was found between the pre-MTP and the MTP-I groups; 18 versus 19 min ($P = 0.45$; Table S5).

Discussion

Massive transfusion plays a crucial role in resuscitating patients with exsanguinating injuries, though scientific reports on the effect of MTPs are contradictory.[14] As a result, MTPs differ between institutions, and the effect of the protocols varies as well. A meta-analysis in 2013 of observational studies in trauma centres with exposure to massive haemorrhage on average 40 cases a year, showed no benefit of introduction of an MTP.[15]

Survival

In our study, introduction of an MTP did not improve survival in massively transfused trauma patients. The low number of patients in the MTP-II group (39/67 patients, 58.2%) in which the target transfusion ratio of 1:1:0.5 (PRBC : FFP : PLTs) was reached, may be a significant aspect to this result. However, this study and its outcomes are a reflection of real-life medicine where an MTP could give guidance in the hectic clinical situation of exsanguination, yet it might not always be attainable. Exposure to trauma patients with massive transfusion in our hospital averaged 10–12 patients per year and this seems limited compared to bigger centres that did find a survival advantage.[15] However, even in the busiest civilian trauma centres, the number of patients that receive massive transfusion is likely to be less than 100 patients per year.[16]

Compliance

The absence of clear recommendations in the MTP field may lead to poor compliance.[17] Cotton *et al.*[7] found that only 27% of all trauma exsanguination protocol activations had full compliance during a performance improvement investigation and compliance could only be improved to a maximum of 50%. Bawazeer *et al.*[17] found a mean compliance rate of 66% with a clear association between survival and a higher level of compliance. The retrospective design of our study did not allow us to evaluate compliance to our MTP. However, besides the low number of patients in which the target transfusion ratio was reached, 12.8% in the MTP-I and 19.4% in MTP-II group had transfusion ratios higher than 3:1. According to Johansson *et al.*,[12] in that case early outcome was much worse with an early mortality of 57%. Thus, when interpreting our findings poor compliance to the MTP should be taken into account. Although challenging in a level 1 trauma centre with only one to two MTP cases per month, increasing protocol compliance should be a priority as it may save lives.

Amount of blood products

In the MTP-II group, a decrease in blood product usage was found. This is consistent with other studies.[6,7] The intended target ratio of these studies was PRBC : FFP : PLTs of 1:1:1, which might explain

why the same decrease was not found in the MTP-I group with a target ratio of 6:4:1.

Unlike other studies, no difference was found in FFP usage in the MTP-II group. Until 2010 already thawed FFP, like in other MTPs, was not available on demand in our hospital.[18] Hence, it is possible that patients in the MTP-I group may not have received sufficient numbers of FFP in a timely fashion, while transfusing PRBC. Furthermore, the lower usage of PLTs we found, may have been affected by the introduction of cryoprecipitate to the MTP in 2008. As an effect, fewer units of PLTs were transfused. This may in turn bias the effect of the MTP-II on the lower usage of PLTs.

We expected that introduction of the MTP would reduce the time between admission and administration of the first blood product. However, the reduction found in this study appeared statistically not significant, which could in part be due to low compliance. Aside from a blood utilization and cost standpoint, the reduction in blood product usage may potentially lead to a reduction in morbidity among survivors as lower blood product administration is associated with fewer complications.[7]

Recombinant factor VIIa

Recombinant factor VIIa (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) was used as a 'last resort' for the treatment of coagulopathy in trauma patients since 2003.[19,20] However, the CONTROL trial was terminated early in 2010 because of futility, and rFVIIa became less popular.[21] Congruent with this result, the use of rFVIIa was found to be lower in our MTP-II group compared to prior.

Hospital stay and complications

No differences were found regarding ICU and hospital lengths of stay, and ventilator days, in contrast to the study of Cotton *et al*.[7] The same study also found a decrease in the number of complications, such as ACS, MODS and infections after introduction of an MTP. Our study did find a significant decrease in the number of infections in the MTP-I group compared to the pre-MTP group. However, since no other differences were found between groups, our finding may not be associated with the implementation of aMTP but rather improvements in trauma care overall, and specific aspects of ICU care may be responsible.[22]

Limitations

Our study is a single centre, observational study with the limitations of all retrospective registry reviews introducing information bias; however, data collection for the Liverpool Hospital Trauma Registry was done prospectively and by a limited group of three specially trained nurses, which contributes positively to the validity of our data. Additionally, survival bias and reverse survival bias should be taken into account, as severely injured patients may have died before they received a 10th unit of PRBC, or achieved haemostasis and therefore received less than 10 PRBC, and were therefore excluded.

During the years covering this study, tranexamic acid, prothrombin complex concentrates and cryoprecipitate became increasingly used and may have affected treatment and outcomes. Furthermore, the use of ventilator and ICU days as an outcome can be challenging as many patients die before extubation or ICU discharge. The concept of ventilator- and ICU-free days has been proposed as an alternative combining mortality and mechanical ventilation duration. However, Bodet-Contentin *et al*.[23] concluded that use of ventilator-free days as an outcome has many drawbacks.

Despite the power of this study is limited, due to the relatively small sample size, the use of historic controls and the high protocol failure, it does reflect the realities of MTP use in an Australian major trauma centre and may reflect common practice at civilian level 1 trauma centres with similar exposure.

Recommendations

Survival improves significantly when the target ratio of PRBC : FFP : PLTs of 1:1:1 is reached.[18,24] Therefore, at a local level, further effort is needed to improve both the MTP design and the logistics of its implementation so the target ratio is more often realized. Improving compliance to the protocol should be priority, as compliance independently improves survival.[17] To that end, a human factors-supported approach could be used to guide the design and implementation of a new support system for MTP to optimize the practice and performance of trauma and blood bank staff by gathering qualitative and quantitative data on current clinical practice regarding damage control resuscitation.[25] This approach may lead to more successful implementation of an updated MTP by promoting good decision support, providing different options for getting consistent and improved outcomes and offering a way to measure the effects of these types of complex interventions.[25]

Ongoing data collection will allow us to analyse outcomes in some of the subgroups and may allow for a more precise determination of the effect of an MTP. Recently, literature on MTP is carefully recommending the implementation of viscoelastic haemostatic assays such as thromboelastography and thromboelastometry in the protocol.[26] Mortality improved as an effect of goal-directed resuscitation in at least one study according to Stensballe *et al*.[27] Closely monitoring the results of the ongoing trial on this topic is recommended as results so far are promising.

Conclusion

Initial introduction of an MTP (MTP-I) did not affect survival, blood product usage or the incidence of patient complications in this Australian level 1 civilian trauma centre. However, the introduction of an updated MTP (MTP-II) significantly reduced blood product usage though there remained no discernible effect on patient mortality, or the incidence of complications.

Although an MTP can give guidance in the hectic clinical situation of exsanguination, precise and exact MTP compliance in real-life medicine can be challenging. The results from this study demonstrate MTP effect in a moderate volume environment and may be useful in similar trauma system settings. Although this study demonstrates issues in MTP compliance which need attention, there are also encouraging results with regard to decreased blood product usage. Further efforts towards improved MTP compliance are warranted.

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Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Table S1. Characteristics.
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Appendix S1. MTP-I.
Appendix S2. MTP-II.