A Survey of U.S. and Canadian Hospitals' Paediatric Massive Transfusion Protocol Policies

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Abstract

Background: Trauma is the leading cause of death in children >1 year of age, with haemorrhage as the most common cause of medically preventable deaths. While massive transfusion protocols (MTPs) have been investigated and used in adults to reduce death from haemorrhage, there **are** a paucity of published data on MTP practices and outcomes in children. This study aimed to survey current MTP policies and the frequency of activation at paediatric care centres.

Study Design and Methods: We conducted a survey of MTPs at hospitals in the U.S. and Canada, including children's general hospitals, children's specialty hospitals, and children's units in general hospitals. We collected information on how the MTP is activated, what therapeutics are given, frequency of its use, and how it is audited for compliance.

Results: Forty-six survey responses were **analysed**. Physician discretion was the most common activation criteria (89%). A majority of sites (78%) targeted a "high" ($\geq 1:2$) ratio of plasma to red blood cells (RBC). Fifteen percent of sites use antifibrinolytics in their MTPs. Eighty nine percent of sites have type-O RBC units and 48% of sites had thawed plasma units stored in an immediately available location.

Conclusion: There is a wide variation in MTPs among paediatric hospitals with regard to both activation criteria and products administered. This underscores the need for future prospective studies to determine the most effective resuscitation methods for paediatric populations to improve outcomes and therapeutic safety for massive bleeding.

Keywords: Massive Transfusion Protocol, Haemorrhage, Paediatrics, Red Blood Cells, Damage Control Resuscitation

Introduction

Trauma is the most common cause of death in children >1 year of age (Center for Disease Control, 2010). Haemorrhage, the most common cause of *medically preventable* death for patients with traumatic injuries, typically occurs within 6 hours from the initiation of bleeding (Demetriades, Murray *et al.*, 2004). Additionally, life-threatening bleeding in children may also occur from **aetiologies** other than trauma, such as intra and post-operative bleeding, gastrointestinal bleeding, and disseminated intravascular coagulation (DIC). In order to prevent death from **haemorrhagic** shock, transfusion strategies for massive haemorrhage are evolving, based on recent military and adult civilian trauma data (Spinella and Holcomb, 2009). Damage Control Resuscitation (DCR) is the term used to describe the current treatment approach for traumatic haemorrhagic shock (Spinella and Holcomb, 2009). The goal of DCR is to prevent death from haemorrhage by the rapid identification and treatment of traumatic shock and coagulopathy.

In retrospective studies, DCR principles have been independently associated with reduced mortality in adults with traumatic and intra-operative bleeding (Borgman, Spinella *et al.*, 2007; Gunter, Au *et al.*, 2008; Perkins, Cap *et al.*, 2009; Spinella and Holcomb, 2009; Holcomb, Wade *et al.*, 2011). Massive Transfusion Protocols (MTPs) **have** been developed to implement some aspects of DCR principles. In adults with traumatic injury, MTPs have been associated with reduced mortality (Cotton, Gunter *et al.*, 2008; Gunter, Au *et al.*, 2008; O'Keeffe, Refaai *et al.*, 2008; Cotton, Au *et al.*, 2009; Dente, Shaz *et al.*, 2009). However, **in some institutions, MTPs are applied to all patients with massive bleeding and not just those with traumatic injury. In addition, the current literature on MTPs in children is scant and includes case reports, as well as studies discussing the feasibility of implementing MTPs at children's hospitals, the risk of hyperkalaemia, and the ability to continuously monitor**

haemoglobin during the MTP (Nylund, Borgman *et al.*, 2009; Dressler, Finck *et al.*, 2010; Hendrickson, Shaz *et al.*, 2012; Agrawal, Beethe *et al.*, 2013; Nosanov, Inaba *et al.*, 2013). There is one prospective cohort study of paediatric patients who received blood products according to a MTP versus no MTP. The MTP group consumed a higher overall amount of blood products, but there was no significant difference in the transfused plasma to red blood cell (RBC) ratio (Chidester, Williams *et al.*, 2012). There are no paediatric multi-centre data published on the epidemiology of MTP activations, which DCR therapies are most commonly used in children, and associated outcomes according to the cause of massive bleeding.

Despite a paucity of evidence supporting DCR in children, it is being generalized to paediatric practice within MTPs for both traumatic and non-traumatic aetiologies (Nylund, Borgman *et al.*, 2009; Dressler, Finck *et al.*, 2010; Chidester, Williams *et al.*, 2012; Agrawal, Beethe *et al.*, 2013; Nosanov, Inaba *et al.*, 2013; Palmieri, Greenhalgh *et al.*, 2013). Therefore, it is essential that DCR be studied specifically in children. Anatomical and physiological differences in children may alter the efficacy and safety of certain DCR principles compared to adults. Children have reduced blood volume compared to adults and, as a result, may not tolerate large blood volume losses relative to a similar injury. Conversely, the lack of cardiac and vascular disease in children may also permit for increased ability to compensate during haemorrhagic shock. In addition, haemostasis is known to change through infancy and also in females during their first menstrual cycle (Guzzetta and Miller, 2011; Appel, Grimminck *et al.*, 2012; Jaffray and Young, 2013). It is possible that these developmental changes may have implications for the efficacy and safety of haemostatic therapies in children with life-threatening bleeding (Andrew, Vegh *et al.*, 1992). As a result, the use of haemostatic adjuncts, such as tranexamic acid or prothrombin complex concentrates, may have an improved safety profile in children compared to adults.

The objective of this survey was to determine current MTP policies and the frequency of MTP activations at paediatric hospitals. We hypothesized that there is a high degree of variability in MTPs in hospitals caring for children. The data from this survey will be used to develop a prospective observational study at paediatric tertiary care centres, which ultimately will allow development of trials to determine which DCR concepts are appropriate to apply to paediatric populations with life-threatening bleeding.

Materials and Methods

We conducted a survey of MTPs at paediatric hospitals, including children's general hospitals, children's specialty hospitals, and children's units in general hospitals. Study centres were identified through a query of the National Association of Children's Hospitals and Related Institutions (NACHRI) database. The survey was developed in REDCap (Research Electronic Data Capture) with the assistance of an expert in survey development and was pilot tested for clarity of questions at three study centres. An email that introduced the survey and provided instructions was sent electronically to paediatric trauma program directors at each site, with the rationale that, in most circumstances, **trauma services require the development of MTPs for certification**. The email address for the trauma directors from each institution was obtained via multiple methods, including Internet searches and review of contact lists from multiple research networks. The trauma program directors could delegate completion of the survey to another person in a different specialty at the site if that individual was more familiar with specific aspects of their MTP (i.e. the blood bank director or emergency medicine director). Once centres completed the survey, we removed them from our distribution list and they were not contacted further.

We solicited survey responses three times via a secured web-based interface to REDCap on January 15, January 27 and February 4th of 2014. Only one response per site was permitted. The last survey was accepted on March 31, 2014. Of note, the survey was administered prior to the publication of the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial (Holcomb, Tilley *et al.*, 2015). Survey data were analysed using descriptive statistics and Chi Square or Fischer Exact tests as appropriate (IBM SPSS Statistics for Macintosh, Version 22.0.0.0). This study underwent administrative review by the institutional review board at Washington University in St. Louis and it was deemed that full review and approval was not necessary. Funding required for survey construction was provided by the Department of Paediatrics at Washington University School of Medicine.

The content of the survey is available in the appendix. Sites self-reported as urban, suburban, or rural – these terms were not defined. Sites also self-identified with NACHRI designation listed as follows: children's general hospital, children's specialty hospital, children's unit in a general hospital, or not identified by NACHRI. For the rest of the manuscript, we will use the term "free standing children's hospitals," which will include both children's general hospitals and children's specialty hospitals." The vast majority of centres in this study are provided blood products from a centralized blood services in the U.S., where approximately 85% of RBCs are leukocyte reduced. In the U.S., according to the American Association of Blood Bank, plasma can be thawed and stored at 2-6C for up to 5 days.

Results

Of the 62 surveys sent to children's hospitals, we received completed surveys from 50 unique sites. If more than one response was received from a single site, we accepted the first fully completed survey. Four of these sites did not have an MTP policy and their survey

responses were not included in this analysis; therefore, we analysed 46 survey responses. Please see Table 1 for site demographics. The specialty role of the 46 survey respondents were as follows: 28% (13/46) were intensive care unit directors or attending physicians (consultant), 26% (12/46) were trauma directors or trauma program managers, 20% (9/46) were transfusion medicine directors, 11% (5/46) were emergency department directors or attending physician, 9% (4/46) were other, and 7% (3/46) were administrative coordinators.

MTP activation criteria

Most sites, 89% (41/46), listed physician discretion as a criterion for activating their MTP. The survey offered several laboratory data as options for activation criteria, but only a small minority, 3 of the 46 respondents (7%), listed specific laboratory threshold as an activation criterion: haemoglobin 4% (2/46), international normalized ratio (INR) 4% (2/46), base deficit 4% (2/46), prothrombin time (PT) 2% (1/46), partial thromboplastin time (PTT) 2% (1/46), platelet count 2% (1/46), rapid/standard thromboelastography (TEG) values 0%. In contrast, more sites, 17% (8/46), answered “yes” for specific vital signs or physical exam findings as MTP activation criteria. The specific vital signs or physical exam findings answers were as follows: systolic blood pressure 15% (7/46), heart rate 11% (5/46), mean arterial pressure 9% (4/46), respiratory rate 7% (3/46), Glasgow Coma Scale 7% (3/46), oxygen saturation 4% (2/46), tissue oxygen saturation 2% (1/46), and temperature 0%. When asked if mechanism of injury was considered an activation criterion according to their MTP, 9% (4/46) responded “yes,” with 9% (4/46) specifying penetrating injury and 4% (2/46) specifying blunt injury. Interestingly, 26% (12/46) responded with “other” MTP activation criteria; seven sites included a threshold amount of transfused blood product as activation criteria (Table 2).

Blood products administered according to MTP

General Questions

When asked, “Does your MTP policy specify a ratio of plasma to Red Blood Cell (RBC),” 89% (41/46) replied “yes.” Sixty one percent (28/46) of sites indicated cryoprecipitate was included in their MTP policy. Whole blood was available at 9% (4/46) of sites. There was a maximum RBC storage age at 15% (7/46) sites. Specific stipulations for maximum storage days were as follows: three of the 46 sites specified 7 days, one site specified 8 days, two sites specified 14 days, and one site specified a maximum of 21 days.

Plasma:RBC ratios

Table 3 displays the plasma:RBC ratios suggested for transfusion in the first and subsequent blood packages according to hospital MTP. In the first blood package, when defining “high” plasma:RBC ratio as $\geq 1:2$, 78% (36/46) specified high ratios and 4% specified (2/46) low ratios; 13% (6/46) of sites did not specify a ratio or had missing data; and 4% (2/46) replied with “other.” Two of the sites that reported a policy to transfuse a “high” plasma:RBC ratio also reported that plasma:RBC ratios varied according to the patient’s weight. One site used a 1:1 plasma:RBC ratio for children $<30\text{kg}$ but used a 0.5:1 ratio for children $>30\text{kg}$. The other site specified a 1:1 plasma:RBC ratio for patients less than 5 kilograms or greater than 50 kg but used a 1:2 ratio for patients that were 5 to 49 kg. For subsequent blood packages, 85% (39/46) stipulated high ratios and 2% (1/46) stipulated low ratios. For these subsequent blood packages, respondents indicated “not applicable” or “did not specify ratio” in 11% (5/46) and “other” in 2% (1/46) of responses. One of the sites that reported a policy to transfuse a “high” plasma:RBC ratio also responded that their policy for subsequent blood packages varied ratios based on weight.

Of the respondents with answers that could be grouped as “high plasma:RBC” or “low plasma:RBC” ratios, 93% (27/29) of free standing children’s hospitals indicated that their MTP’s specify a high plasma:RBC ratio in the first group of blood units, while 100% (9/9) of general hospitals with children’s units specify a high ratio.

Platelet to RBC ratios

Table 4 displays the platelet to RBC ratios reported for the first and subsequent blood packages. Of the 46 respondents with MTPs, 65% (30/46) reported that a ratio of apheresis platelets to RBC units was specified in the first group of blood units. The survey provided answers in terms of both apheresis platelets and donor platelets, specifying one apheresis platelet unit was equal in volume and platelet number to approximately 5 random donor platelet units. When defining “high” ratio as $\geq 1:10$ apheresis platelet to RBC or $\geq 1:2$ random donor platelet (RDP) to RBC, 54% (25/46) had high ratios (with one site specifying varying ratios based on weight), 35% (16/46) did not specify a ratio, 11% (5/46) classified as “other,” and none were identified as low ratio. Of the sites classified as “other,” two sites had varying ratios based on weights and three sites did not specify any platelets. For subsequent blood packages, 54% (25/46) had high ratios, 37% (17/46) had missing data or not applicable, 7% (3/46) replied “other,” and none had low ratios. Of the sites that replied “other,” 2 sites had varying ratios based on weight and one did not include platelets in the second blood package.

Intravenous haemostatic agents

Among respondents, haemostatic agents incorporated into MTPs were as follows: 24% (11/46) recombinant factor VII (rFVII), 15% (7/46) antifibrinolytics (tranexamic acid and/or aminocaproic acid), 13% (6/46) fibrinogen concentrates, 11% (5/46) prothrombin complex

concentrates, and 24% (11/46) did not include **haemostatic** agents in their MTP. Of the 46 respondents, 15% (5/34) of freestanding children's hospitals use antifibrinolytics in their MTPs versus 17% (2/12) of general hospitals with children's unit.

Laboratory data after MTP activation

Fifty percent (23/46) of centres require laboratory measures after MTP activation; however, one site answered "yes" but then answered "no" to subsequent questions. Specified laboratory measures were as follows: INR/PT/PTT 49% (22/45), **haemoglobin** or **haematocrit** 47% (21/45), fibrinogen 44% (20/45), platelet count 40% (18/45), ionized calcium 29% (13/45), potassium 24% (11/45), base deficit 18% (8/45), lactate 18% (8/45), TEG 9% (4/45), and none require thromboelastometry (ROTEM). Respondents were asked if their site's MTP specified the frequency of post activation laboratory data and 26% (12/46) centres responded "yes." The laboratory data frequency was based on the amount of product given at 6 centres (13%) while the frequency of labs was time-based at 6 (13%) of 46 centres. Laboratory data were to be obtained every 30 minutes at 11% (5/46) and every 6 hours at 2% (1/46) of centres.

Blood products immediately available

Type O RBC units were stored in an immediately available location at 89% (41/46) of sites. The location of immediate release type O RBC storage was as follows: emergency department 37% (17/46), operating room 20% (9/46), intensive care unit 11% (5/46), blood bank 63% (29/46), and 7% (3/46) stated "other" (hall fridge = 1, neonatal intensive care unit = 1, and missing data = 1).

Thawed plasma units were stored in an immediately available location at 48% (22/46) of centres: blood bank 46% (21/46), emergency department 4% (2/46), and 2% (1/46) of

centres stated “other” (specified as satellite blood bank). Specifically, 54% (18/33) of free standing children’s hospital had thawed plasma immediately available while 33% (4/12) of general hospitals with children’s units had thawed plasma immediately available.

MTP activation frequency

Respondents were asked how often the MTP was activated from January 1, 2013 through December 31, 2013. Of the 46 respondents, 27 (59%) reported an exact number of activations, however there were missing data from 4 centres. The median number of activations was 6, with IQR (3-10). In contrast, 41% (19/46) of respondents reported estimated activations, although 4 respondents answered “unknown.” The median number of estimated MTP activations was 5, with IQR (4-5).

Compliance measures

The following committees were responsible for audit of MTP activations: transfusion committee 41% (19/46), trauma committee 30% (14/46), “other” 9% (blood bank = 2, emergency transfusion subcommittee = 1, multidisciplinary team = 1), no committee 2% (1/46), and 17% (8/46) did not know. Compliance to specific metrics was tracked at 54% (25/46) of sites. These specific metrics were not surveyed.

Discussion

This survey is the first of our knowledge to report on massive transfusion protocol policies among children’s hospitals in the United States and Canada. As expected, the responses revealed a wide range of clinical practice.

Results from our survey indicate that MTP activation criteria are most often based on “physician discretion,” a non-specific entity. Activation criteria such as vital signs, laboratory

values, and previous amount of blood products transfused were uncommon. A possible explanation for this finding may be the lack of data in children that identify paediatric patients at risk for massive bleeding or the need for massive transfusion. Seven sites included a specific amount of transfused red blood cells to be administered as one mechanism for MTP activation. There was significant variation between these seven sites, as some use only RBCs, while other sites use all blood products transfused as MTP activation criteria. Neff et al recently published that more than 40 ml/kg of all blood products (total volume) administered indicated an increased risk of mortality (Neff, Cannon *et al.*, 2015), potentially indicating that total blood product volume administered may be a more appropriate definition of massive transfusion. This approach allows for the blood bank to identify a patient who may have massive bleeding when the clinical team has potentially not recognized this or has inadvertently forgotten to activate an MTP. Additional investigation focusing on predictors of massive bleeding in children or the need for massive transfusion is necessary to improve outcomes. Accurate prediction of who is at risk for massive bleeding may allow for more rapid treatment and even prevention of the need for massive transfusion, which may have the potential to improve outcomes.

We were quite interested in the ratio of plasma, red blood cells, and platelets that were specified in the MTPs. A major principle of DCR includes early empiric balanced transfusion (1:1:1 unit ratio of red blood cells (RBCs), plasma, and platelets) termed “Haemostatic Resuscitation” (Spinella and Holcomb, 2009). A recent prospective randomized clinical trial of severely injured adults who were predicted to require massive transfusion revealed that more patients in the 1:1:1 ratio of plasma:platelets:RBC group compared with the 1:1:2 ratio of plasma, platelets and RBCs group achieved haemostasis and fewer experienced death due to exsanguination. However, there was not a significant difference in mortality at 24

hours or at 30 days between the two groups (Holcomb, Tilley *et al.*, 2015). Although the adult literature is stronger, there are a few small studies that have evaluated higher plasma:RBC ratios in children. One retrospective study by Nosanov indicated that there was not an association between higher plasma:RBC ratios and survival in a cohort of children transfused greater than 50% of their blood volume (Nosanov, Inaba *et al.*, 2013). A second prospective pilot study in children with burn injuries compared a 1:1 to 1:4 plasma:RBC ratio strategies, with more plasma and less RBCs administered in the 1:1 group, but no difference in PT/PTT, INR, haemoglobin, or platelets between groups (Palmieri, Greenhalgh *et al.*, 2013).

Our results show a large majority of sites specified a high ($\geq 1:2$) plasma or platelet to RBC ratio and incorporate cryoprecipitate in their MTP. Sites frequently targeted 1:1 ratios for both plasma and platelet to RBC ratios. We believe this practice reflects the application of adult evidence to children. It is possible that many aspects of DCR can and should be applied to children; however, high quality studies are needed in children to determine if these adult guidelines are appropriate for the resuscitation of paediatric patients with massive bleeding.

There was no statistical difference between the percentage of free standing children's hospitals and general hospitals with children's units MTPs regarding high plasma:RBC ratios. We expected the opposite, with higher ratios being used for children at general adult hospitals that have paediatric units within them, since there are predominantly adult data that supports this approach and the increased frequency of MTP activation at adult hospitals allowing for the immediate availability of plasma. Interestingly, two sites called for varying plasma:RBC ratio based on weight. The rationale for this is not evident, but may be based

on the concept that hemostasis changes with development and transfusion requirements may be different based on age.

In regard to hemostatic adjunct use, only 15 percent of sites used antifibrinolytics (tranexamic acid or aminocaproic acid) in their MTPs. The CRASH-2 trial, a randomized controlled study enrolling 20,000 adults, revealed a 32% reduction in death due to bleeding when tranexamic acid was given within one hour of injury, with no increase in vascular occlusive events (collaborators, Shakur *et al.*, 2010). Although antifibrinolytics reduce mortality in the adult trauma population, the use of antifibrinolytics has not been well studied in children. While the use and safety of antifibrinolytics has been shown in children requiring cardiac surgery, craniofacial surgery, and scoliosis surgery (Schouten, van de Pol *et al.*, 2009), no mortality analyses were performed. A recent retrospective study of paediatric trauma patients cared for in a combat hospital revealed an association between tranexamic acid use and improved survival, although the data set were limited as there was not information on blood loss, laboratory response to tranexamic acid, or tranexamic dose timing (Eckert, Wertin *et al.*, 2014). Although 15% of sites use antifibrinolytics, 23.9% (11/46) of sites in this survey used recombinant factor VIIa (rFVIIa). A recent systematic review of transfusion interventions in critical bleeding requiring massive transfusion found that rFVIIa had no benefit in mortality outcomes in critical bleeding or trauma, and that a modest reduction in RBC transfusion and blood loss was off set by the increased risk of thromboembolic events (McQuilten, Crighton *et al.*, 2015). Clinical trials are needed to determine the indications and appropriate dosing of antifibrinolytics and other hemostatic agents for children with massive bleeding.

Fifty percent (23/46) of sites required laboratory measures after MTP activation and, as expected, nearly all of those sites required INR/PT/PTT, as these labs are traditionally used to monitor coagulopathy. In contrast, only four sites required the use of TEG. Research is required to determine which laboratory measures are most accurate at measuring coagulopathy and are effective at permitting a goal directed therapy strategy for the treatment of haemorrhagic shock in children.

While 89% of sites had type O RBC units stored in an immediately available location (most commonly in the blood bank or emergency department), only 48% of sites had thawed plasma units stored in an immediately available location. Our recent survey of 132 US adult tertiary care centres indicated that 66% have thawed plasma immediately available (Camazine, Hemmila *et al.*, 2015). We expected general hospitals to be more likely to have thawed plasma available, as there may be difficulty providing pre-thawed plasma at free standing children's hospitals due to lower frequency of MTP events compared to large adult facilities, and the increased waste of product that may result. However, there was no statistical difference between the percentage of free standing children's hospital with thawed plasma immediately available compared to general hospitals with children's units ($p = 0.314$). This may be due to our modest sample size.

The low use of whole blood available was expected, as there has been a transition from the use of whole blood to component therapy over the last several decades. Component therapy is the primary transfusion approach due to concerns for resource utilization and safety (Spinella and Holcomb, 2009). However, a retrospective study from adult military data demonstrated that warm fresh whole blood is independently associated with improved survival in trauma patients compared to component therapy (Spinella, Perkins *et al.*, 2009).

A randomized controlled trial (RTC) in children with congenital heart disease indicated that when whole blood was transfused postoperatively, there was a reduction in bleeding compared to those transfused blood components (Manno, Hedberg *et al.*, 1991). On the other hand, the complications associated with whole-blood transfusion, such as renal failure or respiratory distress has been thought to be attributed to the white blood cells in the whole-blood units. Therefore, the use of leukocyte-reduced whole blood with platelet sparing filtration may be safer, as is routinely done at the Children's Hospital of Philadelphia for Cardiac surgery (Murdock, Berseus *et al.*, 2014; Jobes, Sesok-Pizzini *et al.*, 2015).

There was a maximum RBC storage age at 15% (7/46) sites. Recent randomized controlled trials have indicated that the use of fresher RBCs does not improve outcomes (Fergusson, Hebert *et al.*, 2012; Lacroix, Hebert *et al.*, 2015; Steiner, Ness *et al.*, 2015). However, none of these trials been performed in patients with traumatic injury nor those who require a significant amount of blood products for resuscitation, where the risk of the storage lesion may be highest (Steiner and Stowell, 2009). Additional studies in the paediatric population are needed to determine if whole blood or fresh RBCs improve outcomes in children with severe bleeding.

This study had some limitations. Due to some non-mandatory questions, there were missing data. In addition, we allowed estimates, as well as the answer "unknown," in regard to MTP activations, which did not allow for accurate estimations of MTP frequency. The decision to allow non-mandatory questions and estimates was made in an effort to increase survey response, although we recognize this may introduce bias. Many of the sites that responded seemed to be from larger paediatric institutions, as 89% had ECMO capabilities and 91% performed solid organ transplants, which limits the generalizability to sites that do not offer

these services. Only 20% of survey respondents were transfusion medicine directors; however, the survey was initially sent to paediatric trauma directors who could delegate completion of the survey to another person in a different specialty at the site if that individual was more familiar with specific aspects of their MTP (i.e. the transfusion medicine directors). The wide range of survey respondents may be evidence of broad interest in MTPs among multiple specialties. Due to length of survey limitations, we were not able to expand on certain topics, such as the timing and indications for rFVIIa or TXA use, or if laboratory data **were** used to alter plasma to RBC ratios. Finally, this study surveyed policy rather than actual practice, which may be different, as other studies have demonstrated that physicians may perceive adherence to recommendations or guidelines to be better than it actually is (Brunkhorst, Engel *et al.*, 2008; Oderda, Shiozawa *et al.*, 2014).

Implementation and support of MTPs is resource intensive, further highlighting the importance of identifying which transfusion strategies are most effective. This is especially relevant at children's hospitals that have a low frequency of massive bleeding, where the cost of making blood products available for the application of DCR may exceed its utility. Further study is needed to examine the benefits versus possible detriments of MTPs, as there is also evidence that adults who receive a higher plasma to RBC ratio *and who are at low risk for life-threatening haemorrhage* are at increased risk for organ failure and increased number of ventilator days compared to similar patients transfused a low plasma to RBC ratio (Borgman, Spinella *et al.*, 2011). This also highlights the importance of recognizing which patients are at low risk for life-threatening haemorrhage, which has not yet been characterized for the paediatric population.

A prospective observational study is currently being performed that will collect epidemiologic, practice range, and outcomes for all children who have an MTP activated. These data from over 300 children will serve as preliminary data for trials in children that can assess the efficacy and safety of DCR principles in children. Costs of multiple trials can be reduced by conducting well designed comparative effectiveness trials (Spinella, Leonard *et al.*, 2015).

Conclusion

In conclusion, there is a wide variation in MTPs among paediatric hospitals with regard to both activation criteria and transfusion support. Most units have embraced the principles of DCR but have not formalized when to initiate it and whether the same protocols should be used in trauma and non-trauma. This underscores the need for future prospective studies assessing the epidemiology of MTP activations, which therapies are most commonly used in children, and associated outcomes according to the cause of massive bleeding to determine the most effective resuscitation methods for paediatric populations in order to improve outcomes and therapeutic safety for massive bleeding.

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Table 1. Institution Demographics**N = 46**

	#	%
NACHRI Designation		
Freestanding Children's Hospital*	34	74%
Children's General Hospital	16	35%
Children's Speciality Hospital	18	39%
Children's Units in a General Hospital	12	26%
Location		
Urban	36	78%
Suburban	7	15%
Rural	3	7%
Capabilities		
ECMO	41	89%
Solid organ transplant	42	91%
Trauma Designation		
ACS level one	30	65%
State verified level one	22	48%

*"Freestanding Children's Hospital" is not a specific NACHRI designation, but is used throughout the manuscript to include both children's general hospitals and children's specialty hospitals.

KEY: NACHRI = National Association of Children's Hospitals and Related Institutions. ECMO = extracorporeal membrane oxygenation. ACS = American College of Surgeons

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Table 2. The amount of transfused blood product to be given before MTP activation at seven different sites

Amount transfused equals more than 50ml/kg
Thirty ml/kg and on-going uncontrolled bleeding
Administration of > 40ml/kg PRBC (2 sites)
RBC transfusion requirement of greater than 20 ml/kg in the first hour of resuscitation or approaching 40 ml/kg in 12 hours or 80 ml/kg in 24 hours
Actual or anticipated administration of > 40 ml/kg PRBC in 2 hours or less.
Administration of one estimated blood volume (approximately 10 units of RBC in 24 hours in an adult, 80ml/kg for paediatric patients) or >50% of total blood volume in 2 hours and continuing need for transfusion.

Table 3. Plasma:RBC ratios in first and subsequent blood packages*

	1:1 plasma:RBC	2:3 plasma:RBC	1:2 plasma:RBC	1:3 plasma:RBC	Ratio varies with weight	No plasma in first package
1st blood package Plasma:RBC	54.3%(25/46)	4.3% (2/46)	15.2% (7/46)	4.3% (2/46)	4.3% (2/46)	4.3% (2/46)
Subsequent blood package Plasma:RBC	65% (30/46)	2.2% (1/46)	15.2%(7/46)	2.2% (1/46)	2.2% (1/46)	None specified

*Does not include sites with missing data or whose MTP does not specify a ratio.

Table 4. Platelet:RBC ratios in first and subsequent blood packages.

	1:4 apheresis platelet:RBC	1:5 apheresis platelet: RBC or 1:1 RDP:RBC	1:6 apheresis platelet:RBC	1:8 apheresis platelet:RBC	1:10 apheresis platelet: RBC or 1:2 RDP:RBC	Ratio varies with weight	No platelets in first package
1st Platelet:RBC	4.3% (2/46)	34.8% (16/46)	2.2% (1/46)	4.3% (2/46)	6.5% (3/46)	6.5% (3/46)	6.5% (3/46)
Subsequent blood package Platelet:RBC	4.3% (2/46)	32.6% (15/46)	2.2% (1/46)	4.3% (2/46)	10.9% (5/46)	4.3% (2/46)	2.2% (1/46)

Key: RBC=Red Blood Cell, RDP=Random Donor Platelet

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