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Review

Update on Current Concepts in Management of Severe Hemorrhagic Shock and Optimal Individualized Fluid Therapy in Critically Ill Polytrauma Patients

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Abstract: Worldwide, one of the main causes of death among young adults is multiple trauma. In these patients hemorrhagic shock represents the leading cause for worsening of the clinical status and for increased morbidity and mortality. This is due to a multifactorial complex involving cellular, biological, and biophysical mechanisms. The most important mechanisms affecting clinical outcome are oxidative stress, the augmentation of pro-inflammatory status, immune deficiency, disruptions in the coagulation cascade, imbalances in electrolyte and acid-base homeostasis. Polytrauma patients in hemorrhagic shock need adequate fluid management to ensure hemodynamic stability that must consider not only the maintenance of adequate blood pressure, but also the adequate oxygenation of tissues for optimal cellular function. In the current clinical practice, fluid resuscitation in polytrauma patients uses a variety of widely studied pharmacological products, such as crystalloids, colloids, blood transfusions, and the infusion of other blood products. Although these products exist, an agreement was not reached on a standard administration protocol that could be generally applied for all patients. Moreover, numerous studies have reported a series of adverse events related to fluid resuscitation and to the inadequate use of these products. This review aims at describing the impact the administration of all the solutions used in fluid resuscitation might have on the cellular and pathophysiological mechanisms in the case of polytrauma patients suffering from hemorrhagic shock.

Keywords: hemorrhagic shock; multimodal monitoring; individualized therapy; fluid therapy; critical care; trauma

1. Introduction

Multiple trauma is one of the main causes for disability in patients under 40 years of age. A recent study has reported that in the United States of America, over 150.000 of

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persons die because of multiple trauma with a significant social impact. The main causes of death in the case of polytrauma patients are represented by the organic injuries including cerebral trauma, spinal trauma, injuries to other vital organs, as well as indirect causes that refer to secondary injuries related to the multiple trauma constellation. Among these secondary injuries, the most important seems to be circulatory failure due to hemorrhagic shock, as it has multifactorial implications at cellular and tissue level, and it is responsible for augmenting the inflammatory response, for generating the systemic inflammatory response syndrome (SIRS) , oxidative stress (OS), severe coagulopathy, ventilatory dysfunction, multiple organ dysfunction syndrome (MODS), and finally leading to death [1–7].

During a recent consensus meeting that has analyzed over 28000 patients from trauma registries, the mean age was 42,9 years, 72% of patients were male, mean injury severity score (ISS) was 30,5, mean mortality rate 18,7%, the participants have drawn conclusions towards the definition of the polytrauma patient that has to include not only an ISS score > 16 and AIS > 2 for at least one of the following variables: hypotension (systolic blood pressure <90 mmHg), level of consciousness (Glasgow Coma Scale <8), acidosis (base excess >=6), coagulopathy (International normalized ratio 1.4/ partial thromboplastin time >40 s) and age (>70 years) [8,9]. Hemorrhagic shock in patients with severe multiple trauma and the fluid resuscitation management applied, as well as the ICU length of stay are directly correlated with the mortality rate due to their multifactorial impact. The main challenges in fluid resuscitation remain the ability to appreciate the volume of blood lost, the ability to correctly choose one or more solutions for infusion, but also the volume to infuse and the appropriate infusion timeline [10]. Therefore, a series of guidelines and protocols have been developed that include the optimization of fluid management in polytrauma patients with hemorrhagic shock. These include permissive hypotension, hemostatic resuscitation, making adequate use of blood transfusion and of other blood products, as well as individualizing fluid management for each patient [11].

2. Pathophysiology pathways in hemorrhagic shock

The severity of the injuries and its impact on the survival rate are both associated with acute blood loss, that leads to hypoperfusion and tissue injury, responsible for the activation of the immune response and of the coagulation cascade. This in turn will lead to an accelerated biosynthesis of the pro-inflammatory and pro-oxidative molecules, and to an imbalance in the aerobic biochemical pathways with severe increase in lactate levels. This multifactorial phenomenon was initially described by Denver and was named the lethal triad – hemorrhage, acidosis, and coagulopathy [12–15].

The main mechanisms underlying the physiology of hemorrhagic shock is a decrease in the delivery of oxygen needed by the cells to sustain molecular mechanisms involved in vital functions, leading to anaerobic mechanisms and dangerous increases in lactate levels. Under normal conditions, the oxygen delivery (DO_2), is 1000-1250 ml O_2/ minute in males and 925-1100 ml O_2/minute in females. Biophysically, DO_2 is characterized by the rate of blood flow that is the equivalent of cardiac output multiplied by the oxygen bound to hemoglobin in a known blood volume. An important aspect regarding tissue oxygenation is the oxy-hemoglobin dissociation (OHD) curve and the oxygen binding affinity of hemoglobin. Both mechanisms can be significantly influenced by a series of variables that are often seen in critically ill polytrauma patients, among which pH values and temperature. An increase in the concentration of H^+ ions shifts the OHD curve to the right, leading to an increased unload of oxygen to the tissues, while a decrease in temperature shifts the curve to the left, leading to a decreased oxygen delivery to the tissues. Moreover, tissues that had been affected by the multiple trauma have a different behavior regarding oxygen extraction. Under normal conditions, the systemic oxygen consumption (VO_2) is 250 mL O_2 / minute. The oxygen extraction ratio (O_2ER) represents ratio of the body's oxygen consumption (VO2) compared to the systemic oxygen delivery ($O_2ER = VO_2/DO_2$). Physiologically, oxygen consumption is different for each organ, which can increase the imbalance

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between delivery and consumption especially in critically ill polytrauma patients. For example, renal O_2ER is 15%, liver O_2ER is 45%, while for the heart it is 60%.

During hemodynamic instability due to massive blood loss with implicit oxygen delivery and consumption imbalance, there is a compensatory mechanisms mediated by O_2ER. Up to a loss of 30% blood volume VO_2 stays constant and is independent from the flow because a drop in DO_2 leads to an increase in O_2ER. In case DO_2 continues to drop, O_2ER can be increased compensatory up to 60-70%. After this threshold the O_2ER reaches a plateau. If blood loss continues the compensatory mechanism will be overcome and VO_2 will be dependent on flow [16–19]. Depending on the amount of blood lost, there are four stages of hemorrhagic shock and fluid resuscitation is based on these 4 stages.

Shortly after the traumatic injury, a series of molecular mechanisms are activated, either self-induced or through external, non-self involvement. Both are capable of augmenting the biochemical pathways responsible for inflammation and injury at tissue level and cellular level [8]. An important link in the systemic inflammation mechanism is neutrophile activation and their invasion in the tissues [20–24].

The activation of the complement system is another pathological mechanism activated after a traumatic injury. This will lead to the production of highly reactive molecules that are involved in the transmission and alteration of intercellular signaling. Among these molecules recent studies have highlighted the importance of the under expression of C1qrs and C3b opsonin responsible to the excessive bioproduction of C3a and C5a. Complement activation leads to an augmentation in the pro-inflammatory status through the production of excessive amounts of cytokines. These cytokines will further be involved in mitochondrial dysfunction, impairing the mitochondrial respiratory chain, as well as the cellular respiration, increasing systemic inflammation and generalized capillary leakage. All the aforementioned dysfunctions are in the first phase restricted to a cellular level, but as the trauma advances they affect all body tissues, leading in the end to multiorgan dysfunction, worse clinical outcomes, and increased death rates [25,26]. Bogner-Flatz et al., have analyzed the role played by neutrophiles in post-traumatic pro-inflammatory activity at 6, 12, 24, 48 and 72 hours after trauma. To identify correlations between the neutrophile expression and pro-inflammatory activity, they have quantified the expression of IL-1β, and of the c-JUN, BCL2a, c-FOS, TIMP-1, MMP-9, ETS-2 and MIP-1β genes. The samples from 40 patients with a mean ISS of 36±14 have been included in the study; the study revealed a significant correlation between the expression of BCL2a, MMP-9, TIMP-1 and ETS-2 and 90 days survival rates. Another important issue highlighted by this study are the significant correlation observed between the expression of IL-1β, MIP1β, MMP-9 and BCL2a and the need for blood transfusion [27].

The redox balance is also affected in patients with hemorrhagic shock, leading to an overexpression of oxidative stress [28]. The superoxide ion (O_2^-) will be produced in this situation especially by the activation through the complement factors of the arachidonic acid pathways and of other pro-inflammatory cytokines in the nicotinamide adenine dinucleotide phosphate (NADPH-oxidase) membrane. The body's enzymatic antioxidant activity will intervene in order to block the oxidative reactions induced by the reactive oxygen species, reducing it to hydrogen peroxide after catalyzing the superoxide dismutase in the cytosol (SOD1), the superoxide dismutase in the membrane (SOD3), and the mitochondrial superoxide dismutase (SOD2). Once the enzymatic resources of the body have been exhausted, the reactive oxygen species tend to accumulate and to interact with the myeloperoxidase to form new reactive oxygen species, such as the hydroxyl radical (OH^-). They will also attach lipids and proteins leading to a destruction of endothelial and parenchymal cells. These reactions will interfere with the NO biochemical pathways, activate specific enzymes, and generate increased nitrogen free radical species. All these cellular events will increase the general pro-inflammatory status and will negatively impact the clinical outcome of the patients due to microvascular injury, increased capillary leakage, as well as impacting the hemodynamic stability [29].

Numerous studies have shown that pro-oxidative activity is directly related to an augmentation in the inflammatory status. The imbalance in the mechanisms and

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biochemical pathways leads to the production of a series of mediators that are further responsible for the biosynthesis of pro-inflammatory cytokines and chemokines. Two hours after the traumatic injury the first species that show an aggressive increase in expression are IL-1β and TNF-α. Their biosynthesis will afterwards lead to the production of impressive amounts od IL-6 and IL-8 that will be responsible for the activation of neutrophiles and for a disruption in the function of macrophages. Moreover, shortly after they had been synthetized, IL-12 and IL-8 will be involved in modulating interferon-γ and high motility group protein-1 (HMG-1). Different studies have shown an increase in serum TNF-α, IL-1β and IL-8 in patients with systemic inflammation, thoracic trauma, or acute respiratory distress syndrome. Claude et al., have carried out a study on the activity of TNF-α and IL-6 in two categories of patients suffering form a systemic inflammatory response – polytrauma patients with hemorrhagic shock and patients suffering from septic shock. Their prospective study included 24 patients with septic shock and 60 patients with trauma. From the trauma group 8 patients also presented with hemorrhagic shock, while 8 did not. The septic patients showed increased expressions only for IL-6. Interestingly enough, in the case of patients suffering from septic shock, increased values of TNF-α and IL-6 corelated with higher mortality rates. Furthermore, the authors have identified a strong and statistically significant correlation between the expression of IL-6 and the incidence of hospital-acquired infections. IL-6 concentration before the diagnosis of pneumonia was made was 433 ± 385 pg/ml, with a maximum peak of 3970 ± 1478 pg/ml on day 7 and a reduction to 219 ± 58 pg/ml on day 11. Following this study the authors concluded that IL-6 can be useful as an indicator for the development of infections in trauma patients, and that it directly correlates with clinical outcome.

3. Updates – in fluid resuscitation formulas

In the daily practice more than one type of fluid is used for the volemic resuscitation, among which crystalloids, colloids, and blood products. From a chemical point of view, crystalloids are aqueous solutions to which inorganic ions are addes, as well as organic molecules with low molecular weights. During the last decades new formulas for crystalloid solutions have been developed, with different concentrations of potassium, magnesium, calcium, and other inorganic ions such as lactate and acetate. The composition of these solutions is extremely important, as it has a direct impact on cell and tissue function, as well as an indirect impact on the functionality of certain organs, as well as of certain physiological pathways such as the coagulation cascade [30].

After administering normal saline, it is redistributed in a short period of time between the compartments of the extracellular space, and it stays in the body for a long time. Greenfield et al., have evaluated the effects intravenous normal saline administration has on hematocrit levels in 28 healthy volunteers. The participants in the study received 10, 20 si 30 ml/kg NaCl 0,9% as bolus, at a rate of 115 ± 4 ml/min, followed by a continuous infusion at 1-5 ml/kg/h. immediately after the bolus administration they determined the blood hematocrit and compared it to the stating value, with the measurements showing statistically significant differences. The administration of 10 ml/kg bolus of normal saline led to a decrease in hematocrit with 4,5 ± 0,6 ($p<0,001$), 20 ml/kg bolus led to a decrease with 6,1 ± 0,4 ($p<0,01$), while in the group that received 30 ml/kg bolus of normal saline the hematocrit dropped with 6,3 ± 0,6 ($p<0,01$). Twenty minutes after the infusion was started hematocrit was measured again and compared to the value after the bolus dose, showing an increase in all three patient groups with 1,5 ± 0,8 ($p=0,03$), 2,4 ± 0,4 ($p=0,004$), and 2,3 ± 0,7 ($p=0,005$) respectively. This study demonstrated that normal saline solution will diffuse in less than 20 minutes in the extravascular space when administered as intravenous bolus [31]. A similar study was carried out by Mullins et al., in 126 patents that were administered 2 L of normal saline over 2 hours, one day before surgery. They compared hemoglobin before and after the infusion and have calculated the change in blood volume. The differences before and after the infusion were 1,06 ± 0,06 which shows a 18-24% retention of the infused solution [32]. Other studies have shown that up to 60% from

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the volume of the administered fluid will stay in the body even longer than 6 hours, and approximately 13% will stay in the intravascular space [33].

For a long time, fluid resuscitation was based on high amounts of normal saline (NaCl 0,9%), but numerous studies concluded that it leads to hyperchloremic metabolic acidosis. Waters et al., carried out a prospective study on the impact of normal saline administration on the acid-base balance in non-cardiac/non-vascular surgery, which included 12 patients undergoing surgical procedures with a duration longer than 4 hours. They have analyzed arterial blood gas parameters and serum and urinary electrolyte values, preoperatively and postoperatively. The statistical analysis has shown a significant increase in lactate from 1,1± 0,6 in the preoperative period to la 1,8 ± 1 postoperatively, and a change in base excess from 0,8 ± 2,3 to -2,7 ± 2,9. Serum chloride concentrations also increased significantly form 106 ±3 to 110 ± 5 ($p<0,001$, $r^2=0,92$) [34]. These findings can be explained by the fact that the intravenous administration of normal saline increases the extracellular volume which in turn will dilute the buffer systems, especially the bicarbonate buffer system, this phenomenon being called dilution acidosis. Gattinoni et al., have simulated this dilution phenomenon by infusion hydrogen peroxide, normal saline, and Lactated Ringer's solution. After this study they concluded that the pH of the system is only modified when CO_2 is infused in the solution, which in turn will change the pK constant following the dissociation of CO_2 and bicarbonate [35].

Cervera et al., in an experimental animal study divided the subjects in two groups - one receiving intravenous normal saline, and the other intravenous lactated Ringer's. They have identified statistically significant differences between the groups, with a drop in pH from 7,4 ± 0,7 to 7,36 ± 0,6 in the normal saline group, in comparison to the lactated Ringer's group where no significant change in pH was noticed, from 7,4 ± 0,7 to 7,4 ± 0,9 [36].

Scheingraber et al., carried out a randomized study on 12 patients that were allocated to two study groups – one receiving normal saline and the other Ringer's lactate with equivalent doses of 30 ml/kg/h. They have measured pH, serum sodium, potassium, chloride, and lactate, as well as the partial pressure of carbon dioxide. In the case of patients receiving normal saline a hyperchloremic metabolic acidosis could be seen (104 mmol/L vs 115 mmol/L, pH 7,4 vs pH 7,2), as well as a decrease in base excess [37].

Recent studies have shown that the acidosis induced by the administration of crystalloids can be avoided by using solutions that contain anions that the body is able to metabolize, such as lactate, acetate, citrate, and malate. These are termed balanced crystalloids and a few examples of widely used balanced solutions are Sterofundine, Plasma-Lyte, Hartmann Solution, Lactated Ringer's, and Acetated Ringer's. One side effect of administering these solutions is the slight decrease in plasma osmolarity, as Lactated Ringer's osmolarity is 273 mOsmol/L while measured osmolarity is 254 mOsmol/kg. Intravenous administration of hypotonic solutions can lead to an increase in cerebral edema or an increased diuresis.

In polytrauma patients one of the main organs affected by the metabolic imbalances is the kidney. The kidney can suffer from a direct traumatic injury or can be injured indirectly through massive blood loss leading to hypoperfusion, through delayed resuscitation or rhabdomyolysis. Up to 40% of trauma patients can develop acute kidney injury in the first phase of treatment, but in this case, it is a reversible dysfunction if correct and optimal hemodynamic management and fluid resuscitation occur [38,39]. However, kidney injury can also be precipitated by the type and volume of solutions used for fluid resuscitation.

Feinman et al., in a study on fluid resuscitation in trauma, concluded that the administration of a high volume of fluids can be associated with the development of hypoxia, acidosis, coagulopathy, dilution induced hyperfibrinolysis, and multiple organ failure. Recent guidelines recommend adopting a restrictive fluid management in the first phase of treatment and avoiding using lactated Ringer's solution in traumatic brain injury, especially because of the correlations reported between increased incidence of cerebral edema and the infusion of large volumes of lactated Ringer's [40]. Young et al., in their

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study on the initial resuscitation in trauma have highlighted the increased capacity of acetate Ringer's to maintain a better acid-base balance compared to normal saline. Regarding the use of artificial colloids, European guidelines suggest a restrictive use especially due to their adverse effects on homeostatic mechanisms. On the other hand, Weiskopf and the Trauma Hemostasis and Oxygenation Research Network (THOR) have reported that using hydroxy-etyl-starches (HES) products can lead to an adequate fluid resuscitation in trauma patients, reducing the need for crystalloids and blood products, and without a negative impact on the kidney [41]. A similar study was carried out by Qureshi et al., showing that colloid administration does not increase mortality rates compared to crystalloid administration in trauma patients [42].

Another serious complication associated with normal saline administration is due to the over-physiological chloride concentration that leads to renal vasoconstriction and a decrease in glomerular filtration rate. Wilcox et al., carried out an experimental study on the impact of crystalloids on the glomerular filtration rate. They have infused intrarenal hypertonic saline, Na acetate, dextrose, $NaHCO_3$, NH_4Cl, and NH_4 acetate. Following the administration renal blood flow increased abruptly with 10-30% for all types of hypertonic solutions, which demonstrates that a rapid increase in plasma tonicity leads to renal vasodilation. After the renal infusion of $NaHCO_3$, , NH_4 acetate and Dextrose the glomerular filtration rate stayed the same, while in the case of hypertonic saline and NH_4Cl renal blood flow and the glomerular filtration rate decreased after 1-5 minutes to values lower than those measured before the infusion ($p<0,01$) due to a severe vasoconstriction. Therefore, they concluded that glomerular filtration rate and blood flow are both directly affected by the increased reabsorption of chloride following the administration of crystalloids with high chloride concentrations [43].

Modifying the Ca^{2+} plasma concentration through an inadequate fluid resuscitation can have a direct negative impact on coagulation by the changes in induces in cell polarization, leading to changes in the expression of coagulation factors and in the acid-base balance. Crowell et al., studied the impact that changes in pH have on coagulation and reported that a decrease in pH will lead to disturbances in the coagulation factors activity [44].

Meng et al., have analyzed the impact of pH and temperature on coagulation factor VIIa (FVIIa) proving a 20% decrease in activity with a decrease in temperature from 37° C to 33° C and up to 90% decrease in activity was associated with a decrease in pH from 7,4 to 7 [45]. Engstrom et al., after a similar study have shown that a pH decreases from 7,4 to 6,8 will determine an 158% prolongation of the coagulation time [46].

Laszlo et al., have compared the impact of normal saline fluid resuscitation with that of lactated Ringer's fluid resuscitation in animal models. They have studied the impact on coagulation status by analyzing the values of prothrombin time (PT), fibrinogen, and partial thromboplastin time (PTT). At baseline there were no significant differences between the two groups. After 30 minutes of fluid resuscitation no significant differences were seen compared to baseline values in the normal saline group ($p=0,17$), while in the lactated Ringer's group significant differences were observed ($p=0,02$). At the end of the study, when comparing the two groups, statistically significant differences were seen in PT and PTT values ($p<0.05$), while in the normal saline group increased blood loss was observed. The conclusion of the study was that using lactated Ringer's for fluid resuscitation decreases blood loss and increases hypercoagulability [47].

Another important element in fluid resuscitation is the distribution of the infused fluids between the intracellular and extracellular compartments, a distribution that is modulated by the osmotic pressure in different biological compartments. Based on the osmolarity theory, osmotic pressure is characterized by the quantity of solute and it osmolarity coefficient. Physiologically, measured osmolarity of plasma is 288mOsmol/kg H_2O, which is equivalent with the calculated plasma osmolarity of 291 mOsmol/L [48].

Jeffrey et al., in a metanalysis compares the clinical effects different balanced crystalloid solutions. The metanalysis included 24 trials comparing lactated Ringer's, Hartmann's solutions, bicarbonate Ringer's, Normosol, Ringerfundin, Sterofundin, Kabilyte

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and Plasmalyte. One o the conclusion was the Plasmalyte determines the lowest increase in chloride concentration in plasma after infusion (mean difference 0,83 mmol/L, 95%CI 0,03 to 1,64 mmol/L) and the lowest increase in serum lactate (mean difference 0,46 mmol/L, 95% CI 0,05 to 0,87 mmol/L) compared to any other balanced crystalloid. No statistically significant differences were reported for the serum potassium levels or the pH values for the solutions included in the study [49].

Ramanathan et al., studied the impact preloading with crystalloid solutions before cesarean section has on the lactate and pyruvate concentrations and on the base excess levels. The study was carried out on 4 groups of patients that received normal saline 0,9%, lactated Ringer's, lactated Ringer's with 20 g glucose and Plasmalyte. A significant increase in lactate concentration could be seen in all four groups, while pyruvate concentration only increased significantly in the group receiving lactated Ringer's and lactated Ringer's with 20 g glucose. No significant differences have been shown for base excess and the conclusion of the study was that there was no significant differences between the four solutions in this scenario [50].

Pfortmueller et al., have studied the impact of fluid resuscitation with lactated Ringer's vs acetated Ringer's on the clinical prognosis of patients undergoing major cardiac surgery. Two groups of patients were included in the study, 73 receiving lactated Ringer's, while 75 acetated Ringer's. No statistically significant differences were found following the study regarding acid-base balance or hemodynamic status. Both balances solutions bring about the same benefits [51]. Bradley et al., compared in their study the impact the administration of colloid vs the administration of crystalloid has on blood volume, kidney function, and cardiac output. The study included healthy volunteer men that received 1,5 L Sterofundin Iso, 0,5 L 4% Gelaspan, 0,5 L 4% Gelaspan + 1 L Sterofundin Iso. The changes in blood volume were calculated by analyzing weight and hematocrit. Cardiac index, renal cortex perfusion, renal cortex diffusion, renal volume and renal artery blood flown have been then analyzed by magnetic resonance imaging. Following the analysis the authors have found an increase in weight and extracellular volume in patients receiving 1,5 L Sterofundin Iso and 0,5 L 4% Gelaspan + 1L Sterofundin Iso compared to the volunteers receiving 0,5 L 4% Gelaspan, but no differences in blood volume could be proven. Renal volume was increased in all groups, but without statistically significant differences. Furthermore, no significant differences were found regarding cardiac index, renal cortex perfusion, or renal cortex diffusion [52].

Rajan et al., have studied the impact of intraoperative administration of lactated Ringer's on the serum lactate concentrations in patients with no hepatic dysfunction undergoing long surgeries. There were two study groups that received either lactated Ringer's or Sterofundin. They concluded that patients receiving lactated Ringer's had significantly higher serum lactate levels at 2, 4, 6, and 8 hours. The pH was comparable between the two groups, except from the 8-hour analysis when the pH was statistically lower in patients receiving lactated Ringer's (7,42 ± 0,1 vs 7,4 ± 0,1). No significant differences were shown on the bicarbonate, chloride, sodium, potassium, and pCO2 values. The authors concluded that in the case of longer surgical interventions it is recommended to administered balanced solutions with acetate rather than lactate [53]. Hassan et al., studied the changes in acid-base balance and plasma electrolyte concentration after the administration of normal saline 0.9% compared to Sterofundin Iso in patients with severe traumatic brain injury. The study included 66 patients that were randomized in two groups receiving one of the solutions. After 24 hours in the normal saline group the authors identified a significant decrease in base excess (-3,2 vs -1,35, p=0,0049), a decrease in plasma bicarbonate (22,03 vs 23,48 mmol/L, p=0,031), and an increase in serum chloride (115,12 vs 111,74 mmol/L, p< 0,001). In the Sterofundin Iso group they have noted an increase in serum calcium levels (1,97 vs 1,79 mmol/L, p=0,03) and an increase in serum magnesium levels (0,94 vs 0,80 mmol/L, p<0,001) compared to the other study group [54].

Lu et al., studied the impact these solutions have on the immune system on animal models. They analyzed changes in the expression of T-lymphocytes following the administration of normal saline vs hypertonic saline in 18 Sprague-Dawley hemorrhagic shock

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rats. After fluid resuscitation CD4+ lymphocytes in peripheral blood had an increased expression in both study groups, but the immunological disorders were less severe in the group receiving hypertonic saline [55].

Wu et al., evaluated the use of the Na^+/H^+ exchanger inhibitor (NHE-1) on cardiac protection during fluid resuscitation in hemorrhagic shock. This prospective experimental study included three groups: one control group, one group that received 15 ml/kg HES and one that received 3mg/kg benzamide, N-(aminoiminomethyl)-4-[4-(2-furanylcarbonyl)-1-piperazinyl]-3-(methylsulphonyl), methanesulfonate (BIIB513) (NHE1-inhibitor) + 15 ml/kg HES. In both study groups the infusion time was 40 minutes. In the group receiving NHE-1-inhibitor the authors reported a decrease in TNF-α, C-reactive protein, intracellular adhesion mollecule-1 and a decrease in neutrophile infiltrate in the liver tissue. Moreover, using NHE-1 decreases the concentration of alanine aminotransferase in plasma 24 hours after the resuscitation [56].

More recently it was observed that one of the main adverse reactions that should be minimized during fluid resuscitation is metabolic acidosis due to its negative impact on multiple organ systems. Yu et al., carried out a prospective study including 96 patients with hemorrhagic shock that were divided in two study groups – one control group receiving normal saline 0.9% and one study group receiving bicarbonate Ringer's solution. Shortly after the administration of bicarbonate Ringer's a decrease in heart rate, lactate, chloride and sodium concentration was observed. Regarding pH and base excess they have shown a significant differences between the two groups ($p<0,05$). The patients in the bicarbonate Ringer's group have undergone shorter mechanical ventilation time (2,3 vs 3,5, $p<0,05$) and have shorter stays in the intensive care unit (3,8 vs 4,1, $p<0,05$) with a lower incidence of acute respiratory distress syndrome (8,3% vs 22,9%, $p<0,05$). No statistically significant differences have been seen regarding 28 day survival [57].

Hafizah et el., in their prospective, randomized trial, compared the changes in acid-base balance and serum electrolyte concentrations in patients undergoing elective neurosurgical procedures depending on the type of solution that was used as maintenance fluid intraoperatively. There were 2 study groups with 15 patients each, which received either normal saline 0.9% or Sterofundin ISO. Statistically significant differences were seen in the group receiving normal saline as a maintenance fluid regarding base excess, bicarbonate levels and pH ($p<0,01$). Four of the patients in this group presented with a drop in pH under 7,35 and 5 patients with a decrease in base excess value under -4 at the end of surgery. Serum sodium concentration was significantly higher in this group at the end of surgery (142,6 ±2,4 vs 138 ± 2,7 mmol/L, $p<0,01$), as well as serum chloride levels (105,7 ± 4,1 vs 113,2 ±3 mmol/L, $p<0,01$). The authors concluded that by using Sterofundin ISO a significantly better control of the acid-base status and ion homeostasis can be attained [58].

Colloids were designed to maintain the infused volume for a longer time in the intravascular space through their increased oncotic pressure. Colloids can contain blood components such as human albumin or can be synthetic or semi-synthetic such as Dextrans, Hydroxyethylstarch (HES) and Gelatines. Their main characteristic is that of plasma volume expansion and this process depends on and is directly influenced by the oncotic pressure, molecular weight, and half-life of the product [59].

In clinical practice human albumin is used under its iso-oncotic formulation (4-5% concentration) or hyper-oncotic (concentration 20-25%). Administering human albumin for volume replacement and fluid resuscitation in critical patients have proven advantageous when compared to crystalloids or other colloidal solutions, but until now the cost-efficiency benefit has not been proven. Finfer et al., have carried out a randomized multicenter study on the impact of fluid resuscitation with human albumin compared to crystalloids. 6977 patients were included in the study that were randomized in two groups. The first group included 3497 patients that received human albumin, and the second group included 3500 patients that received normal saline. The two groups were statistically homogenous regarding their baseline characteristics. No statistically significant differences have been reported between the two study groups regarding number of days on mechanical ventilation (4,5 ± 6,1 vs 4,3 ± 5,7, $p=0,74$), length of stay in the ICU (6,5 ± 6,6 vs

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6,2 ± 6,2, p=0,44), length of hospital stay (15,3 ± 9,6 vs 15,6 ± 9,6, p=0,30), number of days on renal replacement therapy (0,5 ± 2,3 vs 0,4 ± 2, p=0,41). The two groups were similar also regarding de incidence of multiple organ failure (p=0.85) and mortality rates were similar (726 vs 729, relative risk of death 0,99, 95CI 0,91 to 1,09, p=0,87). Following this study, the authors came to the conclusion that in the case of critically ill patients using normal saline or human albumin 4% for fluid resuscitation returns similar results with no impact on 28-day mortality [60]. Ernest et al., designed a study on the distribution of fluid in the extracellular space and its impact on oxygen delivery following the administration of 5% albumin or 0.9% normal saline in patients undergoing cardiac surgery. This randomized prospective study included 40 patients. For data analysis the authors monitored cardiac index, plasma volume, extracellular fluid volume, and arterial oxygen concentration at T0, as well as after each fluid infusion. At T0 there were no statistically significant differences between the two groups. Following study analysis significant differences have been observed regarding the increase in plasma volume in the group receiving albumin 5% (52 ± 84% vs 9 ± 23%, p<0,05). No significant differences were seen for fluid volume or DO_2. The authors therefore concluded that in the case of cardiac surgery the infusion of albumin 5% does not bring any benefit over the administration of normal saline when considering DO_2 or interstitial fluid volume, but it can increase up to 5 times the plasma volume acting as a plasma expander [61]. Horstick et al., studied the impact of early administration of albumin on the hemodynamic status and mesenteric microcirculation in patients suffering from hemorrhagic shock. This was an experimental study on 17 laboratory animals that undergone controlled hemorrhagic shock by losing 2,5 ml/kg body weight of blood in 60 minutes. The animals were assigned to two groups, one group receiving 20% Albumin as a continuous infusion in 30 minutes and the other group 0.9% normal saline. They concluded that the administration of Albumin increases mesenteric microcirculation by significantly decreasing leukocyte adhesion [62]. One of the largest trials on Albumin administration in fluid resuscitation in patients with traumatic brain injury included 460 patients, divided in two groups. 231 received Albumin, while 229 received normal saline. After 24 months, 71 of the patients in the Albumin group did not survive, compared to 42 patients in the normal saline group (relative risk 1,63, 95%CI 1,17 to 2,26, p=0,003). Out of the patients with severe TBI (Glasgow Coma Scale, GCS 3-8), 61 of the Albumin group died, compared to 31 receiving normal saline (relative risk 0,74, 95% CI 0,31 to 1,79, p=0,50). This trial has shown that fluid resuscitation with Albumin is associated with higher mortality rates compared with resuscitation with normal saline [63].

HES are produced under different concentrations based on the mean molecular weight (MW), C^2-C^6 ratio and molar substitution (MS). Depending on their composition the pharmacokinetics differ as follows: HES 670/0.75 (concentration 6% balanced solution, MW 670 kDa, MS 0,75, C^2-C^6 ratio 4,5:1, maximum daily dose 20 ml/kg), HES 600/0.7 (concentration 6% saline, MW 600 kDa, MS 0,7, C^2-C^6 ratio 5:1, maximum daily dose 20 ml/kg), HES 450/0.7 (concentration 6% saline, MW 480 kDa, MS 0,7, C^2-C^6 ratio 5:1, maximum daily dose 20 ml/kg), HES 200/0.62 (concentration 6% saline, MW 200 kDa, MS 0,62, C^2-C^6 ratio 9:1, maximum daily dose 20 ml/kg), HES 200/05 (concentration 6% saline, MW 200 kDa, MS 0,5, C^2-C^6 ratio 5:1, maximum daily dose 33 ml/kg), HES 130/0.42 (concentration 6% saline, MW 130 kDa, MS 0,42, C^2-C^6 ratio 6:1, maximum daily dose 50 ml/kg), HES 130/0.4 (concentration 6% saline, MW 130 kDa, MS 0,4, C^2-C^6 ratio 9:1, maximum daily dose 50 ml/kg), HES 70/0.5 (concentration 6% balanced solution, MW 70 kDa, MS 0,5, C^2-C^6 ratio 3:1, maximum daily dose 20 ml/kg) [64,65].

From a biochemical point of view, the molecules are degraded intravascularly through slow substitution of hydroxyl radicals in position C2, C3, and C6 with hydroxyethyl radicals, that will lead to their accumulation in different tissues such as in the spleen, liver, and kidney. It was proven in numerous studies that this can contribute to histological changes such as osmotic necrosis. Most of the studies have reported a series of adverse reactions to HES administration on the kidney function. Schortgen et al., led a study on the impact of HES fluid resuscitation on kidney function in patients with severe sepsis.

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The study time was 18 months and it included 129 patients, divided in 2 groups – one group receiving HES and the other group Gelatine compounds. At the beginning of the study baseline values for serum creatinine were similar in the two groups (143 vs 114 μmol/L). For the patients in the group receiving HES the incidence of acute kidney failure was higher than in the group receiving gelatins (27/65, 42% vs 15/64, 23%, p=0,028), and incidence of oliguria was also higher (35/62, 56% vs 23/63, 37%, p=0,025). The highest creatinine value was seen in the HES group (225 vs 169 mol/L, p=0,04). After a multivariate statistical analysist the authors reported a strong correlation between the risk of renal failure and HES administration in patients with sepsis. (odds ratio 2,57, 95%CI 1,13-5,83, p=0,026) [66].

A similar study was caried out by Brunkhorst et al., showing that using HES 10% 200/0,5 compared to lactated Ringer's in patients with severe sepsis, leads to a significant increase in the need for renal replacement therapy [67]. Huter et al., led an experimental study including 24 animal kidneys with an experimental model of isolated kidney perfusion over 6 hours. The animals were divided in 3 groups that received 10% HES 200/0,5, 6% HES 130/0,42 and lactated Ringer's. Immediately after the infusions they observed a decrease in diuresis in the two groups receiving HES (p<0,01). After analyzing the macrophage infiltrate, they have observed an increased macrophagic expression in the group receiving HES 200/0,5 compared to the group receiving HES 130/0,42 (1,3± 1 vs 0,2 ± 0,04, p=0,044). Osmotic nephron lesions were seen in the two groups receiving HES compared to the group receiving lactated Ringer's (p=0,002). Through their study the authors demonstrated that the administration of 10% HES 200/0,5 solution has a more pronounced proinflammatory effect compared to 6% HES 130/0,42 and it leads to significant tubular injury compared to the lactated Ringer's [68].

Verheij et al., investigated myocardial function in patients that had undergone major cardiac or vascular surgery and received colloids or crystalloids for the treatment of hypovolemic hypotension. The study was based on two groups of patients that received either 0.9% normal saline, HES 6% or Albumin 5%. In the group receiving colloid solutions the cardiac index increased with 22% compared to the normal saline group where CI increased with only 13% (p<0,005).

Moreover, in the group receiving colloid solutions the left ventricular work index was higher than in the controls. Plasma volume in the group receiving normal saline increased with 3%, while in the groups receiving colloids it increased with 9% (p<0,001). The authors concluded that fluid resuscitation for the treatment of hypovolemic hypotension in patients undergoing cardiac or vascular surgery is preferred to be achieved using colloids as they significantly increase plasma volume and preload- recruitable cardiac and left ventricular stroke work index [69]. Annane et al., presents in an international randomized trial on the fluid resuscitation in hypovolemic shock (The CRISTAL Randomized Trial) that at 28 days there are no significant differences regarding mortality of hypovolemic patients resuscitated with colloid vs those resuscitated with crystalloid. However, the mortality rate at 90 days was lower for patients receiving colloids compared to those receiving crystalloids for fluid resuscitation. In this trial the authors have highlighted the fact that in the case of patients receiving colloid solution the mechanical ventilation free days survival was higher (at 7 days, mean 2,1 vs 1,8 days, mean difference 0,30, 95%CI 0,09 to 0,48 days, p=0,01 and la 28 days, media 14,6 vs 13,5 days, mean difference 1,10, 95%CI 0,14 to 2,06 days, p=0,01). Furthermore, they found significant difference in vasopressor requirements, with higher doses in patients receiving crystalloid solutions (at 7 days mean 5 vs 4,7 days, mean difference 0,30, 95%CI -0,03 to 0,50 days, p=0,04 and la 28 days mean 16,2 vs 15,2 days, mean difference 1,04, 95%CI -0,04 to 2,10 days, p=0,03) [70].

Tissue oxygenation can have a significant impact on clinical outcome in patients with hemorrhagic shock, being directly related with hemodynamic status, and especially with tissue perfusion pressure, blood flow, and cardiac output. Kurita et al., in an animal experimental study analyzed the impact hemorrhagic shock has on gas exchange. Hemorrhagic shock was induced through the aspiration of 600 ml of blood, followed by the infusion of 600 ml of HES. After each blood aspiration apnea was induced and desaturation

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time to SpO_2 <70% measured. The difference in desaturation time between baseline and the first blood loss was 11,2 seconds (p=0,0052), and 16 seconds after the second blood loss (p<0,0001). Oxygen consumption decreased during hypovolemia and DO_2 was recovered following the normalization of perfusion pressure [71]. However, aggressive fluid resuscitation in trauma is known to be associated with a series of complications that have a significant impact on mortality. This is the reason why a new concept appeared, meaning the maintenance of permissive hypotension that is able to reduce bleeding, maintain adequate organ perfusion, and reduce mortality [72]. Tran et al., following a metanalysis including 722 papers and 1158 patients concluded that permissive hypotension brings further benefits in patient survival compared with conventional fluid resuscitation in the case of hemorrhagic shock. Moreover, it reduces the need for blood transfusion and improves coagulation status, decreasing bleeding [73]. Another metanalysis of Owattanapanich et al., identified a decrease in mortality rates in patients in which fluid resuscitation was carried out maintaining a degree of permissive hypotension. No significant differences were identified between the study groups regarding incidence of AKI, but statistically significant differences were shown for acute respiratory distress syndrome and multiple organ dysfunction [74]. Albreiki et al., in a similar metanalysis on fluid resuscitation with permissive hypotension in trauma patients with hemorrhagic shock, concluded that the strategy has a favorable impact on both mortality and recovery [75].

4. Blood transfusion in hemorrhagic shock

In the last decade, the transfusion of blood and blood products has been widely studied and, in many countries, it is considered one of the components of national security. Blood and blood products that are currently used in clinical practice are red blood cells, platelets, and plasma. From plasma fibrinogen concentrate and cryoprecipitate can be further obtained [76]. In trauma patients with hemorrhagic shock, a series of studies and guidelines recommend using red blood cells (RBC), platelets and plasma in different combinations and concentrations. The efficiency of RBC is given not only by the volume, but also by their age and storage [77]. Chang et al., analyzed the quality of RBC depending on the time and temperature of storage of the blood. They compared blood stored frozen to fresh blood at 7, 14, 21, 28 and 42 days. Frozen blood in comparison with fresh blood after 7 days had a lower number of red blood cells (3,7 vs 5,3 x 10^6 cells/uL, p<0,01, hematocrit 33 vs 46,5%, p<0,01, hemoglobin 12 vs 16,5 gram/dL, p<0,01 and pH 6,27 vs 6,72, p<0,01). The authors concluded that frozen blood loses efficiency in time and the cells become less resistant to osmotic pressure [78]. Other complications and reactions associated with transfusions have been described in the literature, such as increased systemic inflammation, risk of infection, transfusion lung injury (TRALI), and errors concerning administration [79]. An important trial was carried out by Holcomb et al., regarding the clinical prognosis of the mixture plasma: platelets: red blood cells 1:1:1 vs 1:1:2 ratio in patients with severe trauma. 338 patients received blood and blood products 1:1:1 during fluid resuscitation, and 342 patients received the blood products 1:1:2. Mortality rates did not differ significantly between the two groups at 24 hours after resuscitation (12,7% vs 17%, difference -4,2, 95%CI -9,6% to 1,1%, p=0,12), and at 30 days after resuscitation (22,4% vs 26,1%, difference -3,7%, 95%CI -10,2% to 2,7%, p=0,26). No statistically significant differences were seen regarding secondary adverse effects associated to trauma such as multiple organ failure, sepsis, venous thromboembolism, acute respiratory distress syndrome, or other complications related to transfusion. However, the patients that received transfusion based on the 1:1:1 protocol presented with better hemodynamic stability and shorter bleeding times [80].

In a study carried out by Sohn et al. regarding statistical correlations between lactate concentrations and shock index, 33,4% out of a total 302 patients in hemorrhagic shock needed massive transfusion. Lactate concentration correlated positively with the need for massive blood transfusion (86,1 specificity and 67,8% positive predictive value). By

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combining lactate concentration (>4 mmol/L) and shock index >1, the specificity for massive transfusion requirements increases to 95,5% and positive predictive value to 82,4% [81].

Many studies have identified the advantage of plasma administration in the initial phases of fluid resuscitation in the case of hemorrhagic shock, although different metanalysis also reported a higher incidence for multiple organ failure. D'Alessandro et al., in an animal experimental study, showed the positive impact the administration of plasma has in hypovolemic shock in lactate levels, on the mitochondrial metabolism, and on protein oxidation. The author group concluded that this also has a positive impact on coagulation [82].

Makley et al., also carried out an experimental study on animal models with induced hemorrhagic shock where they compared two groups of subjects, one receiving lactated Ringer's for fluid resuscitation, and the other fresh whole blood. The IL-6, IL-10 and macrophage derived chemokines was significantly higher in the animals receiving lactated Ringer's compared with those in which resuscitation was based on fresh whole blood. The group that received crystalloid solutions suffered lung injury, with increased pulmonary capillary permeability. No significant differences have been noted between the study groups regarding mortality rates [83].

Seheult et al., studied retrospectively the clinical impact of transfusion of less than 4 low titer group O whole blood (LTOWB) units in trauma patients. They included 135 patients receiving a mean of 2 units of LTOWB and 135 patients receiving conventional blood products. The found significant differences of mortality between the groups (24,4% vs 18,5%, p=0,24), mortality at 24 hours (12,6% vs 8,9%, p=0,033%), length of ICU stay, and length of hospital stay. The time passed until normalization of lactate levels was also different between the two study groups with median 8,1 hr. vs 13,2 hr., p=0,05 in patients that received LTOWB [84]. A similar study was carried out by Zhu et al. on remote damage resuscitation. They administered LTOWB during transport in the pre-hospital phase and compared it with the administration of crystalloids. The study results showed a decrease in mortality for patients that benefited from the LTOWB resuscitation formula compared to conventional crystalloid resuscitation [85].

In trauma patients one of the main complications refers to dysfunctions in the coagulation cascade; these can also be influenced by the transfusion management [86]. Spinella et al., studied the impact of warm fresh whole blood (WFWB) transfusion on acute coagulopathy in trauma patients and compared it with the administration of stored components (CT). There were two study groups; the first included 100 patients that received WFWB, red blood cells, and plasma. The second group included 254 patients that received red blood cells, plasma but no WFWB. Baseline values such as hemoglobin, international normalized ratio, base deficit, systolic blood pressure, ISS and Glasgow Coma Scale were comparable in both groups. An increased survival rate was seen in those patients who received WFWB compared to those who received CT (96% vs 88%, p=0,018) [87].

A similar study was conducted by Sperry et al., with 501 participants with trauma associated with a risk of hemorrhagic shock, on the efficacy and clinical impact of prehospital administration of thawed plasma. Study participants were divided into two groups, 230 patients receiving plasma, and 271 patients receiving conventional resuscitation with crystalloid and colloid solutions. Mortality at 30 days was significantly lower in patients receiving plasma during the fluid resuscitation (23,2% vs 33%, difference -9,8%, 95%CI -18,6 to -1%, p=0,03). No differences have been noted for acute respiratory distress syndrome, nosocomial infections and multiorgan failure [88].

Adverse effects of hemorrhagic shock in trauma patients are related to a series of multiorgan complications that are further associated with endothelial hyperpermeability. Endothelial hyperpermeability is a consequence of apoptosis of endothelial cells. Yu et al., in an experimental study on the molecular pathways involved in endothelial dysfunction associated with hemorrhagic shock have identified an increase in the expression of CD146+ AnnexinV+ that further increases apoptosis of these cells. Animal models with induced hemorrhagic shock received fresh frozen plasma (FFP) transfusion, and have

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shown a decrease in the expression of pro-apoptotic cells, a decrease in vascular hyperpermeability, leading the authors to the conclusion that early plasma administration in fluid management of trauma patient with hemorrhagic shock might be beneficial [89].

Curry et al., has led a randomized trial on the impact of cryoprecipitate administration in the early phases of resuscitation of trauma patients with hemorrhagic shock. There were two study groups – one group received standard treatment, and the other received cryoprecipitate in the early fluid resuscitation phase. 85% of the patients the study group received cryoprecipitate in the first 90 minutes following hospital admission, and fibrinogen values were maintained in the higher range (approx. 1,8g/L) throughout the time of active bleeding. No statistically significant differences have been shown regarding 28-day mortality following this study [90].

A series of new components based on blood and blood products have recently been developed in the attempt to minimize vascular hyperpermeability, to reduce endothelial inflammation and edema following hemorrhagic shock. One of these components is the prothrombin concentrate. Shibani et al., carried out an in vitro study on the protection of endothelial cells derived from the prothrombin complex concentrate and compared it to that given by fresh frozen plasma or albumin. In the same study the authors also designed an in vivo component in hemorrhagic shock patients that also suffered from lung injury. The in vitro analysis has reported a strong inhibition of the endothelial cell permeability after the administration of FFP and prothrombin complex concentrate, as well as an increased restoration on adherence junctions in endothelial cells. The in vivo results showed significant protection again vascular permeability induced by FFP and prothrombin complex concentrate [91].

5. Conclusions

In the last decade important progress has been made regarding the understanding of mechanisms underlying hemorrhagic shock, but also of cellular and molecular mechanisms involved in adverse effects of shock, but also of fluid resuscitation. Fluid resuscitation management has changed considerably through the development of new colloid and crystalloid solutions meant to counteract and minimize associated adverse effects. The research focused on the most important pathological mechanisms associated with hemorrhagic shock, such as coagulopathy, inflammation, infection, and complications related to massive transfusion. Nevertheless, currently there is no standard formula to be applied to all patients. The key in the day-to-day practice regarding therapeutic management and fluid resuscitation of these patients is in the optimization of therapeutic models and adapting these models based on the individual clinical features of each patient. Further studies are needed in order to establish a therapeutic protocol and a combination of substances to be standardly used in fluid resuscitation, that could minimize side effects and maximize the efficacy of fluid resuscitation methods for trauma patients.

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