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Chapter

Hemorrhagic Shock

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Abstract

Hemorrhagic shock is a type of hypovolemic shock, where intravascular blood loss and consequent alterations in the cell due to the hypoxia result in tissue and organ dysfunction, leading to death, once a certain threshold level is exceeded. Inadequate oxygen delivery results with Na/K ATPase pump dysfunction and cell death by this way, but erythrocytes do not use oxygen for their survival. A depolarizing protein can be a reason under in vivo conditions. In severe injury, rapid loss of 25% and more blood volume cause irreversible shock. For blood restoration, crystalloid solutions temporarily provide a practical approach, but they cannot replace the lost erythrocyte mass occurred due to bleeding, and they have no therapeutic value. Excessive use causes several problems, especially coagulopathy and increases the mortality risk. The prompt transfer of patient to an ultimate center for treatment, use of blood and blood products in the treatment, and a swift restoration of hemorrhage source are essential. Tourniquet use in the extremities and balloon occlusion of the aorta can be lifesaving.

Keywords: hemorrhagic shock, hemorrhage, blood restoration, injury

1. Introduction

Hemorrhagic shock develops as a result of intravascular volume loss due to bleeding out of the body or into the anatomical spaces inside, causing insufficient oxygen delivery to the cells. Hemorrhagic shock is a type of hypovolemic shock. If the bleeding does not stop, inadequate oxygen supply may lead to death. Hemorrhagic shock in trauma patients is a predictor of worse outcomes and contributes to early mortality [1]. Intracellular synthesis of anaerobic metabolites impairs hemostasis, resulting in cell death, apoptosis, or necroptosis. Shock may develop due to several reasons including trauma, maternal hemorrhage, gastrointestinal hemorrhage, perioperative hemorrhage, or ruptured aneurysms [2]. Mortality due to bleeding is substantial on a global scale. Annually, 60,000 people in the US and 1.9 million people in the world lose their lives due to hemorrhage and its consequences. Out of them, 1.5 million people die of physical trauma around the world each year [3]. Unexpectedly, trauma affects young people; 1.5 million deaths per year cause an approximate loss of 75 million life year. In addition, functional outcomes are poor, and the long-term mortality rates are high in the hemorrhage survivors [4, 5].

Hemorrhage and hemorrhagic shock treatment is quite difficult and complex procedure as mentioned above. Although our knowledge related to hemorrhagic shock physiopathology has increased, our success in the treatment is limited by failure in injuries and still has high mortality rates. Control of bleeding should be the first priority, but resuscitation should be conducted through crystalloid fluids in the way that it will not form coagulopathy in order to protect hypoxia at the cellular level

and so tissues and organs in case where the control cannot be assumed. Crystalloid solutions do not have superiority over each other, and there is not any type of treatment which is absolutely recommended apart from that they are kept limited.

1.1 Brief history

As proposed by the historians, the first written definition of shock is made by Celsus (AD 20) after a penetrating heart injury as "The pulse fades away, the color is extremely pallid, cold and malodorous sweats break out the body as if the body has been wetted by dew, the extremities become cold and death quickly follows" [6]. LeDran, a military surgeon, derived a word from shock as "The bullet thrown from the gunpowder acquires such rapid force that the whole animal participates in the jarring (shock and agitation)" in his article in 1743 [7].

The emergence of biochemistry at the beginning of the twentieth century started serious scientific studies on the pathogenesis of circulatory shock. A number of physiologists agreed on the existence of a toxin released in response to injury, and it was identified to be histamine by Walter Cannon in the US and by Sir Henry Dale in England [8, 9]. However, neither histamine nor other identified vasoactive amines could successively mimic the picture of shock. In the late 1920s and 1930s, Blalock suggested an alternative hypothesis for shock and defined it as direct fluid loss from blood circulation culminating in peripheral vascular failure, a persistence of poor peripheral perfusion. After the proposal of this hypothesis, fluid replacement has become the principal therapy for circulatory shock.

Compilation of Artz and Fitts on that blood and fluids with salt are needed for closing the volume gap occurring after hemorrhage was not commonly appreciated [10]. This concept was supported by highlighting that saline solution should be given in ongoing hemorrhage later [11]. Kinney and Wells criticized the current immediate therapeutic attention to the many problems associated with trauma without regard to the patient's ventilation. Their article established a new objective: therapy in all injured patients should look beyond blood pressure so as to ensure provision and maintenance of effective gas exchange of tissues [12]. While Lansing et al. defended the need for vasoactive medicines for perfusion of vital organs, Nickerson and Gourzis defended the disadvantages of vasoconstriction [13, 14].

The term "golden hour" is widely attributed to R. Adams Cowley, founder of Baltimore's renowned Shock Trauma Institute, who in a 1975 article stated, "the first hour after injury will largely determine a critically injured person's chances for survival"—this was in an era characterized by a lack of an organized trauma system and inadequate prehospital care. The validity of this concept remains controversial. An analogous concept, the "platinum 10 minutes" places a time constraint on the prehospital care of seriously injured patients: no patient should have more than 10 min of scene-time stabilization by the prehospital team prior to transport to definitive care at a trauma center [15].

2. Physiopathology and metabolic alterations

Early theories suggesting that hemorrhagic shock resulted from nervous system dysfunction or from a toxin released from ischemic tissue have been disproved completely. The current view for the underlying mechanism of hemorrhagic shock states that the blood loss leads to an insufficient oxygen delivery to the tissues and consequently activates several homeostatic mechanisms in order to maintain vital organ perfusion [2]. The metabolic changes observed in hemorrhagic shock sustain energy homeostasis to ensure cell vitality [16]. When looking at the cellular and

tissue level and if whole organism is taken into consideration, it is observed that the complexity of these events is clarified via the physical trauma-related tissue damage and by the relative effects of hypoperfusion due to hemorrhage. Sufficient oxygen to meet the metabolic requirements of the tissues cannot be supplied due to hemorrhagic shock. Cells switch from aerobic to anaerobic respiration due to hypoperfusion. Lactic acid, inorganic phosphates, and oxygen radicals begin to accumulate as a result of the mounting oxygen debt [17]. In 1877, Claude Bernard discovered that hemorrhage stimulated liver to provide glucose from the lasting glycogen stores [18]. The Second World War enforced the investigators to better understand the pathophysiology of shock. Cuthbertson described the metabolic alterations in two phases: "ebb" phase and "flow" phase. The former representing the reduction in the requirement for both oxygen and temperature followed by the latter is characterized by increase in energy and temperature requirement with consequent elevation of body temperature [19]. With fatal injuries or blood loss, a stage called "necrobiosis" occurs prior to death as defined by Stoner, where the oxygen consumption is reduced and the body temperature decreases [20–22]. Hypoxia due to shock leads to reduction in energy consumption and leads to a hypermetabolic state, where neurohumoral homeostasis increases glucose uptake to supply muscles. If shock persists, glycogen stores are depleted, and glucose is supplied by gluconeogenesis stimulated by hormones. If this process fails, the hyperglycemia turns into hypoglycemia. Pearce and Drucker suggest that glucose infusion during hemorrhagic shock is the cause for extension of life span, since homeostasis uses glucose as an energy substrate for its defense mechanisms [23]. Gann and Foster provided an alternative explanation by defining nonmetabolic role of glucose that is a critical factor. The glucose level is elevated rapidly as a result of hormonal response to injury and this causes the intracellular fluids to move to facilitate restoration of blood volume [24].

The release of damage-associated molecular patterns (DAMPs or alarmins) containing mitochondrial DNA and formyl peptides triggers systemic inflammatory response (SIRS) [25]. Eventually, the cellular homeostasis collapses by depletion of ATP resources, and membrane rupture results in necrosis, apoptosis or necroptosis and cell death [2]. At the tissue level, hypovolemia and vasoconstriction cause hypoperfusion and end organ damage in kidneys, intestines, and skeletal muscles, leading to a multiorgan failure. In the body, pulselessness occurs after a blood loss due to a severe hemorrhage and causes hypoperfusion to the brain and the myocardium, resulting in consequent cerebral anoxia and fatal arrhythmias developing in minutes [26]. Hemorrhage also causes substantial alterations in the vascular endothelium all over the body. Blood and endothelium act together for forming thrombus in the bleeding area [27].

Hemorrhage and shock continue, and both adaptive and maladaptive changes begin to occur in the blood. The coagulation cascade and platelets are activated to form a hemostatic plug in the hemorrhage source [28]. Probably to prevent the development of microvascular thrombosis, fibrinolytic activity increases away from hemorrhage site [29]. The mounting oxygen debt and the elevated catecholamine levels cause a sort of endotheliopathy due to the systemic degradation of the endothelial glycocalyx barrier. Autoheparinization due to increased plasmin activation and glycocalyx degradation result in hyperfibrinolysis and diffuse coagulopathy [27, 29, 30]. A hypercoagulable phenotype is present in almost half of the trauma patients [30]. Reduced platelet activity and margination contribute to hemorrhage and decreased platelet counts, increasing the mortality [31, 32]. Excessive fluid crystalloid resuscitations reduce the coagulation factor levels and decrease oxygen transfer capacity. Cold infusions increase hemorrhagic heat loss, cause energy store depletion, and reduce enzyme functions in the coagulation cascade [33]. Acidosis caused by hypoperfusion becomes more intense due to the excessive administration

of the acidic crystalloid solutions. This eventually impairs the functioning of the coagulation factors and results in a vicious cycle, where coagulopathy, hypothermia, and acidosis occur [34].

The valid opinion is that the first response to a serious injury and shock is a robust and innate SIRS followed by a relative immunosuppression state called as compensatory anti-inflammatory response syndrome (CARS), bringing along a period of recovery. If a complication occurs, the cycle will repeat with a newly formed SIRS followed by CARS. While the innate proinflammatory and anti-inflammatory immunity genes are upregulated after the injury, the adaptive immunity genes are downregulated simultaneously. During the recovery period of patients without complications, these responses rapidly decrease to baseline. On the other hand, in patients with complications, the reduction of the excessive response to normal levels occurs more slowly [35].

2.1 Volume restoration

For restoration of impaired energy metabolism, reduced intravascular volume should be replaced immediately. Baue et al. have found out that both colloidal and erythrocyte free fluids meet the requirements for the oxidative metabolism to take place; however, the rapid dilution of hematocrit increases the cardiac output, cardiac workload, and the peripheral circulation [36]. The intravascular circulating volume is more effective in maintaining the energy metabolism compared to the circulating erythrocyte mass [37]. An acute loss in the circulating volume of less than 25% requires an urgent attention since the hematocrit level can be reduced more than 50% before a critical shortage of red blood cells becomes evident. The restoration of the plasma volume after a long duration of hemorrhage has been attributed to the osmotic activity in the capillary bed, induced by the hyperglycemia occurring as a result of hypovolemic shock; however, this has not been proven to be true because a transcapillary osmotic gradient does not develop. Monitoring the cardiac output is a reliable method to evaluate the reduction in the blood flow and to observe the effects of the oxidative metabolism and catecholamine response [38]. Consistent with the observations of Blalock, at the beginning of the shock, blood pressure is an insufficient parameter to demonstrate the status of the circulation. Similarly, no correlations have been found out among the blood glucose levels, hemodynamic changes, and the levels of plasma insulin during hypovolemia [16].

Maintaining the blood volume after the hemorrhage occurs in two phases. The first is initiated by a fall in the capillary of hydrostatic pressure, stopping until when the sum of the capillary hydrostatic pressure and the oncotic pressures equals the sum of interstitial hydrostatic and oncotic pressures. In the second phase, albumin is moved to the capillaries in response to the increase in interstitial pressure. This increase of osmotic pressure in the interstitial space is maintained by the osmotic gradient in the cell membrane caused by the presence of extracellular glucose. While glucose is produced due to the effects of counter-regulatory hormones including cortisol, glucagon, catecholamines, vasopressin, and angiotensin, insulin secretion is inhibited concomitantly. Blockage of any of these hormones will impair the restoration of blood volume. Cortisol is the most critical hormone because the absence of it, the restoration of the blood volume will fail completely [39].

In order for blood volume to be completely restored, all cardiovascular variables, including the cardiac output, are required to be reestablished [40, 41]. In hemorrhage up to a blood loss of 25% of the whole volume, reestablishment of the parameters takes approximately 48 hours. If the hemorrhage-associated blood loss exceeds 26% or more of the blood volume, the restoration of the blood volume will fail [42]. Na/K ATPase pump is essential for the sustainability of the cellular transmembrane potential;

however, the activity of this pump is inhibited in all kinds of circulatory shock. This inhibition is considered to be associated with the impairment in the oxygen delivery. The disturbances in the Na/K ATPase activity cannot only be due to the impairments in the oxygen delivery since erythrocytes do not consume oxygen. The findings of Shire show that intravascular volume loss more than 26% indicates the same threshold value as that of an experimental reduction in the transmembrane potential. This phenomenon is initially observed in the muscle cells followed by the observation in the erythrocytes as well [43, 44].

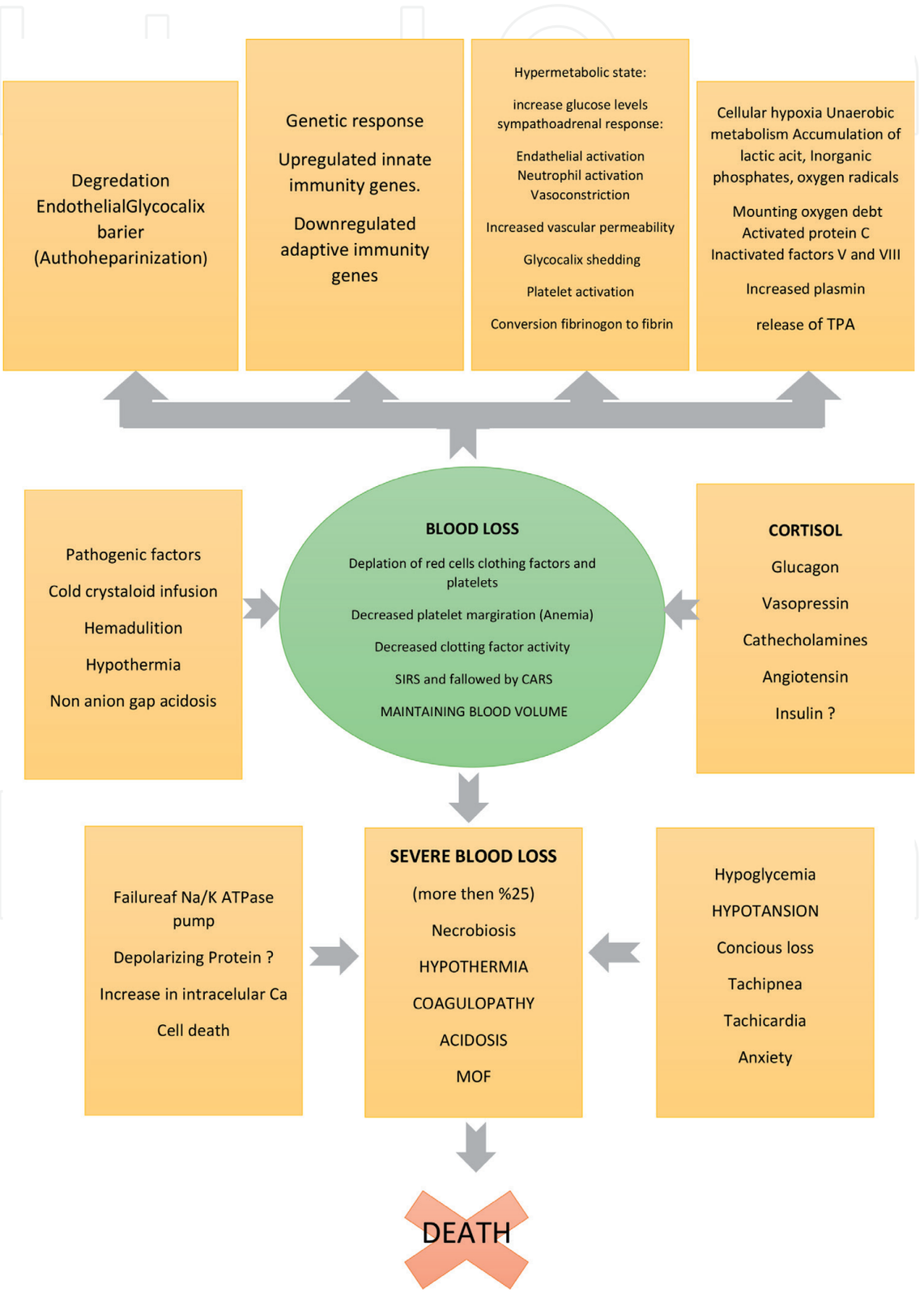

Figure 1.
Physiopathologic alterations in hemorrhage and hemorrhagic shock.

Evans et al. have reported a protein, which occurs in the first 20 minutes of serious hemorrhage in the rats, depolarizing several cells in a number of species [45]. Boulanger et al. have confirmed this finding in dogs with serious hemorrhage [46]. Jones et al. noted that this substance reduced both the contractility and velocity in the isolated and perfused rat hearts, reporting that this depolarizing protein was potentially effective in the development of cardiogenic shock [47]. This led to the conclusion that this hypothetical protein should be the similar underlying cause for three types of circulatory shock.

The experiments testing this hypothesis and looking for the significant consequences of cell depolarization isolated adenosine as the stimulating factor [48]. It was demonstrated that adenosine enhanced the ATPase activity and provided survival for hours during the experimental hemorrhagic shock in rats. Following these results, the stimulation of the Na/K ATPase pump showed the significance of inhibition in shock states. The inhibition of the pump should have a critical effect on mortality [49] (**Figure 1**).

3. Diagnosis

The early recognition of hemorrhagic shock and stopping hemorrhage is lifesaving as it takes only 2 hours from its start until death [50]. In order to limit the severity level and duration of shock and to replace mounted oxygen debt, a prompt control of the origin of hemorrhage and the restoration of the intravascular volume and oxygen transfer capacity is essential [51].

Traumatic injuries are the fourth and are the first reason for deaths under the age of 45 in the United States. About 80% of traumatic injuries are blunt and the majority of the deaths progress as secondary following the hypovolemic shock. Intraperitoneal bleeding occurs in 12% of blunt traumas, and it is essential to be promptly detected. The optimal test should be rapid, accurate, and noninvasive. Diagnostic peritoneal lavage (DPL) was historically conducted in the diagnosis of hemoperitoneum. While DPL is extremely sensitive (96–99%) and specific (98%), it is an invasive procedure with a complication rate more than 1%. However, it is quite confusing to assess hemodynamically unstable patients for whom it is late and who are brought out of the emergency service [52].

In an emergency situation, ultrasonography can provide guiding insights into a patient's condition or injury pattern and is considered to be a highest priority technological tool that deserves evaluation. The ultrasound protocols used comprised focused assessment with sonography for trauma (FAST), prehospital lung ultrasound (PLUS), and focused echocardiography in emergency life support (FEEL). By combining the standard examination according to the FAST protocol (detection of internal bleeding) with pleural and lung ultrasound (PLUS) and echocardiography (FEEL), important life-threatening conditions, such as pneumothorax and cardiac tamponade, can be ruled out [53].

In irreversible shock, sodium accumulates within the cell due to the inhibition of Na/K ATPase pump. The direction of exchange of sodium and calcium is reversed, and calcium starts accumulating within the cells. Increasing levels of intracellular calcium causes proteolytic enzyme activation leading to degradation of the organelles of cells and at end cell death [54]. This definitely irreversible condition was first observed by Holden et al. under the electron microscope [55].

3.1 Assessment of hemorrhagic shock

The recently introduced physiological or therapeutic classification of hemorrhagic shock is based on basic physiological principles. It takes the fluid-blood replacement

resistant hypotension and natural hemostatic mechanisms of the body into account as well as considering the role of the I-R and SIR triggered by ischemia [56].

In critical shock conditions, the circulating blood volume is insufficient, and brain and heart internal circulations are merely holding as a result of the systemic vasoconstriction from chemoreceptor and central nervous system receptor stimulation. Although the endogenous vasomotor/vasoconstrictor compensatory mechanisms are impaired in severe shock, blood volume sufficient to maintain the perfusion exists. In moderate shock, the compensatory mechanism is ongoing, while a mild shock state means only a little blood loss [56].

The total blood volume in relation to body weight is determined to be 70 ml/kg in adults, 80 ml/kg in infants, and between 80 and 90 ml/kg in newborns. Transfusion blood or erythrocyte suspension of 10 U or more in volume is defined as a massive blood transfusion, receiving more attention how to determine the required amount. Cancio et al. pointed out the need for identifying logistic requirements during combat to prevent mortality [57].

To measure the efficacy of fluid replacement, it was attempted to measure the diameter of the vena cava by ultrasound before and after the fluid resuscitation. A failure of an increase in the diameter suggested an inadequate treatment [58]. Ferrada et al. examined the inferior vena cava in echocardiography in order to quantify the volume status in severely injured patients. They used this technique to determine pharmacological interventions and monitor the fluid treatment [59].

3.2 Signs and symptoms

It is difficult to identify the signs and symptoms of hemorrhagic shock, especially if hemorrhage is originated from occult source. The presence of hypotension is an insensitive marker due to compensatory mechanisms until the blood volume loss reaches up to 30% of the total blood volume. Early posttrauma hypotension is associated with multiple organ failure (MOF) and development of infectious complications [60]. Nonspecific clinical symptoms including anxiety, tachypnea, and weakened peripheral pulses and mottled, pale, and cold extremities can be more indicative for diagnosis of shock. In regard to classification for severity of shock, for a 70-kg male patient in Class I shock, the blood volume loss is less than 750 ml, which accounts for 15% of the total blood volume, and the only clinical symptom may be a mild form of anxiety. Class II hemorrhage involves blood volume loss to 1500 ml, accounting for 30% of total blood volume. Patients look moderately anxious with a narrow pulse around 120 beats per minute. The respiratory rate is increased and reached over 20 breaths per minute. In Class III hemorrhage, blood volume loss is up to 2000 cc, accounting for 40% of total blood volume. The patient has tachycardia with a heart rate up to 140 beats/min, while the blood pressure is reduced. The patient is observed to be severely anxious, and the loss of consciousness may occur. Class IV patients are lethargic with severe hypotension and tachycardia. The respiration rate is over 35/min. Promising technologies, such as portable incident darkfield microscopy allowing for a simultaneous assessment of the compensatory reserve index and the microvascular bed, may help clinicians to promptly diagnose the patients in shock [2, 61, 62].

Potential bleeding source, such as hematemesis or hematochezia, significant vaginal bleeding, or bleeding from an aneurysm of the abdominal aorta should be identified. Bleeding from the extremities can easily be observed after trauma; however, the intensity of bleeding may not be severe in shock states. The body regions including the proximal thigh and retroperitoneal region can accumulate large amounts of blood, and this volume loss can easily be missed unless it is examined during the initial assessments. The intracavitary spaces in the body like the chest, abdomen, and the pelvis should immediately be examined after trauma by

radiologic imaging [2]. An immediate examination of these cavities with chest and pelvic radiograms and focused assessment with sonography for trauma (FAST) can help diagnose the potential sites of bleeding [63]. Ultrasound is also used in the diagnostic evaluation of ectopic pregnancies, abdominal aortic aneurysm ruptures, and uterine hemorrhages, which may remain hidden as bleeding foci. Echocardiography is used for assessing cardiac filling and contractility [64] (**Table 1**).

3.3 Laboratory measures

Blood gas analysis and the markers of hypoperfusion may help quantify the base deficit and the lactate levels. The ratio of heart rate to systolic arterial pressure termed as shock index and better predicts massive transfusion compared with traditional vital signs in trauma patients. In a retrospective study including 302 primary postpartum hemorrhage patients, Sohn et al. confirmed that an increased initial shock index is associated with the need for massive transfusion, and also lactate is a better predictor for blood requirements in trauma patients. Also, it is a robust predictor of requirement for massive transfusion in hemodynamically stable shock patients [65].

In a study, Lee et al. lactate has a prognostic role in patients with nonvariceal upper gastrointestinal bleeding higher lactate clearance rate (%/hr) within 24 hours after admission was associated with lower 30-day rebleeding rate. Higher initial, maximal, and average lactate levels within 24 hour after admission were associated with higher 30-day mortality rate and a more frequent admission over 7 days [66].

Hemoglobin and international normalized ratio (INR) values are used to determine the need for a massive blood transfusion in patients with severe hemorrhage [67]. Thrombocyte count and fibrinogen levels should be examined and treated to return to normal levels. Electrolyte levels, especially the levels of calcium and potassium, should be monitored at frequent intervals because fluctuations may occur during resuscitation with blood or blood products [33, 68]. Finally, any presence of coagulopathies should be diagnosed and resuscitation with blood products should be monitored by evaluating the clot-formation kinetics by means of viscoelastic testing such as thromboelastography or rotational thromboelastometry [69]. All these tests allow for determining the severity of shock, the extent to which the blood bank resources will be used, and will identify the type of coagulopathy.

3.4 Radiology

A computed tomography scan, which is commonly used for diagnostic means, should be immediately performed in critical patients for whom the origin of the

Critical HS	Shock with heart and brain involvement or > 40% TBV loss (impending CV collapse) → Stand-by surgery for source control
Severe HS	Shock with hypotension not responding to blood/fluid load-test (unstably unstable) → Rapid surgery for source control
Moderate/ Mild HS	Moderate shock is hypotensive shock responding with normotension and reverse tachycardia trend to blood/ fluid overload (unstably stable); mild shock is normotensive tachycardic from start → Investigate, Ponder surgery, Interventional radiology/ Non-operative intervention

*Hypotension may occur at ≥ 20% and is always present at ≥ 30% TBV loss; **By response is meant reverse tachycardia trend and normalization of pressure; HS: Haemorrhagic shock; TBV: Total blood volume; CV: Cardiovascular

Table 1.
Summary of hemorrhage/hemorrhagic shock and treatment modalities.

bleeding cannot be identified once the clinical picture is stable. CT remains the gold standard for diagnosing intra-abdominal injuries detecting as little as 100 cc of intraperitoneal fluid [52]. CT prompt approaches with intraoperative exploration, angiography, embolization, or gastrointestinal endoscopy may help in achieving better diagnostic and treatment outcomes [2].

Ultrasound has severe benefits on evolution and treatment of trauma patients. Bedside examination, easy way and cheap, never needs contrast and radiation source, reproducibility are advantages of it. In Europe, during the 1970s, the use of ultrasound to detect intraperitoneal fluid was first described. FAST is an ultrasound protocol for assessing hemoperitoneum and hemopericardium. Sensitivity of this protocol is 85–96% and specificity is over 98%. In the subset of hypotensive trauma patients, the sensitivity of the FAST exam approaches 100%. Experienced physicians perform the FAST exam less than 5 minutes, and its use decreases time to surgical intervention, patient length of stay, and rates of CT and DPL. Recently, many institutions have introduced the Extended FAST (eFAST) protocol into their trauma algorithms. The eFAST examines each hemithorax for the presence of hemothoraces and pneumothoraces [52].

4. Resuscitation

4.1 Prehospital care

Time is everything. Causa prima: optimization should be performed in cardiogenic shock, and treatment should be aimed at the underlying cause in hemorrhagic and septic shock. Survival of the patients with time-sensitive disorders like myocardial infarction or stroke can be made possible with prehospital arrangements, which should be performed in the patients with severe hemorrhage as well [70]. Minimizing the bleeding and limiting fluid resuscitation with large peripheral vascular access and immediate transfer to a center for ultimate treatment are limited options for prehospital care. Recent findings have demonstrated that when the patient can immediately be transported to the healthcare center for treatment, applying tourniquets to the proximal extremities to the origin of bleeding is lifesaving without leading to dysfunction or amputation of the extremities [71, 72]. Recent guidelines accept application of tourniquets in patients in whom direct compression cannot be performed during the first-aid procedures or during the prehospital interventions [73, 74]. In large injuries or injuries in joints such as groin and axilla, where tourniquets cannot be applied, a group of newly introduced homeostatic dressings have been demonstrated to be of benefit [75]. Canon demonstrated that, in a patient with a penetrating injury in the torso, delaying the intravenous fluid treatment starting from the urban treatment center until admission to the hospital for final treatment contributes to survival probably by preventing the development of dilutional coagulopathy [76].

Bickell et al. compared the outcomes of immediate and delayed fluid therapies in hypotensive patients with penetrating injuries and found out that survival rates at 62 and 70% were higher and serious complication rates from 30 to 23% were lower in delayed fluid treatment. In contrast to the predictions, the delayed fluid treatment was not disadvantageous but timesaving. The principal motivation of the treatment is to ensure a fast recovery in the patient with an acute injury favoring the transport of the patient compared to primary stabilization [77]. A number of experimental studies on animals' standard resuscitation associated with decreased oxygen delivery, increased rates of hemorrhage, reperfusion injuries, organ failures, and coagulopathies [16].

Duton et al. challenged the findings reported by Bickel et al. and suggested to limit the fluid therapy maintain systolic blood pressure around 70 mmHg using an

intermediate approach rather than 100 mmHg as it is in the conventional standard methods. The results did not demonstrate any significant benefit in mortality [78].

In regard to damage control resuscitation (DCR), Holcomb suggested an exchange of plasma with limited amounts of volume and crystalloids and proposed an early use of plasma with limited support for systolic blood pressure [79]. Plasma helps prevent coagulopathy due to acidosis and hypothermia. In the daily clinical practice, the patients treated with conventional methods were compared with the patients to whom DCR was applied, resulting in findings favoring DCR. Increasing the blood volume may prevent the development of both acidosis and hypothermia. Plasma contains coagulation factors activated by temperature and brings the hydrogen ion concentrations to normal levels [80].

There is not any proof on that fluids are superior over each other in patients with trauma in the literature. Due to the fact that colloidal fluids quickly increase oncotic pressure, they are much faster than the plasma expansion colloidal fluids. Although crystalloids are cheap, benefits of colloid applications on survival could not be proved in the studies [81]. In a review of clinical studies dating back to 2002 with safety data documented in ICU patients who received hydroxyethyl starch (HES), gelatin, dextran, or albumin, Groeneveld et al. showed that impaired coagulation, clinical bleeding, and acute kidney injury were frequently reported after HES infusion [82].

Although blood to plasma ratios have not been definitely established yet, their increase from 1:8 to 1:1.4 provided a decrease in the mortality rates from 64 to 9% in injured patients with approximately the same severity [83]. Kashuk et al. reported that blood-plasma ratios of 1:2 improved the mortality rates and that fluid replacements with lactated ringer solution resulted in increased international normalized ratios [84]. A multi-center study reported that the daily clinical use of plasma-red blood cell ratios at 1:1 or more in civilians reduced the 24-hour mortality rates by half [85].

In the treatment of hemorrhagic shock, Velasco et al. brought resuscitation with hypertonic saline solution (HTS) to the forefront. Their studies were conducted both on animals and on the patients in hemorrhagic or septic shock using either HTS alone or HTS and 6% dextrane combination [86]. Vassar et al. reported the efficacy of the latter combination in injured patients in their country [87]. The purpose of this combination lied on the fact that HTS moved the intracellular fluid to the extracellular space, while dextrane kept a significant amount of that fluid in the vascular bed. The relative efficacy of 7.5% NaCl did not cause a significant change in the survival rates regardless of its use either alone or in combination with dextrane; however, it has been demonstrated that this mode of treatment increased the costs [88]. The Resuscitation Outcomes Consortium found out that neither HTS nor hypertonic dextrane solution provided benefits compared to the fluid resuscitation with normal saline solution during the prehospitalization period in a mixed population of patients with either penetrating or blunt injuries [89]. Similarly, albumin did not provide any benefits over crystalloid solutions [90]. A recent retrospective analysis of a cohort, where trauma patients in the war were compared, demonstrated that a prehospital transfusion of an erythrocyte suspension or plasma or a combination of both, all provided significant benefits on survival. However, a number of studies being conducted currently have reported that they do not provide benefits in the daily practice [91]. Current practice shows that the radial pulse should be maintained in the patients with serious hemorrhage in the prehospital interventions, and crystalloid solutions should be used in relatively smaller quantities to keep the patients conscious [92].

4.2 Treatment

A successful resuscitation requires to stop the hemorrhage at all sources and to replace the intravascular volume immediately. These allow for preventing the mounting oxygen debt and replacing it [51]. In the trauma patients, a combination of damage-control surgery and damage-control resuscitation helps to achieve these objectives. In several hemorrhage cases except trauma, the patients similarly benefit from controlling the bleeding upon identifying the hemorrhage source and from resuscitation with blood and blood products [93–95].

The arrival of a patient with hemorrhage at the hospital first requires restoration of the intravascular volume with fluid replacement and hemorrhage control. The strategies in replacing the intravascular volume include the conventional fluid resuscitation with plasma, platelet, red blood cells, or whole blood. Massive blood transfusion can be performed with universal blood products including packed red cells, plasma, platelets, and cryoprecipitate in predetermined volumes accompanied with the administration of several pharmaceutical agents like calcium and tranexamic acid at the patient bedside. These treatment protocols provide benefits for patients with acute hemorrhage in regard to survival [95]. Multiple scoring systems guide the therapeutic teams in identifying the need for massive blood transfusion. Any delays in actualizing the treatment protocols increase the mortality rates [96].

A panel moderated by Sheldon et al. announced a warning stating that blood is the most dangerous drug we have ever used [97]. Potentially, the best alternative to replace the blood is the crystalloid solutions without colloid; its use should be followed by type-specific blood according to the specific need of a patient. The required multiple component therapy is provided by transfusing a single unit of whole blood. Increasing the hematocrit levels over 30% provides no benefits in injuries [98]. In a review evaluating the use of whole blood and blood expanders during the Vietnam war, Sheldon et al. suggested the use of type-specific fresh whole blood preferably [99]. Although the experts in the area agree that blood is the best fluid replacement therapy in hemorrhagic patients, blood transfusion is not free of risks. Therefore, the use of "blood substitutes" or administration of a blood component therapy or acellular oxygen carriers should be considered [98]. Gervin and Fischer have reported type-specific noncross-matched blood as a safer alternative option to the use of cross-matched blood [100].

Red blood cell, plasma, and platelet ratios provide clinical values; however, the ratios have not been definitely established yet. A systemic review and two prospective studies reported that plasma, platelet, and red blood cell ratios around 1:1:1 were safe and decreased the mortality rates in trauma-associated hemorrhages. The general use is to administer six units of plasma and one unit of platelets processed by apheresis for each six units of red blood cells, which constitute an equivalent to six units of pooled thrombocytes [95, 101, 102]. A platelet to red blood cell ratio of over 1:2 has been demonstrated to reduce the mortality in the first 48 hours; however, plasma use at these ratios has not provided any benefits [103]. Barry et al. a total of 17 studies were included in this meta-analysis and including total of 10,610 patients. High fresh frozen plasma (FFP) to packed red blood cell ratios result low posthemorrhage mortality; however, the need for further optimization is highlighted as evidenced by reported increase in post-damage control resuscitation (DCR) sepsis, MOF, and hospital lengths of stay among survivors [104].

All of these blood products contain citrate as an anticoagulant, which is metabolized rapidly by a healthy human liver. However, the use of high volumes of blood products may reach toxic doses in the patients in hemorrhagic shock and may lead to the development of life-threatening hypoglycemia and progressive coagulopathy

[68, 105]. Empirically, 1 gram of calcium chloride infusion can be administered following four units of blood product infusion, and the electrolyte levels should be monitored at frequent intervals.

Resuscitation with isotonic crystalloids has been in use for decades since the historical treatments for hemorrhage. However, isotonic crystalloids provide no intrinsic benefits other than increasing the intravascular volume temporarily. Complication rates are increased after high-volume infusions of isotonic crystalloids. The potential complications may include respiratory failure, compartment syndromes in the abdomen or in the extremities, and coagulopathy. In acute hemorrhagic trauma patients, it is recommended to administer crystalloid infusions in the first 6 hours of admission to the hospital, but the volume of infusion should not exceed 3 l [106]. Blood products are not included in this limit. No benefits of prehospital resuscitation with colloid, dextran, and hypertonic saline infusions have been demonstrated as discussed previously.

Pruit et al. found out that fluid resuscitation with normal saline was sufficient to replace both the blood loss and the sequestrated extravascular fluid in males with a moderate level of hemorrhage [107]. Lactated ringer's solution has found to be superior probably because it does not contain acetate or magnesium, and its chlorine content is low [108]. Recent studies stress that infusion of normal saline may lead to hyperchloremic acidosis. In addition, caution is advised against uncontrolled use of crystalloids [109, 110]. The experiences during the times of war showed that administration of blood in combination with protein-free fluids did not cause edema and did not lower the serum albumin levels in severely injured persons [111].

Procoagulant hemostatic such as activated recombinant factor VII, tranexamic acid, prothrombin complex concentrate, and fibrinogen concentrate can be included in the treatment in patients with hemorrhage [112] The use of procoagulant hemostatic is off-label in patients receiving warfarin and in patients with hemophilia except for the use of prothrombin complex concentrate in the former group of patients and the use of activated recombinant factor VII and tranexamic acid in the latter, respectively. Vasopressin, included in the treatment of patients in hemorrhagic shock, reduces the need for administering blood products and fluids [113].

Prolonged hemostasis in pelvic fractures or in patients with a ruptured aneurysm of aorta or with gastrointestinal bleeding causes an increased need for blood transfusion, elevates the risk levels for mortality, or it may cause both of them simultaneously [114–116]. The duration of emergency department stay should be less than 10 minutes to make a diagnosis and start the initial treatment for trauma patients with hemorrhage in the body in order to keep the mortality risk at a relatively lower level [116]. Patients bleeding out of their extremities, who were applied tourniquets, should be immediately operated to perform a vascular exploration. In a patient bleeding into more than one space in the body, vascular exploration should be performed in the space where most of the bleeding occurs in order to reduce mortality [117].

Regardless of the origin of bleeding, the patients with abdominal or pelvic hemorrhage may benefit from the endovascular occlusion of the aorta as a temporary measure. This approach is called as resuscitative endovascular balloon occlusion of aorta (REBOA). In severe bleeding, this approach reduces the perfusion pressure distal to the origin of bleeding, increases the afterload, and the remaining blood volume is redirected especially to the brain and heart. REBOA reduces intraoperative mortality in patients with a ruptured aneurysm of the abdominal aorta [118]. The method can also be used in gastrointestinal bleeding or in peripartum hemorrhages [119].

Aoki et al. reported that the use of vasopressor agents increases mortality in the traumatic hemorrhagic shock in the retrospective cohort study [120].

5. Conclusion

The definite treatment of hemorrhage is to stop the bleeding in its source as soon as possible. However, almost all of these hemorrhages occur at locations away from the hospitals. The time from the start of the bleeding until the time of intervention and the ultimate treatment is critical in the management of hemorrhages occurring due to an illness or due to trauma. Then, the primary approach should aim to shorten this period. Critical time is considerably exceeded when the time required for fluid resuscitation is added to the time elapsed at the scene where hemorrhage occurred. Crystalloid solutions are always at our disposal, and they are cheap and available fluids for intravenous use. Physiological saline administration in high volumes is a cause for increased mortality. No kinds of crystalloid fluids are superior to the other. What can be their alternatives? Type-specific blood and blood products have limitations in their supply, storage, and transport to the event scene. If the supply of these products and their storage can be achieved especially in the absence of cold chain facilities, they can provide solutions to the existing issues; however, the near future is not promising at all in this respect. There is continuing research on the use of 0-type whole blood and the use of freeze-dried plasma in the management of patients with trauma-associated hemorrhage [121, 122].

Systems, preventing the blood loss mechanically, such as REBOA can be developed. Generally, the first people to arrive at the scene are paramedics and young doctors. The required time and feasibility of applying these systems to a patient with weakened or no peripheral pulses in the adverse conditions of the scene during the induced sense of panic should be reviewed and estimated in detail.

We may suggest that hemorrhage and hemorrhagic shock has been an issue since the initial existence of humanity. Initiated by a toxin hypothesis, the understanding in physiopathology of shock has already been advanced; however, our achievements in terms of creating solutions to the existing problems are still limited. Technology progresses at a faster pace in terms of creating a trauma, causing injuries, and killing people compared to its advances in maintaining survival.

Conflict of interest

There is no conflict of interest

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