

If not now, when? The value of the MTP in managing massive bleeding

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There is mounting evidence that providing blood transfusion to trauma patients as soon as possible -well within the first hour after injury- improves the odds of survival. A recent randomised controlled trial of severely wounded civilian trauma patients with relatively long helicopter transport times from the scene of the accident to the hospital showed that adding plasma to the standard of care reduced mortality at 30-days compared to receiving the standard of care alone¹. Interestingly, a secondary analysis of these data revealed that receipt of any blood product, RBCs alone, plasma alone, or a combination of these two products, produced superior survival compared to receipt of crystalloid alone². There are similar data in favour of early transfusion from the military³; a study of 502 combat casualties demonstrated that the provision RBCs, plasma, or a combination of these two products within 15 minutes of medical evacuation (MEDEVAC) rescue improved both 24 hour and 30 day survival compared to patients who did not receive any blood products or who received them later in the resuscitation. Available data also suggest that replacing the functionality of the patient's lost whole blood with either whole blood, or a mixture of RBCs, plasma, platelets and cryoprecipitate, is likely to improve outcomes compared to transfusion of mostly RBCs with little to no plasma or platelets⁴. Development of the optimal combination of blood products remains an active area of research.

So, it is apparent that blood products are important in the resuscitation of bleeding patients, especially when transfused early in massively bleeding trauma patients. Definitions of massive transfusion vary, but the intention of the massive transfusion protocol (MTP) is to provide a large quantity of the full complement of blood products at the clinical team's disposal so as to reduce (or ideally eliminate) the time required for the blood bank to supply individual components to the emergency department or the site of the resuscitation. While the contents of the MTP can vary between institutions, and some hospitals even have different contents for different bleeding etiologies⁵, the purpose of the MTP remains the same: a formal process for providing an "ectopic" blood bank at the site of the resuscitation in an evidence-based and coordinated fashion. By expediting the provision of blood products in a high-stress clinical environment, MTPs potentially reduce transfusion administration errors and improve clinical decision-making, and the value of these benefits cannot be understated. While MTPs have been in place at some institutions for many years, a fundamental question remains: do they result in a demonstrable improvement in patient clinical outcomes independent of other recent improvements in haemostatic resuscitation?

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This issue of Blood Transfusion features two papers that seek to answer this question. The first by Sanderson *et al.* is a scoping review of quality indicators (QI) reported in studies of MTPs⁶. This multinational group of authors analysed 107 articles where the effect of the institution's MTP was studied alone or relative to the hospital's pre-MTP era, while a few of the other studies looked at other aspects of the resuscitation or the nature of the bleeding. Interestingly, the authors found that only 9.3% of the studies they analysed reported whether the activation of the MTP was appropriate or not. While this seems likely to be a very important QI, one could turn the question around and ask "What is an appropriate MTP activation?". How can massive bleeding be predicted in real time and not just after the total number of blood products transfused is known? Although there are numerous scoring scales to predict massive bleeding⁷⁻¹³, in a recent survey of trauma centers participating in the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP), all sites reported that they used trauma surgeon judgement as a trigger for MTP activation, with hypotension and administration of uncrossed matched blood products used as a trigger about half of the time¹⁴. This subjectivity highlights the difficulty in predicting which haemorrhaging patient may eventually require a massive transfusion. Furthermore, imagine a situation where a trauma patient is hypotensive with some bruising, but is not visibly bleeding ... why is this patient hypotensive? From internal bleeding? Or maybe from traumatic brain injury or a medication effect? While the patient is being wheeled down to the CT scanner to check for bleeding, do you want to take the chance that he is bleeding and risk "getting behind" in terms of managing his coagulopathy and potentially rapidly developing anemia? No, one doesn't, so one would probably give him a small quantity of RBCs and plasma (or better yet low titer group O whole blood, LTOWB) while awaiting the results of the scan. If it turns out that the hypotension is not related to haemorrhage, that is, in retrospect once the etiology of the hypotension is known, it could seem that these early transfusions were not appropriate but they could be considered appropriate and pragmatic risk mitigation because the consequences of not treating a presumptive massive bleed can be catastrophic. When LTOWB was introduced at one of

the authors' institutions, its intention was for use only in massively bleeding patients but in the transfusion service we noticed that some patients received only one or two LTOWB units and no other blood products during their resuscitation. We initially thought that these were inappropriate utilisations until we were made aware of the dynamics, and especially the uncertainties, of blood product use in trauma. Our philosophy now is to over-provide blood products to a presumably massively bleeding patient and to do so quickly rather than undersupplying the resuscitation effort, knowing that this approach can lead to wastage of some blood products at some institutions.

Sanderson *et al.* also propose some quite reasonable novel QI indicators that could be included in future MTP-related studies. In addition, while the authors suggested "use of blood products prior to MTP" as a novel QI, we would like to suggest that this QI be specifically specified for the trauma patient population by the setting in which the pre-MTP blood products were transfused, i.e. in the pre-hospital setting (in ambulances or helicopters) *versus* in the ED or trauma bay. Given the recent evidence supporting the use of blood products in the pre-hospital part of the resuscitation, they are surely going to be used more frequently in the future so keeping an accurate count of when the pre-MTP blood products were administered is important. Using standardised QIs when reporting data on complex patients like those in trauma will allow future meta analysts and reviewers to combine data from the various studies to draw conclusions that are potentially more meaningful than those obtained in one study alone. Taking a standardised approach to data collection and reporting will progress the field, reduce confounding, and improve the care of these sick patients.

Another interesting point raised by Sanderson *et al.* is that few, ~6%, of the studies reported on the use of viscoelastic haemostatic assays (VHA) before and during the resuscitation effort. Perhaps these assays were not commonly used during the period of time in which the analysed studies were published (2007-2019), although the authors point out that nearly two thirds of the studies they analysed were published between 2015-2019. This is too bad because these assays can be used to customise the blood products that are provided to massively bleeding

patients¹⁵, which brings us to another important point to consider about MTPs. Much has been written about ratios of blood products in trauma resuscitation, and it is easy to confuse two separate concepts: the ratio of transfused blood products, and the ratio of blood products provided in the MTP. While it's true that there isn't a single optimal ratio for blood product transfusion for all trauma patients (because every patient is different), ratios that approach 1: 1 early in the resuscitation ensure that the patient receives balanced resuscitation, that is, they don't end up receiving for example 12 RBCs, 2 plasma units, and no platelets. Whatever the reader's preconceptions about high vs. low ratios might be, most will agree that an obviously imbalanced ratio like this example cannot be helpful for the patient (hence the increasing use of LTOWB at least early in the resuscitation¹⁶⁻¹⁸, but that's another story¹⁹). Nevertheless, just because there are, for example, 10 RBCs and 10 plasma units supplied in the MTP does not mean that this 1: 1 ratio is the ratio at which the blood products have to be administered throughout the resuscitation. The MTP is like an ectopic blood bank and its contents can be used in a more patient-specific manner once the laboratory test results, including VHA results, are known. The MTP is like a picnic basket that contains a variety of things to eat, at the beginning of the picnic you might take scoop of caprese salad and some sardines because you like them both, but if you later on realise that you want more sardines, you are not required to also take more caprese salad if you've had enough. Similarly, laboratory testing can guide the administration of blood products thereby obviating the need to follow a rigid ratio for the duration of the resuscitation.

Sanderson *et al.* described mortality outcomes in their review of primarily trauma patients. They found that at least one mortality outcome measure was reported in almost all of the studies they analysed, with in-hospital mortality being the most commonly reported outcome. In the other review paper on MTP utilisation in this issue, Consunji *et al.* focused their analysis on the effect of MTP utilisation on mortality outcomes, and included a formal meta-analysis of 14 studies of trauma patients²⁰. The authors found that compared to not having an MTP available, the use of an MTP significantly reduced overall mortality, although

there was no statistically significant improvement in either 24 hour or 30-day mortality. The authors conclude that the "signal" of improved survival that followed the implementation of an MTP, whether from the MTP itself or from other, non-transfusion related improvements in trauma management that might occur at the same time as the MTP, should encourage hospitals to implement an MTP right away.

It is important to note that mortality time points in bleeding studies are as diverse as the etiologies of the bleeding that they are studying. Three hour, six hour, 24 hour, 28 day, 30 day, in-hospital etc. are some of the end points that have been used. Which is the most relevant to capture haemorrhagic causes of death? The largest RCT on patients predicted to require a massive transfusion, The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study⁴, found that the median time to death from bleeding was 2.3 hours, which was similar to a median of 1.65 hours that had been reported previously²¹. This suggests that mortality time points that are much beyond this are irrelevant for capturing death by blood loss, as causes of death such as traumatic brain injury and cardiac causes of death occur at a median of 19.6 and 35.9 hours, respectively, after admission²¹. Thus, it was somewhat disappointing to find that 24 hour mortality was not reduced when the MTP was utilised, as this was the only time point in Consunji *et al.*'s study that is close to relevant for measuring bleeding outcomes. However, we shouldn't forget that the studies analysed in this meta-analysis compared the outcomes of trauma patients in a time before the hospital implemented an MTP to a time after the MTP was available. It's not as though they were comparing a period of time when blood products were not available or were only available in smaller quantities. The innovation in these studies was the (presumably) more rapid provision of a lot of blood products at once in something like a balanced ratio. We should temper our expectations of what an MTP itself can do for our patients, for as Sanderson *et al.* point out, transfusion support is an important part of the resuscitation, but it is indeed only *part* of the resuscitation.

Keywords: trauma, massive transfusion, protocol, whole blood, red blood cell.

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