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Massive hemorrhage update: what is known and what we should know?

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1. To the editor-in-chief

Massive hemorrhage protocol (MHP) is an updated term for the formerly used massive transfusion protocol, highlighting crucial aspects of hemorrhage management other than the transfusion itself. This complex intervention includes acute hemorrhage control; administering tranexamic acid (TXA), preventing hypocalcemia, hypothermia, and acidosis; reversing anticoagulation or correcting coagulopathies; and planning for the next steps in definitive hemorrhage control (1). Here, we discuss exciting frontiers and challenges of MHP.

Whereas level I trauma centers benefit from routine MHP activations and therefore, familiarity among staff members and the opportunity to optimize MHP procedures and policies (2), community and rural hospitals do not. Variability in protocol presence, elements, compliance, and threshold to activate among community, rural, and remote hospitals have been described (2). Adopting a protocolized threshold to activate MHP may alleviate this decision-making burden. Several pre-hospital and in-hospital scoring systems have been proposed, each with differing complexities and strengths, such as the shock index and ABC score among others (3). Artificial intelligence and machine learning tools are potentially exciting and rapidly evolving avenue in this area (4).

Evidence has shown a balanced resuscitation of 1:1:1 (packed red blood cells (PRBC): fresh frozen plasma (FFP): platelets) is associated with improved outcomes (5).

However, it is rarely administered in this fashion. For example, most transfusion protocols begin with 2-4 units of PRBC; followed by a first cooler containing 2 units of PRBC and 2 units of FFP, followed by a bag of platelets (5-6 units). This would imply a sequential administration to achieve 1:1:1, and a potential delay to hemostatic factors that trauma patients may immediately require. Further, emphasis on the ideal 1:1:1 transfusion ratio has been re-ignited by slowly accumulating evidence for whole blood transfusions. However, resuscitation with whole blood transfusion is supported mainly by observational cohort studies; only a single randomized control trial (RCT) exists; many studies are often in military settings (6). Several planned randomized trials are actively recruiting to answer this question.

Coagulopathy management in the ED continues to be challenging. Whereas warfarin has clear reversal strategies with prothrombin concentrate complex (PCC) and vitamin K, strong clinical evidence is lacking for the optimal empiric therapy for patients with known bleeding diathesis secondary to direct oral anticoagulants (DOAC's). Adnexanet alpha, the reversal agent for rivoroxaban and apixaban, potentially slows hematoma expansion but lacks mortality benefit, and it is cost-limiting. PCC is recommended, but its efficacy is variable depending on circulating levels of 10a inhibitor level and is mainly demonstrated in observational data looking at coagulation markers. Providing these agents must be balanced against the risk of associated thrombotic events. Finally, a reverse ratio (e.g., 1 to 1.5:1 FFP to PRPBC) may be considered, as higher ratios have been associated with improved outcomes in observational data (7), though its efficacy compared to PCC and direct reversal agents is unclear (8).

After the initial phases of balanced resuscitation in the ED, coagulopathy management decisions usually depend on trends in coagulation studies, platelet, and fibrinogen levels in the emergency department. Viscoelastic assay (thromboelastography and rotational thromboelastometry (TEG/ROTEM)) is rarely accessible in emergency departments but is available in some major trauma centers. This tool may better reflect coagulation function in patients where coagulation studies poorly reflect complex coagulopathies, such as in patients taking antiplatelet or anticoagulants or those with liver dysfunction (9). Although viscoelastic assays may potentially reduce the total number of transfused units, with costs being prohibitive, it is unlikely to be available in the ED until randomized mortality data become available. There is need for mention of special populations. Centers that serve pediatric patients should have their MHP pro-

tocols adjusted with pediatric physiology including, but not exclusive to: age-appropriate vital signs, differing hemodynamic responses and circulatory signs, and weight-based MHP dosing. It should be recognized that TXA has not been experimentally studied in children but deemed safe from observational trials (10).

In women of childbearing age and pregnant patients, MHP should be similar except that O negative blood product (if applicable) should be preferentially administered to prevent RH alloimmunization. If not available, lifesaving resuscitation with O positive blood should never be withheld from an unstable patient, given the high risk of morbidity and low risk of RH alloimmunization. Clinicians should have a higher index of suspicion for placenta abruption even with minor mechanisms of injury and the risk of diffuse intravascular coagulopathy (DIC) in this population. ED Protocols should include left lateral tilt of gravid uteri and gynecologists and neonatologists must be involved early (11).

Elderly patients are often comorbid and take medications that may interfere with coagulation and vital signs. Note that concomitant cardiogenic and septic shock is more common in this group. Clinicians should avoid relying solely on blood pressure (BP) and should integrate other markers of perfusion and point of care ultrasound (POCUS) evaluation of the inferior vena cava and cardiac views to determine the optimal resuscitation strategy and to address other causes of shock. BP targets may differ according to age, suspected traumatic brain injury (TBI), and past medical history of underlying hypertension (12).

While there is no concrete rule to stop MHP, clinical judgement should be based on two aspects: (1) hemorrhage control and (2) evidence of adequate volume/perfusion status. Clinicians should consider permissive hypotension using a mean arterial pressure (MAP) of 65 mmHg for most blunt and penetrating trauma. For any patient with suspected traumatic brain injury, higher targets should be considered: MAP ≥ 80mmHg, or systolic blood pressure (SBP) ≥ 100 mmHg in 50-69 years of age and a SBP ≥ 110 for 15 – 49 and ≥ 70 years old (13). Other clinical parameters of importance include normalized mental status, pulse pressure and strength, capillary refill, skin turgor, and IVC variability on POCUS.

Laboratory parameters include a normal lactate and base excess; hemoglobin does not adequately reflect active bleeding, and therefore, the trend should be followed rather than any single normal value (14).

To conclude, MHP is a complex, multi-step, cognitively heavy process that requires ongoing evaluation throughout the resuscitation. Compliance with MHP principles is improved with dedicated hospital protocols and practice. Trends in MHP literature include an emphasis on protocol development and balanced resuscitation with anticoagulation reversal, and continued coagulopathy management. Several minor modifications to MHP should be made for special, at-risk populations. As trauma team leaders, we look forward to the future of MHP precision and optimization.

2. Declarations

2.1. Acknowledgement

None.

2.2. Authors' contribution

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2.3. Conflict of interest

None.

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