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CONTEMPORARY APPROACH IN TREATMENT OF HYPOVOLEMIC SHOCK

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Abstract

Acute circulatory failure or shock, regardless the etiology, is a life-threatening condition that needs prompt and adequate treatment, as it may progress to organ failure and death. Aggressive treatment of shocked patients must be early and appropriate in order to prevent or limit vital organ injury. Fluid resuscitation with vasopressor coadministration is the first line strategy in the first few hours when treating patients with shock. In bleeding patients with hypovolemic shock, fluid resuscitation and volume restoration are the mainstay of therapy. Giving 1.5L balanced fluids in the first hour and an antifibrinolytic in the first 3 hours after the injury is crucial for preventing tissue damage because of hypovolemia. Crystalloids should be used judiciously until blood products are ready for use with a rate of 1:1:1. Because no human studies exist to support the routine use of vasopressors in the trauma setting, in order to avoid further tissue hypoperfusion and hypoxia due to vasoconstriction, adequate fluid resuscitation should be a priority. Significant benefits of permissive hypotension resuscitation in terms of reduction of mortality due to exsanguination after traumatic hemorrhage were reported. In non-bleeding patients with hypovolemic shock when fluid resuscitation is insufficient adding a vasopressor is recommended. According to the guidelines for treatment of shock, Norepinephrine is the first-choice vasopressor in patients with hypovolemic shock, but when the resuscitation with fluids and vasopressors as a first line strategy is failing, an inotrope should be added to support the failing circulatory system. Recent recommendations for management of shock are strongly against the routine use of inotropes as a first line therapy in patients with hypovolemic shock, but when it comes to usage of inotropes as a rescue therapy dobutamine is the drug of choice.

Key Words: Hypovolemic Shock; Hemorrhagic Shock; Shock.

When it comes to the term "Shock", the first written descriptions were focused on the hemorrhagic shock. No matter the cause and the mechanisms of shock development, often, the shock progression leads to multiorgan failure as a result of an imbalance between the tissue demand and supply of oxygen and nutrients.

Definition and Types of Hypovolemic Shock

Hypovolemic shock is defined as a condition of inadequate organ perfusion caused usually by an acute loss of intravascular volume which reduces the cardiac preload and impairs the systemic circulation and microcirculation. From the clinical point of view, the simplest way of hypovolemic shock differentiation which could have significant therapeutic implications is when we could make a clear distinction in between a hemorrhagic hypovolemic shock and non-hemorrhagic hypovolemic shock. According to Adams HA et al. hypovolemic shock could be divided into four subtypes: (1) Hemorrhagic shock resulting from acute hemorrhage without major soft tissue injury, (2) Traumatic hemorrhagic shock resulting from acute hemorrhage with soft tissue injury with release of immune system activators, (3) Hypovolemic shock in the narrower sense resulting from a critical reduction in circulating plasma volume without acute hemorrhage, and (4) Traumatic hypovolemic shock resulting from a critical reduction in circulating plasma volume without acute hemorrhage, due to soft tissue injury and the release of immune system mediators (1). The mainstay of hemorrhagic hypovolemic shock is the bleeding while the difference between hemorrhagic shock and traumatic hemorrhagic shock is that in the second group because of the trauma, besides the blood loss, tissue damage and consecutive inflammation, activation of coagulation is present as well, having significant impacts in the shock pathophysiology. The simple hemorrhagic shock is a condition of an acute bleeding from an isolated injury to a large blood vessel, gastrointestinal bleeding, nontraumatic vascular rupture as an aortic aneurysm rupture, obstetric hemorrhage as in patients with uterine atony, and hemorrhage in the region of the ear, nose and throat (vascular erosion). In cases of traumatic hemorrhagic shock, blood loss is accompanied with soft tissue injury which implies systemic inflammation activation, as well as coagulation cascade activation both aggravating the condition. Polytrauma is the typical example of this type of shock, which is usually caused by a road traffic accident and falls from a height. In these patients the presence of diffuse bleeding, hypothermia and acidosis could lead to life-threatening coagulopathy (2). In polytraumatized patients even minutes after the damage, a strong immune response of an unspecific inflammation is met which leads to leucocyte activation, release of enzymes, interleukins, prostaglandins and other bioactive substances which will increase the vascular permeability and promote capillary leak leading to further intravascular fluid loss. Tissue damage causes capillary and microcirculatory disruption and destruction of endothelial membrane-bound proteoglycans and glycosaminoglycans by itself, but is even more worsened by the systemic inflammatory response promoting a capillary leak syndrome, which makes the volume loss even more complicated. It should not be forgotten that the systemic inflammatory response following the tissue damage would have a negative impact on the vascular tone leading to vasoplegia. External and internal fluid loss with or without inadequate fluid intake are the main causes of hypovolemic shock in the narrower sense. Hyperthermia could lead to significant fluid loss with intravascular volume depletion, as well as persistent vomiting and diarrhea where electrolyte imbalance is ensured as well. Conditions as diabetes insipidus, traumatic brain injuries with cerebral salt wasting syndrome, hyperosmolar diabetic coma or diabetic ketoacidosis could lead to an uncompensated renal loss of fluids leading to severe hypovolemia. The phenomenon of third space shift and accumulation of large quantities of fluids could be a cause for hypovolemic shock as well, and this pathophysiological mechanism is met in patients with abdominal compartment syndrome, in

patients with ileus, as well as in patients with liver cirrhosis. Traumatic hypovolemic shock without hemorrhage is met in patients with severe burns, chemical burns, deep ulcerative and necrotizing skin lesions, as well as in soft tissue inflammation.

Systemic Responses and Clinical Manifestations of Volume Loss

In patients with hypovolemic shock because of the volume depletion, a strong activation of the sympathetic nervous system with release of significant amount of catecholamines, as well as antidiuretic hormone is ensured to happen as a physiological compensatory mechanism. This is supposed to increase the vascular tone, as well as heart rate in order to preserve or even increase the cardiac output in order to maintain homeostasis. The release of antidiuretic hormone leads to increased fluid tubular reabsorption in order intravascular volume to be preserved. The main goal of every single compensatory mechanism is to sustain a normal perfusion pressure. When the cause of the hypovolemic shock is not treated adequately, further worsening of the circulation is expected where hypotension and tachycardia are seen in shocked patients followed by lowered cardiac output, as well as low perfusion pressure leading to tissue oxygen demand and supply mismatch. The loss of adequate tissue perfusion and oxygen supply is the essence of cellular metabolism transformation from aerobic to anaerobic which leads to accumulation of acidic metabolic byproducts. When the cellular energy is wasted and ATP is not available anymore in an adequate amount, cellular swelling occurs because of Na/K pump disfunction. Systemic acidosis leads to further vasodilation and lowering of the systemic blood pressure, but also impairs the cardiac contractility as it has a substantial cardio depressive effect. Acidosis by itself, as well as inadequate oxygen tissue supply are significant trigger factors for activating a compensatory mechanism of tachypnea by stimulating the central and peripheral chemoreceptors to increase the respiratory rate in order to provide better tissue oxygenation. As in every state of shock the intravascular blood volume is centralized to the heart while significant splanchnic and renal vasoconstriction occurs, which leads to tissue hypoxia and absent urine production in order to preserve as much volume as possible. Poorly perfused tissues will fail in doing their own function, so elevated transaminases, acute renal failure, anxiety, coma or even death could occur if adequate treatment is not established as soon as possible (3).

Diagnostic and Therapeutic Approach in Patients with Hypovolemic Shock

Rapid diagnosis of hypovolemic shock, as well as discovering the etiology of volume loss is more than essential for preventing compensated shock to convert in decompensated irreversible state where there is a point of no return. In polytraumatized patients with visible bleeding, the diagnosis of hemorrhagic shock is more than obvious, but beside clinical signs and symptoms following all trauma protocols, an initial CT scan is a gold standard diagnostic method to reveal injury related internal bleeding. The most significant clinical signs of hypovolemic and hemorrhagic shock that should not be missed are hypotension where SBP is lower than 90mmHg, tachycardia, tachypnea, anxiety, agitation, lethargy, as well as coma, anuria, paleness, cold and sticky skin and delayed capillary refill. Pulse palpation is essential because low filled and filiform pulse or even absent pulse on peripheral arteries can be seen in different stages of shock. When one is uncapable to palpate a pulse on a radial artery, it is expected that SBP is lower than 80mmHg, lower than 70mmHg for femoral artery and lower than 60mmHg for

carotid artery respectively (3). Early recognizing of hypovolemia and detecting its cause in terms of an absent hemorrhage is crucial for good outcome, because even in younger patients compensatory mechanisms could be exhausted perceiving multi-organ failure and death. Metabolic distortions were previously discussed, so elevated serum levels of lactate are more than expected. The serum lactate level should be examined in all shocked patients, not only for diagnosis of circulatory insufficiency, but rather for following up the evolution of shock, as well as a marker for evaluation of the therapeutic approach effectiveness (4).

The main therapeutic endpoint in patients with hypovolemic shock should be restoration of hemodynamics and preserving tissue perfusion through managing the volume status of the patient. In order to restore the hemodynamics as soon as possible, aggressive fluid resuscitation in a narrow timeframe should be achieved. Aggressive fluid resuscitation demands at least two wide bored peripheral veins (16G) and a Central Venous catheter which should be placed immediately. The resuscitation fluids choice and the infusion rate of fluids in hypovolemic patients are the state-of-art activities in every intensivist's daily practice. It is well known that even in actively bleeding patients, giving of blood products prevents death, but one cannot be concentrated only on fluid resuscitation, and rather multidisciplinary approach with surgeons should be established for bleeding termination on time achievement. Nowadays the old techniques of emergency surgeries for definitive treatment of deeply shocked traumatized patients are exchanged with so called Damage Control Surgery. This term was adopted by trauma surgeons to describe the use of abbreviated surgeries to rapidly temporize life threatening injuries with delay of definitive repair after adequate resuscitation (5). Damage control surgery should be done as soon as possible after patient's admission (6).

When it comes to fluids, a vigorous choice has to be made in every patient depending on what type of hypovolemic shock is present. The American College of Surgeons has recommended the use of crystalloids (Ringers lactate or normal saline) in terms of fluid resuscitation of hypovolemic shock (7), while according to Healey MA et al. Ringer lactate is preferred over normal saline in patients with massive hemorrhage (8). In the previously cited study, it has been proven that patients with massive hemorrhage resuscitated with normal saline have experienced more physiologic derangements, as well as hyperchloremic metabolic acidosis was more frequently seen, which was also stated by another study (9). The usage of balanced crystalloids in initial dose of 10-20ml/kg with possibility of repetition of the dose until achievement of hemodynamic stability has been recommended (Recommendation level B) (10). Besides crystalloids in terms of fluid resuscitation of hypovolemic patients, colloids are recommended to be used for rapid volume restoration as well (7). There are studies that have proven that usage of albumin solutions in the initial resuscitation stage is not more effective than using crystalloids (11,12). One meta-analysis of 1,622 patients included in 26 randomized controlled studies, has provided a conclusion that the usage of colloids in the resuscitation process corelated with increased absolute risk for death of 4% (13). Back in 1980, Shoemaker et al., found an association between increased cardiac output, oxygen delivery and survival in critically ill surgical patients that underwent aggressive fluid resuscitation named and popularized as "supra normal" resuscitation (14-16). The supra normal resuscitation implies giving a large volume of crystalloids to drive a supra normal levels of cardiac output in terms of circulation improvement. Balogh et al., in 2003 have also found a strong correlation between the supra normal model of resuscitation and the frequency of abdominal compartment syndrome, multiple organ system failure and mortality (17). Later, it was found that infusing large volume of fluids in aims of

resuscitation interferes and impairs a lot of biochemical processes and basic cellular functions possibly aggravating the condition of already shocked organs. Another study showed conclusions against the supranormal model of resuscitation (18). According to the retrospective study of over 3,000 trauma patients done by Ley et al., infusion of ≥1.5 liters of crystalloid in the emergency department was independently associated with increased mortality (19), while in another study it was proven that giving even more than 500ml crystalloids in the prehospital period is associated with increased mortality (20). It was believed that usage of hypertonic saline in early resuscitation of hypovolemic patients has plenty positive effects including improving cardiac output, microcirculation anti inflammation and alleviating endothelial injury and swelling, but later few studies came with a conclusion that using hypertonic saline in early stages of resuscitation has no benefit over normal saline neither dextran's and promotes coagulopathy as well (21-23).

Permissive hypotension is another significant task that should be discussed in terms of resuscitation of hypovolemic patients. Actually, the findings of Cannon et al., that bleeding has been minimized when hypotension establishment came first, before accomplishment of surgical hemostasis, was the essence of implementing a restrictive resuscitation model when it comes to usage of fluids. The main goal of permissive hypotension is to maintain the minimal necessary blood pressure in order to preserve vital organs perfusion without causing any harm. A large animal meta-analysis study confirmed that conducting a hypotensive resuscitation has better survival outcome over the normotensive resuscitation (24). Some studies found that delayed resuscitation is better than early prehospital resuscitation (25). Another study has shown that using the hypotensive approach with target value of 70mmHg for SBP is better than using a target value of 100mmHg SBP in patients with blunt trauma (26). Hypovolemic patients with traumatic brain injury should be discussed as a special category where permissive hypotension may not be proper manner of resuscitation because the underlying brain injury that aims well preserved perfusion, in order to preserve the brain cell function. In patients with TBI the systolic blood pressure during the resuscitation should not be lower than 90mmHg, and early vasoconstrictor installation is recommended in order to sustain adequate cerebral perfusion pressure (27). According to the study of J. Silva et al., hypotensive resuscitation and conservative approach, with balanced crystalloids and blood, is the most appropriate approach in management of hemorrhagic shock (28). Despite all studies that suggest restrictive and conservative approach in ongoing fluid resuscitation on a hypovolemic patient, there is no clear statement about what is the lowest target value of SBP that has not any harmful consequences, neither how long hypotensive resuscitation should be performed without leading to any adverse events in the already shocked ones. When it comes to fluid resuscitation in patients with hypovolemic shock, it is worth mentioning that liberal resuscitation approach with crystalloids and artificial colloids increases hydrostatic pressure without repairing the endothelial injury leading to edema and edema associated complications.

In severely injured trauma patients with hypovolemic shock, because of major bleeding, it should be given 1 to 2g tranexamic acid during the early stage of resuscitation inside the first 3 hours of the bleeding onset according to the CRUSH II study (recommendation grade: A) and according to the study an early administration of Tranexamic acid safely reduced the risk of death in bleeding trauma patients, but treatment beyond 3 hours of injury is unlikely to be effective (29,30).

As it was previously mentioned, hypovolemic patients should be resuscitated with combination of crystalloids and blood products, but the threshold when to give blood and blood products may not be as clear as it seems. Actually, giving blood to the bleeding patient is recommended when more than 30% of the circulating blood loss will occur, or when the patient is still hypotensive despite administration of 2 liters of fluids (31). Because, when to give and how much to give, is a state-of-art practice. The National Institutes of Health, the American College of Physicians, the American Society of Anesthesiology, and the Canadian Medical Association created guidelines that recommend giving blood at a hemoglobin level between 6 and 8g/dl as a threshold for transfusion in patients without known risk factors (32-35). They strongly recommend no prophylactic blood transfusion in patients with hemoglobin levels greater than 10g/dl who are not expected to benefit from blood transfusion. A higher hemoglobin level maintenance (>10g/dl) is a desirable goal in actively bleeding patients, in elderly patients as well as in individuals who are at risk for myocardial infarction.

Achieving early bleeding control and termination, are stated as possible when plasma is given in the very early hours after the injury. There are few studies that recommend giving fresh frozen plasma early during ongoing resuscitation (36-39). According to the PROMMT and PROPPR studies lowering the plasma to RBC ratio during resuscitation of a hemorrhagic shock in the first 24 hours, as well as establishing a 1:1:1 transfusion ratio, increases survival rate in the first 24 hours. Also, these studies recommend early plasma transfusion in hypovolemic bleeding patients (40,41). It is believed that giving plasma in the severely injured patients with shock, may lower the early death because of improving the coagulopathy, mitigating thrombocytopenia and loss of coagulating factors, repairing the endothelial injury and glycocalyx debridement, as well as minimizing vascular endothelial injury and fluid translocation into the interstitial space. According to the previously cited studies thrombocytes are recommended while managing hemorrhagic shock in the early resuscitation period in the ratio 1:1:1 (40,41).

When guiding damage control resuscitation of patients with hemorrhagic shock, the usage of TEG and ROTEM in therapy adjustment is strongly recommended (42). Measuring the levels of fibrinogen in the early phase of bleeding is recommended as well. American College of Surgeons Committee on Trauma recommends transfusing cryoprecipitate to maintain fibrinogen levels ≥180mg/dL, while European guidelines describe a minimum cutoff fibrinogen value of 150–200mg/dL.

Hemodynamic instability is a mainstay of shock, especially in patients with massive bleeding. Besides fluid therapy and blood products transfusion as a resuscitation measure when no response is seen, the need for early circulatory pharmacological support is more than essential. Norepinephrine is the first-choice vasopressor in patients with hypovolemic shock, but when the resuscitation with fluids and vasopressors as a first line strategy is failing, an inotrope should be added to support the failing circulatory system. Recent recommendations for management of shock are strongly against the routine use of inotropes as a first line therapy in patients with hypovolemic shock, but when it comes to usage of inotropes as a rescue therapy, dobutamine is the drug of choice (43).

According to the ESICM Consensus, blood lactate levels should be measured frequently because the shock is a dynamic process, and lactates change over time due to therapy. Despite measurement of lactate, the process of monitoring should consist of early type of shock recognition using echocardiography, estimating cardiac function to detect and prevent cardiac

suffering in essentially non-cardiogenic shock states. Routine measurement of cardiac output for patients with shock responding to the initial therapy is not recommended, (Recommendation Level 1; QoE low), but measurements of cardiac output and stroke volume to evaluate the response to fluids or inotropes in patients that are not responding to initial therapy is recommended (Recommendation Level 1; QoE low C). Sequential evaluation of hemodynamic status during shock is recommended as well (Recommendation Level 1; QoE low C). In aim of personalizing therapy, it is not recommended using of CVP neither ventricular filling pressures as a sole method for guiding fluid administration, but rather using more than one dynamic variables for predicting and monitoring fluid responsiveness are recommended. Measuring of pulmonary artery pressure, as well as any other invasive procedures are not routinely recommended except in patients with right ventricular failure, but rather echocardiography as a non-invasive method of monitoring is recommended to be used as a monitoring tool (43).

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