

Review article

Fluid Resuscitation and Massive Transfusion Protocol in Pediatric Trauma

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SUMMARY

Trauma is the leading cause of morbidity and mortality in children due to the occurrence of hemorrhagic shock. Hemorrhagic shock and its consequences, anemia and hypovolemia, decrease oxygen delivery, due to which appropriate transfusion and volume resuscitation are critical. Guidelines for massive transfusion, in the pediatric trauma, have not been defined yet. Current data indicate that early identification of coagulopathy and its treatment with RBSs, plasma and platelets in a 1:1:1 unit ratio, and limited use of crystalloids may improve survival in pediatric trauma patients.

Key words: fluid resuscitation, massive transfusion protocol, pediatric trauma

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INTRODUCTION

Trauma-related injuries are the leading cause of death in pediatric patients. Exsanguination, either at the site of the accident, or in hospital, accounts for 45% of all traumatic deaths. Motor vehicle collisions (59% mortality from all accidents in age group 5-14), pedestrian and bicycle accidents, falls, burns, and physical assault are the most common causes of injury in children (1). Many of injured children will require surgical treatment with involvement of the anesthesiologist.

The major cause of morbidity and mortality in traumatized children is anemia and hypovolemia caused by hemorrhagic shock result in oxygen deprivation to vital organs. In order to improve decreased oxygen delivery, appropriate transfusion and volume resuscitation are critical. Although the fast infusion of fluids in trauma patient who is hemorrhagic and who has low pressure may seem undeniable, the end points for fluid administration to hemodynamically stable victims of blunt trauma and severe head injuries are unclear and not well established.

Also, in the pediatric population, there are no clear guidelines for massive transfusion. Adult trauma transfusion protocols can be utilized at children's age until a pediatric protocol is established (2). Here we tried to identify certain principles of fluid and transfusion therapies that are specific for pediatric trauma, and to present a sample of massive transfusion protocol (MTP) that can be used to guide resuscitation.

EVALUATION OF VOLUME STATUS IN PEDIATRIC TRAUMA PATIENTS

Hemorrhagic shock as a result of pediatric trauma is an uncommon but fundamental problem for the treating clinician, especially in cases of massive bleeding. Massive bleeding in children has been defined as the loss of one or more circulating blood volumes and all estimates of blood volume, volume loss and volume replacement are based on weight of children over the age of 3 months having an estimated blood volume of 70 ml/kg, and younger infants having an estimated blood volume of 90 ml/kg (3).

The evaluation of the volume status of the pediatric trauma patients can be difficult since children are able to maintain a normal blood pressure in a supine condition with a loss of up to 20% of their blood volume. Physiologically, children have better

hemodynamic compensation in the early stages of injury. Tachycardia is the first sign of hypovolemia in children, and it should not be overlooked, because children have small blood volumes, and delay in fluid resuscitation may rapidly lead to a significant decrease in hypovolemia (4). Other possible early signs of shock such as mental status change, respiratory compromise, absence of peripheral pulses, delayed capillary refill, skin pallor, and hypothermia must be immediately recognized. Having in mind that children have considerable cardiovascular reserve, the initial normal vital signs should not impart any sense of security with regard to the status of the child's circulating volume. Obvious signs of shock, such as hypotension (a late sign of hemorrhage in children) or a decrease in urinary output, may not occur until more than 30% of blood volume has been lost (5). Clinical monitoring should focus on perceived tissue oxygenation with continuous measurements of heart rate, pulse oximetry, arterial blood pressure. In massively bleeding patients, invasive monitoring can be extremely helpful in this population, and should never be omitted irrespective of the patient's age. Inserting the arterial line facilitates monitoring of blood pressure to a large degree, whereas central venous line provides valuable information about the cardiac filling pressures especially when the blood loss is such that cannot be quantified, for example in cases of internal bleeding or neurosurgical trauma. Experience from the literature suggests that 2-3 mmHg reduction in central venous pressure may reflect a loss of as much as 20% of the circulating blood volume (6).

Emergent procedures should not be postponed by waiting for the imaging and laboratory results. From all chest imaging methods, standard anterior-posterior chest X-ray is a cost-effective screening tool that will reveal most of the thoracic abnormalities (7). On the other hand, urinalysis or serum chemistries are of little use in pediatric trauma. From the specific testing, type and cross match blood, and hematocrit are indicated for a hemodynamically unstable patient. Serial hematocrits may help in the monitoring of solid organ injuries. Since coagulopathy is associated with trauma in general and with head injuries specifically, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) are useful tests in critically injured patients. Serial arterial blood gas testing is invaluable in assessing dynamic changes in hematocrit, oxygenation and acid-base status in critically ill children (8). What is the best

level of haemoglobin for pediatric trauma patients? Children are at least as capable as adults in their ability to compensate for lower hemoglobin concentrations with increased oxygen extraction and cardiac output, despite their limited myocardial compliance (9). Because of that, a specific level of blood loss or anemia that triggers RBC transfusion has not yet been defined in pediatric patients (3). A study done on hemodynamically stable, critically ill pediatric patients, the TRIPICU trial, showed no adverse effects when comparing a restrictive transfusion strategy initiated at a hemoglobin level of 7g/dl to a transfusion threshold of 9.5 g/dl (10). A specific anemia threshold would be difficult to use as a trigger for MTP activation in the case of massive hemorrhage, because hemoglobin and hematocrit levels might not reveal significant anemia until the patient had been volume resuscitated, making a precise estimate of lost blood volume difficult to ascertain based on these laboratory tests (3, 11).

Children with hemorrhagic shock have a physiological predictors of adverse outcome, as a high Injury Severity Score (ISS), shock and high base deficit on admission, which are independent predictors of increased mortality in the general pediatric trauma population. Patregnani et al. (12) found that coagulopathy (INR ≥ 1.5) on admission was common and associated with increased mortality in children with traumatic injuries, independent of the ISS. Vavilala et al. (13) found that the presence of coagulopathy (defined by increased fibrin degradation products) independently predicted poor outcome in children with isolated head injury. Several mechanisms have been proposed to explain the coagulation abnormalities associated with TBI, which show a combination of both hypocoagulable and hypercoagulable states (14). It has also been hypothesized that the trauma causes local release of tissue factor from the injured neurons, which is associated with activation of the protein C pathway, thus triggering the release of anticoagulant mediators (15). Borgman et al. (16) found both admission base deficit < 8 and INR > 1.8 to be independently associated with mortality, and proposed that a score based on these predictors of adverse outcome („BIG“ score: base deficit + $[2.5 \times \text{INR}] + [15 - \text{GCS score}]$) may more accurately predict mortality in pediatric trauma patients than scoring systems currently in use. Measurements of admission base deficit are frequently used as markers of tissue hypoperfusion and shock. The prognostic value of lactate levels has

not yet been defined in pediatric patients. Several investigators suggest using shock index (defined as heart rate/systolic blood pressure) as an indicator of tissue perfusion as it reflects both vascular and myocardial dysfunction (17).

FLUID RESUSCITATION IN CHILDREN

After the initial evaluation of patients with pediatric trauma, it is important to prevent hypothermia. Hypothermia results in vasoconstriction, low-flow state, acidosis, and consumptive coagulopathy. The use of warm intravenous fluids and covering the patient with warm blanket may prevent hypothermia. Connective air rewarmers (e.g. Bear Hugger) and warmed, humidified ventilation can help maintain core body temperature, if hypothermia is detected ($< 35^{\circ}\text{C}$). Peritoneal lavage with warm saline may assist with hypothermia refractory to prior measures (18).

Control of bleeding and fluid resuscitation on an injured child remains to be a crucial step in trauma care. Early intravenous access with appropriate fluid administration continues to be a universal treatment for hypotensive trauma patient. Up-to-date management of hemorrhagic shock still involves the initial resuscitation with crystalloid fluids followed by an infusion of blood components as necessary. Initial fluid resuscitation should begin with the warm isotonic crystalloid solution (Ringer's lactate or isotonic sodium chloride solution) at a bolus of 20 ml/kg. The goal of initial resuscitation should be to achieve hemodynamic stability and to restore adequate tissue perfusion as soon as possible. The end-points of fluid resuscitation in children usually include normalization of pulse rate and urine output > 1 ml/kg/h. Recent literature has questioned the timing, type, and amount of fluid administration during the resuscitative phase. Some authors found insufficient evidence for or against the use of early or larger volume fluid resuscitation in the treatment of uncontrolled hemorrhage. While vigorous fluid resuscitation may be life-saving in some patients, results from clinical trials are inconclusive. In bleeding trauma patients, the liberal use of isotonic crystalloids to correct hypotension was recommended by the Advanced Trauma Life Support (ATLS) protocol of the American College of Surgeons. Nevertheless, they could find no reliable evidence to support or not to support this recommendation. The authors of the recommendation deny the possibility of overlooking a large high-quality randomized controlled

trial, showing that early or larger volume fluid resuscitation is beneficial (19).

The adverse effects of hemodilution in children were described by Hussmann et al. (20), who found that increased prehospital crystalloid volume replacement was associated with increased transfusion requirements, adversely affected coagulation (defined by a prolonged PT) and a tendency towards increased mortality and multiple organ failure (MOF) rates. A comprehensive standard protocol cannot be established for these situations. Prehospital volume replacement in the most severely injured children is associated with a number of perils and should be critically estimated, except in the case of absolute indications, e.g. traumatic brain injury. Excessive prehospital volume replacement (over-resuscitation) with crystalloids in injured children can have a negative effect on the clinical course (e.g. a higher rate of MOF and mortality). The decision to start with the increased volume replacement therapy at the accident site must be made on a case-by-case basis (20).

Hypertonic saline was shown to increase hemodynamic stability and decrease fluid requirements in adult trauma patients, but it did not affect the survival rate (21, 22). One might consider the use of hypertonic saline when trauma is associated with a closed head injury (23). However, more evidence for the use of hypertonic saline in children is needed. Hydroxyethyl starch and albumin have also been used in children with insignificant adverse effects (24, 25). Hemodilution with large amounts of colloids may have negative effects on hemostasis. Comparing the effects of hydroxyethyl starch (HES) and human albumin (HA) on coagulation by thrombelastography in children weighing 3-15 kg (26), Haas et al. (27) found more impaired coagulation after the use of HES. Volume replacement with HA may be associated with higher mortality rate in trauma patients with TBI when compared to saline (27). Caution is therefore warranted, and colloids should not be used for replacement of volume in the trauma patients, given the high rate of early coagulopathy and TBI in the children (28, 29).

In children with head injury, dextrose-containing fluids should not be given because hypotonic solutions may lead to the development of cerebral edema (30). In case of hyperglycemia, children with a head injury have a higher risk to develop poor neurological outcome. However, hypoglycemia is also harmful for a suffering brain, and should be avoided (31).

PEDIATRIC MASSIVE TRANSFUSION PROTOCOL

Children with evidence of hemorrhagic shock who fail to respond to fluid resuscitation should also receive blood and be evaluated by a pediatric surgeon for possible operative intervention. Guidelines regarding transition from clear fluids to blood and blood products are not well-established in pediatric trauma. Clinical decision either follows adult protocols, or is made per individual clinical judgment (32).

Besides containing fibrinogen, which is essential for clot formation, FFP is an excellent volume expander. So is RBC, and patients that require massive transfusion should therefore be given RBC and FFP as volume therapy to treat their hypovolemia causing hypoperfusion with ensuing oxygen debt and coagulation factor depletion, rather than crystalloids (33). Studies in adult populations have shown that an increased ratio of PLT and FFP to RBC show an association with improved survival in massively bleeding trauma and non-trauma patients (33, 34). Nosanov et al. (35) did not find the same association between increased FFP or PLT to RBC ratios and decreased mortality in massively transfused pediatric trauma patients. This group defined massive transfusion as more than 50% of total blood volume lost within 24 hours. The use of warm fresh whole blood for adult patients with traumatic injuries has shown to be independently associated with higher rate of survival for 30 days (36). Some authors found that there was significantly less postoperative blood loss in the group of 161 children undergoing open heart surgery, receiving fresh whole blood, and ascribed this to better functioning platelets (37). Based on these data, whole blood could potentially be used as an alternative to reconstituted whole blood in trauma settings for hemostatic resuscitation in centers that are able to handle and store it correctly. More investigation into the utility of whole blood in the emergency setting for pediatric resuscitation is warranted. Dressler et al. (38) described the use of a MTP in the case of a child with severe intraoperative bleeding (>4 liters). They applied a blood product ratio of 4:4:5 units of RBC:FFP:PLT perioperatively, and did not find the signs of coagulopathy postoperatively. Pickett et al. (39) described the use of MTP consisting of 6:3:5 ratio of RBC:FFP:PLT for pre- and perioperative transfusion in a

15-year old boy with an estimated blood loss of 10 liters due to a gunshot wound to the chest. The patient did not present with or develop coagulopathy after resuscitation. Paterson et al. (40) presented the child with severe intracranial bleeding caused by an arterio-venous malformation, resulting in an estimated loss of more than 5–6 blood volumes. Their MTP, after the loss of 2 blood volumes with expected continued bleeding, consisted of RBC, FFP and PLT given in a ratio of 30:20:20 ml/kg (total 70 ml/kg) in each cycle. The patient survived and was admitted to the ICU with a normal postoperative coagulation profile.

In most institutions that are not only children's hospitals, pediatric massive transfusion protocols would need to reflect or complement adult MTPs. The logistics of blood bank operations and the need for straightforward, unambiguous protocols in the trauma bay would likely demand that existing adult MT protocols, which are centered mostly on a PRBC/FFP/PLT ratio of 1:1:1, be followed for most pediatric patients as well. However, these protocols should not be used for small children (<30kg), for whom transfusions must be given based on their weight. A starting point for a pediatric MT protocol would include the following elements:

1. Initiation of MT protocol in traumatic hemorrhagic shock with persistent hemodynamic instability or ongoing bleeding after 40 ml/kg of crystalloid infusion

2. Blood components delivered to larger pediatric patients (>30 kg) at a ratio of 1:1:1 units of PRBC/FFP/PLT with cryoprecipitate given for low fibrinogen levels (<1-1.5 g/l) or during bleeding after the administration of 1 round of all 3 blood components. For

pediatric trauma patients less than 30 kg, a weight-based protocol at a ratio of 30: 20:20 would be initiated (40).

3. Appropriate maintenance of body temperature, serum calcium, and blood pH.

4. Consideration of use of rFVIIa in extreme cases. Doses between 20 and 180 µg/kg have been given in adults and pediatric patients, although it is important not to forget that use in trauma situations is off-label (3).

5. In the future, the use of hemoglobin substitutes is confirmed in adult patients with additional experience. These products along with other plasma expanders may have a role in pediatric trauma algorithm.

CONCLUSIONS

Management of pediatric patients with trauma requires the knowledge of the special considerations and understanding of the pathophysiology and special requirements of the pediatric population. Current data indicate that early identification of coagulopathy and its treatment with RBC, FFP, and PLT in a 1:1:1 unit ratio achieved with the use of fresh RBCs, thawed plasma, and platelets, limited use of crystalloids, careful consideration of resuscitation adjuncts, such as rFVIIa, may improve survival in uncommon pediatric trauma patients, who presents with severe traumatic injury and life-threatening bleeding. In the future, dedicated multicenter research will be needed to evaluate outcomes associated with implementation of MT protocols in pediatric trauma patients.

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Nadoknada tečnosti i protokol masovne transfuzije kod traumatizirane dece

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SAŽETAK

Trauma je vodeći uzrok morbiditeta i mortaliteta kod dece usled nastanka hemoragičnog šoka. Hemoragični šok i njegove posledice, poput anemije i hipovolemije, smanjuju isporuku kiseonika tkivima, zbog čega primena derivata krvi i nadoknada tečnosti mogu biti od vitalne važnosti. U pedijatrijskoj populaciji, indikacije za primenu masivne transfuzije krvi su još uvek nejasne. Trenutni podaci ukazuju da je rana identifikacija koagulopatije i lečenje ovakvih bolesnika eritrocitima, plazmom i trombocitima u odnosu 1:1:1, ograničeno korišćenje kristaloida, može poboljšati preživljavanje traumatizirane dece.

Ključne reči: nadoknada tečnosti, protokol masivne transfuzije, trauma kod dece