Massive hemorrhage protocol survey: Marked variability and absent in one-third of hospitals in Ontario, Canada

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ABSTRACT

Background: Massive hemorrhage protocols (MHP) are critical to standardized delivery of timely, safe, and resource-effective coordinated care for patients with life-threatening bleeding.

Methods: A standardized MHP survey was sent to all hospitals (n = 150) in Ontario with a transfusion service. This study aim was to determine the proportion of hospitals with an MHP and assess for variability.

Results: The overall survey completion rate was 133 of 150 hospitals (89%) (remaining 17 providing negative affirmation that they did not have an MHP). An MHP was in place at 97 of 150 (65%) hospitals (60% of small (<5000 red cell units/year) vs. 91% of medium/large). A total of 10 different names of protocols were reported, with "Massive Transfusion Protocol" (68%) predominating. Activation criteria were present in 82 of 97 (85%); commonly activated based on volume of blood loss (70%). Blood work was drawn at the discretion of the physician (37%) or at predefined intervals (31%; majority every 60 min). Common routine laboratory tests performed were CBC (87%) and INR (84%). Fibrinogen testing was available at 88 (66%) of 133 reporting hospitals and part of the standard testing at 73 of 97 (75%) hospitals with an MHP. Median targets of hemostatic resuscitations, stated in the protocol at 49% of hospitals with an MHP, were: platelets $>50 \times 10^9$/L, INR < 1.8, fibrinogen >1.5 g/L, and hemoglobin >70 g/L. Protocol required patient temperature monitoring in 65% and specified a reversal plan for patients on anticoagulants in 59%. At 36% of sites all patients are initially managed with O RhD negative blood. Overall, 61% of sites issue blood in predefined packs (vs. on demand). Hemostatic agents in protocols included: tranexamic acid (70%), prothombin complex concentrate (14%), fibrinogen concentrate (13%), and recombinant FVIIa (4%). Quality metrics were tracked in 32% of hospitals.

Conclusions: A third of hospitals lack formal MHPs, with the majority lacking in smaller hospitals. The survey results indicate that there is marked variability in all key aspects of the reported MHPs. This may be due to differences in hospital resources and personnel, lack of supporting evidence to dictate requirements, and differences in knowledge base of the individuals involved in protocol setting.

Introduction

Massive hemorrhage is the leading cause of preventable death in trauma patients [1]. Deaths resulting from hemorrhagic shock typically occur within the first six hours of injury [2]. Management of the unstable trauma patient focuses on transfer to a treatment facility, damage control resuscitation predicated on optimizing patient hemodynamics, and rapid identification and disposition for injuries requiring definitive surgical management. In recent years, effective damage control resuscitation has been shown to prolong the available time for patient transfer, optimize the patient for surgery thereby improving the final outcome, and in some cases even obviating the need for surgical management [3,4].

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The delivery of effective damage control resuscitation is complex and requires a large scale coordinated effort of multiple hospital resources and interdisciplinary teams. To facilitate this delivery, protocolized care has been shown to streamline and improve access to care and blood components, decrease variability of treatment, reduce waste, and facilitate communication [4–8]. The protocol is most commonly known as a 'Massive Transfusion Protocol (MTP)', with some shifting away from this term in preference for 'Massive Hemorrhage Protocol (MHP)', to account for appropriate protocol activations for patients who may not yet require a massive transfusion [7]. Massive transfusion is most commonly defined as $\geq$10 units of red blood cells (RBC) given in a 24 h period [9].

Although MHPs vary across hospitals, they often consist of similar key domains: damage control resuscitation (DCR) principles, activation criteria to trigger the protocol, predefined ratios of blood components transfused, hemostatic adjuncts, reversal of anticoagulants, prevention of hypothermia, and team communication [2–4,6–8,10–12]. Originally, MHPs were designed for the trauma setting but have subsequently been adopted for the management of all types of massive hemorrhage, including postpartum hemorrhage, gastrointestinal bleeding and surgical hemorrhage. Triggers for MHP usually consist of three main criteria: vital signs, laboratory data, and physician discretion [2–4,6–8,10–12].

Once triggered, patients are typically given a set ratio of blood components consisting of RBCs, plasma, and platelets. While whole blood transfusion has been advocated as a preferred strategy, blood component resuscitation remains the predominant strategy [3]. Based on previous studies, most hospitals target high ratios of $\geq$1:2 units of plasma-to-RBC and $\geq$1:2 units of platelet-to-RBC, or using reconstituted whole blood in a 1:1:1 unit ratio [2,4,6,8,10,13]. Along with these ratios, the most commonly used hemostatic adjunct is tranexamic acid (TXA), a drug that has consistently proven to be beneficial by reducing the risk of death from hemorrhage [14–16] Rapid identification of patients on anticoagulants and prespecified agents for their reversal is the standard of care [17].

Although the use of a formal MHP improves timely delivery, access to blood components and adjuncts, decreases treatment variability, and increases resource-effectiveness, protocol adoption and standardization across hospitals is highly variable [2,4,6,10,18]. Previous surveys have shown variability in protocols including activation criteria, communication, team members, transfusion ratios, and laboratory testing. In a 2008 survey, 45% of trauma centers surveyed in the United States had a MHP, rising to 100% of academic trauma centers in 2017, an effect that has been credited for optimizing care by decreasing the cognitive and logistical burden for timely access to the personnel and resources in the hyperacute period. [6,19] The aim of this survey was to determine (1) the proportion of hospitals across Ontario with a formal MHP, and (2) the variability of the MHP specifications. We hypothesized that formal MHPs are still lacking in many hospitals; and when present, protocols are highly variable. Ontario has a population of 13.6 million inhabitants. In the most recent year of data reported from the Canadian Institute for Health Information and the Ontario Trauma Registry (2011), there were 4235 injury cases with an Injury Severity Score over 12 of whom 52% were admitted direct from the scene (vs. transfer from another regional hospital) and a 13% morality rate. [20] The survey was performed in preparation for developing a Provincial-wide, standardized, massive hemorrhage protocol.

Materials and methods

A web-based survey was created using Lime Survey (GmbH, Germany). There were a total of 66 questions divided into nine

categories: hospital demographics, activation criteria, communication, blood work, test availability, temperature management, transport containers, transfusion medicine support and quality metrics tracked. However, due to the logic within the survey, respondents that reported not having an MHP were only required to answer a small subsection of the survey. The survey consisted of both multiple choice and short answer questions and took approximately 20 min to complete. A selected sample of the 66 survey questions are listed in Table 1. The questions surveyed were based on previously identified key areas for the management of hemorrhage by a Canadian expert consensus group, with emphasis on areas of variability that may affect patient outcomes. [21,22]

The target population for the survey was all Transfusion Service Medical Directors and/or Transfusion Medicine Laboratory Managers in Ontario hospitals (n = 150), including institutions who provide care for pediatric patients. The survey was first piloted with a sample group from the target audience to ensure quality of question structure and to validate the data captured. The final validated survey was emailed out on November 30th, 2017 to all Medical Directors of Transfusion Medicine, with request to either complete if appropriate or ask the key individual most responsible for the hospital protocol to complete or assit with completion. In Ontario, 11 (7.3%) of the 150 hospitals have designated trauma programs. Two general non-targeted email reminders were sent to remind hospitals to complete the survey. Respondents were given until December 23rd, 2017 to complete the survey. Hospitals that did not respond were followed up with an email or phone call until all Ontario hospitals with an MHP had completed the survey. Hospitals declining to complete the survey were verified verbally that they did not have an MHP.

Data were analyzed using descriptive statistics in Excel (Microsoft, Redman, Washington, USA). Questions that required short answers from respondents were manually grouped for analysis purposes. Answers where participants elected to provide a number range were converted to a single number based on the average of the range provided. Participants that responded 'No' to whether all patients received O RhD negative blood when blood group was unknown were asked to write a short answer of which patients would receive it. Answers were then manually grouped into the following categories: females less than 45 years, patients with a history of anti-D, females less than 46–50 years, children and women of child bearing age. Additionally, for statistical purposes, the standard male weight of 70 kg was used to convert all answers where a specified dosage was provided in grams/kilograms of body weight to a standardized, comparable dose. An additional subgroup analysis by hospital size was conducted based on the annual number of RBCs transfused as routinely reported to the Canadian Blood Services; hospitals that transfused <5000 were classified as small, 5000–10,000 as medium, and >10,000 as large. We sought to understand the differences in protocols between small community hospital, large regional non-trauma hospitals, and large trauma centers.

Results

A total of 150 (100%) responses were received for the 150 hospitals in Ontario with a transfusion service as to whether they currently had an MHP; 132 (88%) fully completed surveys and 1 (1%) partially completed survey were received and 17 (11%) hospitals provided a negative affirmation that they did not have an MHP. The majority, 74% (98/133), of responses were completed by a member of the Transfusion Medicine Laboratory (physician or technologist) and the remainder by emergency physicians, anatomical pathologists responsible for transfusion medicine, the transfusion safety officer, or the laboratory quality manager.

Of all hospitals in Ontario with a transfusion service, 65% (97/150) had a hospital approved MHP in place. With regard to year of

Table 1
Sample of the 66 survey questions.

Demographics
What is your primary role?
Are you answering this survey on behalf of more than one hospital? Please list all sites.
Do you have a hospital approved MHP?
What is the year the current policy was approved?
Activation Criteria
Do you have activation criteria?
Are the activation criteria the same for all patients?
How do you activate an MHP?
Who is included in the activation roll-out as a team member?
Communication
How are laboratory results communicated to clinical areas?
Are ONLY critical laboratory results called?
How does Transfusion Medicine Laboratory communicate with clinical team?
Blood Work
How often do you draw a set of blood work during an MHP?
Which laboratory tests are routinely drawn?
Test Availability
Which test assays are available on site at your hospital?
Do you have targeted resuscitation?
What is the total number of Lab staff covering all areas at lowest staffing level?
Do you have on-call schedule should the Lab workload exceed staffing levels?
Temperature
Does your protocol require monitoring of patient temperature?
What is the temperature target in Degrees Celsius?
If the temperature is below target, what strategies are in place?
Transport Containers
When red blood cells, platelets, plasma & cryoprecipitate are required during an MHP, are they transported in a validated container?[1]
Which products are routinely stocked on site in the Transfusion Medicine Laboratory?
Transfusion Medicine
Is there a provision in your MHP for the management of patients on anticoagulant/ antiplatelet agents?
During an MHP and when blood group is unknown, what patients receive O Rh negative versus O Rh positive RBCs?
Do you have predefined component packs/boxes that are issued during an MHP? What is included in your MHP box/pack?
What hemostatic agents are included in the protocol?[1]
Quality
Do you ever perform multidisciplinary debrief/ review of any MHP?
Do you track any quality metrics for MHP?
MHP = massive hemorrhage protocol, RBC = red blood cells.
[1]Question was rephrased in order to capture multiple survey questions in one.

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implementation, 78% (76/97) of protocols were implemented or updated within the past five years, with most undergoing a revision or implementation in 2016 (29%). A total of 10 terms were used as the name of the protocol; commonly used terms included "Massive Transfusion Protocol" (68%), "Code Omega" (13%), and "Massive Hemorrhage Protocol" (8%).

Activation: criteria and method

Of the 97 hospitals with an MHP, 85% (82/97) reported having specific activation criteria (with 85% specifying that the same criteria were used for all types of bleeding patients). Protocols were most commonly activated based on the volume of blood loss (70%), units of RBC transfused (60%), and hemodynamic instability (e.g. shock index, blood pressure, heart rate) (32%). A call to the transfusion medicine laboratory (78%) and/or locating for code triggering (25%; overhead announcement in 88% of these hospitals) were the most common methods for activation. Activation details are shown in Table 2.

Interdisciplinary team

Physician leads were the most common members of the activation roll-out team in 94% of hospitals, followed by medical laboratory technologists in the transfusion medicine laboratory (81%), nursing leads (71%) and porters (64%). Of those members, porters were responsible for delivering blood components and laboratory specimens the majority of the time (64% of sites).

Communication

Available methods of communication between the hematology/ coagulation laboratory and clinical areas included phone call to

Table 2
Activation criteria and the method of activation for hospitals with MHPs.

Activation Criteria and Method		
MHPs with Activation Criteria (n = 97)		
Yes	82	85%
No	15	15%
Activation Criteria is the same for all patients (n = 82)		
Yes	70	85%
No	12	15%
Activation Criteria (n = 82)[*]		
Volume of blood loss	68	83%
Units of RBCs transfused	58	71%
Hemodynamic parameters (e.g. shock, index, BP, HR)	31	38%
Need for uncrossmatched blood	18	22%
Need for inotropes and bleeding	10	12%
No response to crystalloid and bleeding	6	7%
Other	22	27%
Method of activation (n = 82)[*]		
Call to the transfusion medicine laboratory	76	93%
Call to locating communication/security for 'code' page	24	29%
Silent page – 3 (13%)		
Overhead alert announcement – 21 (88%)		
Computerized physician order entry	9	11%
Other	20	24%

[*] More than one variable or option could be recorded as part of the hospital activation criteria or method of activation.

local extension 77% (75/97), electronic patient record 62% (60/97), dedicated MHP phone 9% (9/97) and fax 1% (1/97). Similar results were also seen when respondents were asked about methods of communication between the transfusion medicine laboratory and the clinical team. Furthermore, when asked whether only critical laboratory results were called (vs. all test results including those within the normal range), almost all sites (93%) responded 'Yes'.

Laboratory investigations

Laboratory investigations were most commonly drawn at the discretion of the physician (36/97; 37%), at predefined intervals 31% (30/97; majority every 60 min), or at the beginning, end and at predefined intervals 10% (10/97). Laboratory tests routinely performed included: complete blood count (CBC) 87% (84/97), International Normalized Ratio (INR) 84% (81/97), activated partial thromboplastin time (aPTT) 77% (75/97), fibrinogen 75% (73/97), electrolytes 74% (72/97), group and screen 64% (62/97), creatinine 62% (60/97), lactate 61% (59/97), blood gas 60% (58/97), ionized calcium 42% (41/97), calcium 39% (38/97), and rotational thromboelastometry (ROTEM) 4% (4/97). No hospitals utilized thromboelastography (TEG) testing as part of their MHP. When asked about who collected the specimens, respondents were presented with 8 options and asked to select all that applied. Approximately half of protocols (51/97; 53%) required a nurse to draw blood samples followed by 48% (47/97) any trained health-care professional, 34% (33/97) Medical Laboratory Technologist, 31% (30/97) Medical Laboratory Assistant, 25% (24/97) a member of the phlebotomy team, 24% (23/97) allied health professional (e.g., perfusionist, anesthesia assistant) and 23% (22/97) physician.

Tests available at reporting sites (n = 133) included: creatinine 100% (133), electrolytes 100% (133), CBC 99% (132), INR 99% (131), calcium 97% (129), aPTT 96% (128), group and screen 95% (127), lactate 95% (126) and blood gas 93% (124). Fibrinogen testing was available at 88 (66%) and TEG at two sites (although it was not used for MHPs). ROTEM was available at nine sites and was most commonly performed in clinical area(s) 89% (11% testing performed in the laboratory).

Of the 79 hospitals with an MHP (n = 97) that answered 'what is the total number of Laboratory staff covering all areas at lowest staffing level?', 27 stated one laboratory staff (34%), 22 responded two (28%), 13 said three (16%) and the rest reported four or more, thus resulting in a median of 2 responding laboratory staff. Only 34% of hospitals with an MHP had an on-call schedule for when laboratory workload exceeded staffing levels.

Hypothermia monitoring and management

Among hospitals with a protocol (n = 97), 65% (63) required the monitoring of patient temperature. Median (interquartile range [IQR]) target temperature was indicated as 36 °C (35–36 °C). Methods of achieving target temperature were specified in 65% of MHPs and included: 61% (59) warm blankets/forced air blankets, 42% (41) rapid infuser and 28% (27) blood warmer.

Transfusion medicine laboratory

At 73% (96/132) of reporting sites, RBCs were transported in a validated container; most commonly in the boxes provided by Canadian Blood Services (CBS) for regular deliveries. The majority of hospitals also transported plasma in a validated container (55%). Platelets were transported in a validated container at 33% (43/132) and cryoprecipitate at 29% (38/132). Validated containers most commonly used for plasma and cryoprecipitate were CBS boxes while validated platelet containers were the most common for platelet transports. Other responses regarding methods of transportation included: carried by staff, pneumatic tube, and plastic bag.

Products routinely stocked on site in the transfusion medicine laboratory were as follows (Table 3): Prothrombin Complex Concentrate (PCC; 3000 IU or more) 95% (125/132), frozen plasma (4 or more units) 82% (108/132), RBC (of all blood groups) 73% (97/132), cryoprecipitate 61% (80/132), rFVIIa 44% (58/132), fibrinogen concentrate 36% (48/132), platelets (1–2 units) 33% (44/132), platelets (3+ units) 17% (23/132), and pre-labeled trauma stock units 16% (21/132). Thawed plasma units were routinely stocked at 6 (5%) of the 132 reporting sites; most commonly group AB, which were stocked at all six sites. Protocols to allow release components to the clinical team for transport with the patient to another facility was reported in 107 (81%) of 132 hospitals.

Transfusion management

Forty-eight of 97 hospitals with an MHP (49%) reported having targets for hemostatic resuscitation for bleeding patients with median targets of platelets $>50 \times 10^9$/L, INR < 1.8, fibrinogen >1.5 g/L, and hemoglobin >70 g/L. While survey options for targeted resuscitation also included aPTT(s) and measures from the ROTEM/TEG, four or less reported having these tests used for targeted resuscitation.

When respondents were asked whether protocols incorporated predefined packs/boxes to be issued during an MHP 61% (59/97) stated 'Yes'. Those that responded 'Yes' were then further asked to complete the number of predefined units of RBC, plasma, platelet and cryoprecipitate included in the first five boxes/packs issued. 25% (15/59) of hospitals used the same predefined units in all boxes starting from the second box/pack. Most common predefined ratios in each pack were as follows (RBC:plasma:PLT:cryoprecipitate in units): 4:0:0:0 for pack1 and 4:4:1:0 for packs 2 through 5 (note: cryoprecipitate was not included in any of these pre-defined packs). Content of the predefined packs are shown in Fig. 1 and Table 4. Type O RhD negative red blood cells were given to all patients when blood group was unknown at 47 (36%) of the 132 reporting hospitals. For the remainder, respondents were asked to include a short answer stating which patients would receive O RhD negative RBCs. Overall results varied: 60% females <45 years, 27% patients with a history of anti-D, 25% females <46–50 years, 14% all children and 11% women of child bearing age.

Fifty-seven out of 97 (59%) hospitals with an MHP included a specified reversal plan for patients on anticoagulant/antiplatelet agents.

Among hospitals with an MHP, hemostatic agents incorporated in protocols consisted of: TXA (70%; median total dose of 2 g and ranging from 0.7 g to 4 g), PCCs (14%), fibrinogen concentrate (13%) and rFVIIa (4%). The most common answer for which patients are provided cryoprecipitate/fibrinogen concentrate was if fibrinogen level was below target threshold at 44% (43/97); 20% (19/97) of hospitals reported issuing cryoprecipitate/fibrinogen concentrate to 'All MHP patients', and 29% (28/97) stated that neither products were a part of the protocol.

Table 3
Products and hemostatic factors stocked at the 132 reporting sites.

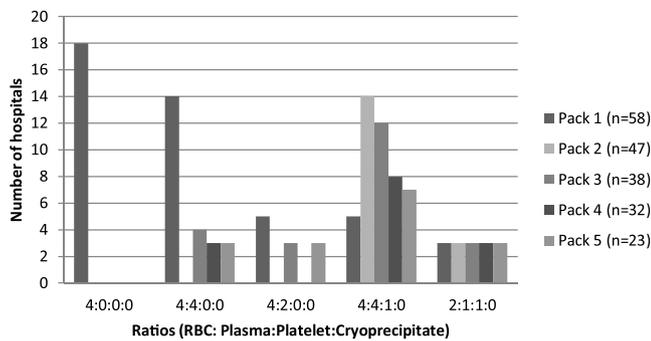| Products routinely stocked on site (n = 132)		
Prothrombin Complex Concentrates (3000 IU+)	125	95%
Frozen plasma (4 or more units)	108	82%
Red blood cells (of all blood groups)	97	73%
Cryoprecipitate	80	61%
Fibrinogen concentrate	48	36%
Platelets (1-2 units)	44	33%
Platelets (3+ units)	23	17%
Pre-labelled trauma stock units	21	16%

Fig. 1. Number of hospitals using the most commonly used predefined ratios found for packs 1–5 for hospitals issuing blood in pre-define ratios. The most common configuration for pack 1 was 4 units of RBCs and the most common pack configuration for packs 2–5 was 4:4:1. Cryoprecipitate as not used in any of the commonly used pack configurations.

Table 4
Summary of the number of unit in the predefined MHP packs.

Pack	RBC (units)	Plasma (units)	Platelet (pool)	Cryoprecipitate (units)
1 (n = 58)	Median 4 IQR (4-4) Range (2-6)	Median 2.5 IQR (0-4) Range (0-4)	Median 0 IQR (0-1) Range (0-1)	Median 0 IQR (0-0) Range (0-10)
2 (n = 47)	Median 4 IQR (2-4) Range (0-6)	Median 4 IQR (4-4) Range (0-6)	Median 1 IQR (1-1) Range (0-2)	Median 0 IQR (0-0) Range (0-10)
3 (n = 38)	Median 4 IQR (4-4) Range (0-6)	Median 4 IQR (2-4) Range (0-6)	Median 1 IQR (1-1) Range (0-4)	Median 0 IQR (0-0) Range (0-10)
4 (n = 32)	Median 4 IQR (2-4) Range (0-6)	Median 2 IQR (1-4) Range (0-6)	Median 1 IQR (1-1) Range (0-1)	Median 0 IQR (0-0) Range (0-10)
5 (n = 23)	Median 4 IQR (4-4) Range (2-5)	Median 4 IQR (2-4) Range (1-5)	Median 1 IQR (0-1) Range (0-2)	Median 0 IQR (0-0) Range (0-10)

Quality

More than half of hospitals with an MHP performed multidisciplinary debriefs/reviews of MHPs; the majority based on select cases of concerns regarding performance. Additionally, 69% of hospitals did not track any quality metrics. Of the 31% (30/97) of hospitals that did, common metrics tracked included: proportion of activations with wastage, appropriate activations, group and screen received, and red blood cells delivered within 15 min. Only 2 sites tracked whether the patient received TXA during the protocol.

Sub-group analysis by size of hospital

The survey results captured 8/9 (89%) large hospitals (1 site gave verbal affirmation that they did not have an MHP), 14/14 (100%) medium sized hospitals and 111/127 (88%) small hospitals. Almost all hospitals considered large 89% (8/9) and medium 93% (13/14) had an MHP in place, while only 60% (76/127) of small hospitals that transfuse <5000 RBCs units per year had an MHP. Moreover, although most laboratory tests were available at large and medium hospitals, survey results indicated that numbers were more variable among smaller hospitals. Testing for ionized calcium was present in 88% (7/8) of large hospitals, 93% (13/14) of medium and 59% (66/111) of small hospitals. While fibrinogen testing was available at all large and medium hospitals, it was only available at 59% (66/111) of small institutions. Additionally, fibrinogen was routinely drawn at 6/8 (75%) large hospitals with an MHP, 13/13 (100%) medium hospitals with an MHP and 54/76 (71%) small hospitals with an MHP.

Discussion

Standardized MHPs yield reduced organ failure and mortality, reduced blood component wastage, and improved cost-effectiveness [7,12,23,24]. In accordance, the Canadian National Advisory Committee on Blood and Blood Products (NAC) suggests that hospitals in Canada with a transfusion service should have a local procedure in the event that urgent transfusion is needed [22]. To ensure the efficacy of the implemented MHP, emphasis should be placed on decreasing variability between protocols, maintaining adherence to MHP criteria, and ensuring adequate interdisciplinary training to optimize delivery.

Results from this survey indicated that a third of all hospitals in Ontario with a Transfusion Service did not have an MHP. In the 97 hospitals that did have an MHP in place, marked variability was found in all aspects of protocols including activation criteria, communication methods, hypothermia monitoring and management, coagulation testing, hemostatic agents and transfusion management. This variability in protocols was consistent with previous survey results in hospitals that did not have a common, standardized massive hemorrhage protocol [2,4,6,10,18]. Variability between protocols can increase cognitive burden, cause delays in care, or lead to inappropriate transfusion practices especially for physicians practicing at multiple institutions, or when transferring care between departments and health care centers. In particular, we show that many protocols have variability in the key areas of transfusion practice that have consensus amongst trauma centers. For instance, TXA utilization and temperature monitoring was absent in one-third of MHPs. Our survey did not investigate the underlying reasons for protocol variability and therefore additional studies are warranted to understand the drivers of protocol differences.

Triggers for transfusion protocol activation are an important source of variation; while 85% of MHPs had activation criteria, triggers used as activation and methods of activation varied all across the province; 70% of MHPs were activated based on the estimated volume of blood loss, 60% based on units of RBCs transfused and 32% on hemodynamic instability. This variability is expected given the lack of prospective studies across all patient groups evaluating the positive and negative predictive value of different criteria. The lack of scientifically validated criteria raises concerns regarding under and over activation of MHPs.

Communication of MHP activation and what hospital personnel were mobilized also varied. Some relied on telephone calls to the blood bank, others for an overhead announcement, with various names used for different sites' protocols. Between interdisciplinary teams, porters were not included in a third of hospital protocols, often leaving other members of the team to handle transportation of samples and blood components while also intermittently removing them from their critical role at the bedside. Communication of laboratory results focused mainly on critical values, and is an area that requires fine tuning as normal results may aid clinical gestalt in withholding transfusions or terminating an MHP.

While numerous tests such as creatinine, electrolytes, CBC, INR, aPTT, calcium, and group and screen were almost always available across hospitals in Ontario, tests routinely drawn in the case of an MHP varied. Surprisingly, ROTEM was only utilized at 4% of hospitals and TEG was available at 2 of the 133 reporting sites, yet neither of these sites incorporated its use in their MHP. The failure to adopt these novel point-of-care technologies may be due to the

lack of large, randomized, controlled trial evidence in the setting of massive hemorrhage, cost, and burden of regulatory oversite on point-of-care tests. There is good evidence for use of ROTEM and platelet function testing from a large trial in cardiac surgery, although the patients studied in this report were not uniformly massively bleeding [25], and small randomized trials in trauma [26,27]. Furthermore, although aPTT testing was routinely used in 77% of MHPs, a recent study showed that turnaround times could be reduced through the removal of the aPTT [28]. Although the aPTT may occasionally be useful in patient management (e.g., may signify the presence of an anticoagulant therapy), Chandler et al. found that an abbreviated massive hemorrhage panel (CBC, INR, fibrinogen) as opposed to a more expanded coagulation panel (and more precision) resulted in a faster turnaround time [28]. Although early fibrinogen replacement use for hypofibrinogenemia is indicated in most guidelines, fibrinogen testing was only utilized in 59% (66/111) of small hospitals and of those 66 hospitals, only 54 incorporated this test into their MHP [29]. Another interesting finding from our survey results was that while group and screen was available at 95% of hospitals, it was only formally a part of the protocol in 64%. Group and screen is critical to ensure rapid transition to group specific RBC and plasma to minimize stress on chronically depleted stocks of O RBCs and AB plasma. Although laboratory-directed hemostatic support alone has the potential to fall behind due to testing delays, laboratory results can be critical in identifying insufficient transfusion support and severity of injury. A retrospective study of trauma deaths at a Level I trauma center in Toronto revealed that 36% of hemorrhagic deaths after blunt trauma could have been prevented; with many patients having an initial base deficit greater than 10, indicating an unrecognized source of uncontrolled hemorrhage (pelvic bleeding in the majority) [30]. In addition, the clinical team must have a high degree of suspicion for serious ongoing bleeding if the baseline or subsequent measure of INR and fibrinogen are abnormal. Lowest staffing level was 1 to 2 technologists at the majority of hospitals, suggesting intra-laboratory MHP protocols need to be simple to allow for rapid release of blood and blood components. When creating a standardized protocol, staffing level and local resources of each hospital must be considered as a one-size-fits-all protocol is unlikely to meet the needs of all hospitals.

In regard to adjunctive care, 35% of MHPs do not specify the monitoring of patient temperature and only 65% of MHPs reported methods for managing hypothermia. Previous studies have indicated that the monitoring and management of patient temperature is a key component for patient outcomes [31,32]. A core temperature of less than 35 °C is a predictor of mortality in patients suffering major trauma, with the onset of hypothermic coagulopathy seen at core temperatures of 34 °C and below [31,32]. In addition, TXA was not included in one third of MHPs. The CRASH-2 and Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) trials found a reduction in hemorrhagic death when administered promptly after injury [14,15]. In another randomized, placebo-controlled trial, deaths from hemorrhage in women with post-partum bleeding were significantly reduced when given tranexamic acid compared to a placebo[16]. Our survey found that hospitals in Ontario administer a median dose of 2 g of TXA, which was consistent with the dose used in the CRASH-2 and MATTERs studies [14,15]. We did not ask the survey respondents the triggers for TXA, protocolized contra-indications to TXA, and when TXA is withheld, and therefore additional studies are warranted in this area of hemostatic resuscitation. The hemostatic agent, rFVIIa was present in only 4% of protocols, which was inconsistent with results from previous surveys. Results from a survey on 132 the American College of Surgeons Trauma Quality Improvement Program trauma centers revealed that 34.1% of trauma centers incorporated rFVIIa as an

intravenous hemostatic agent within their protocol [2]. Another survey in 2010 revealed that rFVIIa was included in 37% of protocols in a study of 186 respondents from hospitals in the United States [10]. However, a Cochrane review in 2009 revealed a lack of evidence to support the use of rFVIIa as a general hemostatic drug and concerns regarding its thromboembolic risk [33]. Results from our survey may be reflecting more current practices in hemostatic resuscitation due to the evolving scientific evidence. In addition, 41% did not have a reversal protocol for patients on anticoagulants.

Overall, 27% of hospitals do not transport RBCs in a temperature validated container. After the termination of a protocol, unused RBCs transported in a validated container can be put back into the blood bank inventory to avoid wastage of scarce resources. Additionally, 36% of hospitals always use O RhD negative RBC, leading to stress on chronically low O RhD negative RBC inventory [9,34–36]. In a recent retrospective study performed by Barty et al. on three academic hospitals in Ontario, findings indicated that there was an increase in the practice of O RBCs transfused to individuals of non-O blood type [34]. In order to reduce this wastage, hospitals should have in place guidelines for restrictive use of O RhD negative RBCs. Current guidelines on which patients should receive O RhD negative RBC were extremely variable across hospitals, with the most common being women less than 45 years old.

Overall, 61% of hospitals with an MHP had predefined packs which were not consistent with the NAC recommendations that hospitals should have an organized and sequential delivery of blood and blood components [22]. Our survey results also indicated variability within the predefined MHP packs (different ratios of RBCs, platelets, plasma), potentially creating additional confusion for MDs who work at different locations and trainees rotating from one hospital to another. Thawed plasma was only available at a small number of institutions; such a product could only be stocked at tertiary care trauma centers with very high volumes of traumas that would mitigate the risk of product wastage. Interestingly, fibrinogen concentrate was incorporated in 13% of protocols, suggesting that many hospitals are currently using fibrinogen concentrate off-label (licensed for use only for patients with congenital deficiencies of fibrinogen with bleeding or going for a surgical procedure). Although fibrinogen concentrate has been reported to be used for treating massive hemorrhage in many jurisdictions based on ROTEM/TEG results, there are no data to support its equivalence or superiority to cryoprecipitate [37,38]. A study is ongoing at 12 centers in Canada (FIBrinogen REplacement in Surgery, FIBRES (clinicaltrial.gov: NCT03037424)) to determine if fibrinogen concentrate is non-inferior to cryoprecipitate in patients bleeding after cardiac surgery. The failure to include trauma packs with plasma and platelets in the majority of non-academic non-trauma centers raises the concern regarding under-resuscitation of the coagulopathy in the massively bleeding patient population. We hypothesize that this may be due to the infrequency of activation, longstanding ingrained protocols for only providing components with a physician order, minimal stocks of plasma (e.g., only 4 units of frozen plasma), and no platelets stocked in house. This begs the obvious question as to how to resuscitate a massively bleeding patient at such a hospital, particularly postpartum hemorrhages and patients in local motor vehicle accidents, before arrival of helicopter transport to a larger facility with the ability to provide ratio based resuscitation. Perhaps, the hospitals that have transitioned to PCCs and fibrinogen concentrates instead of plasma are attempting to simulate formula-driven resuscitation in a resource challenged location. Laboratory hemostatic targets used by the hospitals were concordant with the European guidelines on management of major bleeding and coagulopathy following trauma (platelet count

$>50 \times 10^9$/L, fibrinogen>1.5 g/L) [39], although a target INR of >1.7 was commonly used although this has never been validated as a hemostatic target.

While the survey was created to understand contents of current MHPs, there were no data collected to determine whether hospitals had achieved high levels of compliance with their MHP. In 2014, Bawazeer et al. performed a study at St. Michael's Hospital (a large trauma hospital in Ontario) on MHPs and found a mean compliance rate of 66%, as well as an association between a higher level of compliance and patient survival [21]. Hence, a critical gap may also exist between the existence of a protocol and its appropriate implementation [40].

Our results also indicated that the majority of hospitals with an MHP do not track quality metrics. However, the NAC guidelines recommend that process improvements be conducted with practice runs, periodic process reviews, and continuous data collection to track quality metrics [22]. Process improvement allows hospitals to identify key areas of non-compliance in order to address those issues and determine their impact [40]. Another possible solution to improve compliance would be to perform peer comparisons with standardized performance metrics; this would allow hospitals to evaluate their own performance in comparison to others to identify areas of low performance in need of remediation.

There were multiple limitations to this study. First, responses were submitted by multi-disciplinary individuals completing the survey based on their own knowledge of their hospital protocol. We did not have access to the hospitals' protocols and were therefore not able to ensure that respondents' answers accurately reflected their MHP contents. Second, this survey evaluated the policies in place, rather than actual performance during an MHP.

Conclusion

In summary, MHPs have not been implemented in a third of transfusion services. The contents of existing MHPs are highly variable. Based on our survey results, we found deficiencies across all parts of MHPs from activation to termination. The survey also identified significant resource limitations in laboratory testing, blood component inventory, and qualified human resources in small hospitals. Our data provides evidence that there is significant heterogeneity in MHPs and this could be addressed by a standardized province-wide protocol. Addressing limited resources in remote regions was out of our scope for our survey; however, a protocol tailored to larger vs. smaller community hospitals may allow for the most appropriate patient management, taking into account the local resources.

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Conflict of interest

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Acknowledgments

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