Review Article

Vasopressors: Do they have any role in hemorrhagic shock?

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Abstract

The priority in the management of patients with traumatic hemorrhagic shock is to control the bleeding with simultaneous volume resuscitation to maintain adequate tissue perfusion. Fluid replacement remains the mainstay of initial resuscitation in hemorrhagic shock. Traditionally, vasopressors are contraindicated in the early management of hemorrhagic shock due to their deleterious consequences, although vasopressors may have a role in resuscitation when vasoplegic shock ensues and blood pressure cannot be maintained by fluids alone. Use of vasopressors is not recommended according to the Advanced Trauma Life Support® management principles. The role of vasopressors remains controversial with no clear guidelines on the timing, type, and dose of these drugs in hemorrhagic shock. Among vasopressors, norepinephrine and vasopressin have been used in the majority of the trials, although not many studies compare the effect of these two on long-term survival in trauma patients. This article reviews the pathophysiology of hemorrhagic shock, adverse effects of fluid resuscitation, and the various experimental and clinical studies on the use of vasopressors in the early phase of resuscitation in hemorrhagic shock.

Key words: Hemorrhagic, norepinephrine, shock, vasopressin, vasopressor agents

Introduction

Trauma remains the leading cause of mortality; accounting for more than 5 million deaths every year in the world.[1] The leading cause of preventable death in these patients is uncontrolled hemorrhage, attributing to almost 50% of trauma-related deaths within 24 h of injury.[2,3] The priority in the management of these patients is to control the bleeding with simultaneous volume resuscitation to maintain adequate tissue perfusion. Initial volume resuscitation is achieved with the administration of fluids. However, fluid, when administered in excessive amount, may cause hemodilution and weaken the clot strength, thus exacerbating further bleeding. Fluid therapy also induces hypothermia, which may further contribute to coagulopathy. Traditionally, vasopressors are contraindicated in the early management of hemorrhagic shock, due to their deleterious consequences,[4,5] although in many trauma situations, their use may be required to salvage a severely injured critical patient. In few trauma centers, administration of vasopressors in the early phase of resuscitation is a common practice,[6] although their use is not recommended according to the Advanced Trauma Life Support® management principles.[7] The role of vasopressors is controversial with no clear guidelines on the timing, type, and dose of these drugs in hemorrhagic shock.

This article reviews the pathophysiology of hemorrhagic shock, adverse effects of fluid resuscitation, and the various experimental and clinical studies on the use of vasopressors in the early phase of resuscitation in hemorrhagic shock.

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Pathophysiology of Hemorrhagic Shock

Hemorrhage leads to an immediate release of catecholamines such as epinephrine and norepinephrine, causing an increase in their levels by as much as 10-40 folds and a delayed activation of the renin–angiotensin system as a compensatory response.[8] These mediators act on vessels and lead to vasoconstriction, thus attempting to maintain the blood pressure within normal range. Due to these compensatory responses, as much as 30% blood volume may be lost before signs and symptoms of shock appear in healthy young individuals. Schadt and Ludbrook re-transfused blood in pig model and found a significant elevation in mean arterial pressure (MAP) emphasizing the presence of sympathetic response (vasoconstriction) in the presence of hemorrhage, which may implicate the ineffectiveness of vasopressors at an early stage.[9] The intense vasoconstriction may even result in end-organ ischemia. Due to end-organ ischemia and impaired oxygen delivery, anaerobic metabolism ensues leading to metabolic acidosis. This severe acidosis contributes to inactivation and down-regulation of vasopressor receptors.[10] The total number of adenosine triphosphate, which is the main source of energy for maintaining cellular activity, drastically decreases from 38 to 2. If the hemorrhagic shock is not reversed, the cellular membrane loses the ability to maintain its integrity, causing progressive cellular damage, cellular edema, and eventually cell death. A stage of de-compensation follows in which vasodilation and hypotension occur, which are unresponsive to fluid resuscitation or blood transfusion. Severe vasodilation during de-compensation stage was demonstrated by Dalibon *et al.*, wherein after prolonged shock, the blood re-transfusion did not normalize the blood pressure to baseline values.[11] Fluid unresponsive shock following massive hemorrhage has been implicated to release of various vasodilatory mediators (leukotrienes, interleukins, thromboxane, prostaglandin, prostacyclins, tumor necrosis factor, and complements) resulting from ischemia-reperfusion injury.[12] This eventually leads to end-organ damage and multiple-organ dysfunction syndrome.

Fluid Resuscitation in Hemorrhagic Shock

The causes of hemorrhagic shock in trauma patients are ongoing bleeding and extracellular water depletion. Hence, logically, the treatment should be restoration of blood volume with crystalloids and blood. However, crystalloids are not devoid of complications. Fluids can cause an increase in blood pressure and disrupt the clot and hence actually increase the bleeding. Fluid resuscitation also causes hemodilution, thus diluting the coagulation factors and favoring increased bleeding due to the weakening of clot formation. Administration of fluids also causes hypothermia, which alters the platelet function and coagulation factors and attributes to further bleeding and exacerbation of shock. Hyperchloremic metabolic acidosis, tissue edema, suture loosening, anastomotic leaks, and abdominal compartment syndrome have also been increasingly reported with the use of crystalloids.[13-16]

Rationale for Vasopressor Therapy in Hemorrhagic Shock

The trigger for the initiation of vasopressor is still debatable. Most centers prefer the use of vasopressors only when blood pressure cannot be maintained (systolic blood pressure <80 mmHg) despite initial fluid expansion. Nevertheless, the initiation of vasopressor therapy in the early stages of hemorrhagic shock may have usefulness in restoring hemodynamic parameters and vital organ perfusion, thereby reducing the need for aggressive fluid therapy. Continuous fluid infusion may cause acute respiratory distress syndrome, which is one of the common causes of death on day 3 after injury in critically ill patients.[17] In a prospective observational study conducted in 102 severely injured patients, it was observed that infusion of crystalloid solution during the first 24 h was associated with increased pulmonary dysfunction.[18] Although no direct relationship between fluid loading and pulmonary dysfunction could be established, but a new thought process was evoked for the indication of the use of vasopressors during early stages of resuscitation. Moreover, restrictive fluid therapy and vasopressor therapy to optimize the MAP and the cerebral perfusion pressure (CPP) may also have beneficial effects in head-injured patients. Volume sparing effect of vasopressors may lead to decreased cerebral edema and maintenance of adequate blood pressure in polytrauma patients with head injury, in whom even a single episode of low blood pressure may prove detrimental and worsen the outcome.[19] In a multiply injured patient, hemorrhage leads to prolonged shock and eventually triggers a hyperinflammatory response, similar to sepsis patients.[20,21] In severely hypotensive patients with septic shock, early administration of norepinephrine has been shown to cause venoconstriction and increased cardiac contractility, thus increasing the cardiac preload and hence cardiac output. A similar effect may be observed in hemorrhagic shock patients, who may be vasoplegic and have myocardial dysfunction, upon admission in the emergency room.[20] Another beneficial effect which occurs with vasopressor therapy is splanchnic vasoconstriction in abdominal trauma. This may reduce the portal output resulting in decreased bleeding from splanchnic blood vessels while maintaining organ perfusion. Administration of anesthesia at any stage of shock may produce an exaggerated fall in

blood pressure much more than when compared to an awake individual who has lost the same amount of blood. Trauma patients with hemorrhagic shock are likely to receive anesthesia and/or analgesia/sedation either for surgery or emergency procedures. Hence, it seems rational to initiate vasopressor therapy with ongoing volume replacement, maintaining a target blood pressure between 80 and 90 mmHg to achieve an adequate tissue perfusion. This would limit the sodium–water load caused by fluid resuscitation and may be associated with beneficial consequences during the secondary systemic inflammatory phase.

Various vasopressors have been used in experimental and clinical studies in trauma resuscitation. A search for all studies was conducted in the electronic database PubMed using the keywords such as vasopressors, hemorrhagic shock, trauma, fluid resuscitation, norepinephrine, epinephrine, phenylephrine, ephedrine, and vasopressin. These studies have been analyzed and discussed further.

Experimental Studies

Norepinephrine

Norepinephrine is the recommended vasopressor to restore blood pressure in septic shock states.[22] It is a sympathomimetic agent acting on alpha adrenergic receptors in both veins and artery. Increased vasoconstriction on artery increases the blood pressure directly. Venoconstriction, especially in the splanchnic circulation, causes a shift of venous blood volume into systemic circulation, increasing the circulating blood volume in the central compartment, thus maintaining blood flow to the vital organs.[23] Venous return is also increased due to decreased venous resistance caused by the stimulation of beta adrenergic receptors.[23] Norepinephrine has also been found to increase the myocardial performance and improve the cardiac index and coronary perfusion. It also improves end-organ perfusion in this subset of trauma population. Norepinephrine increases the CPP, although it causes no improvement in cerebral oxygenation which improves only after transfusion in hemorrhagic shock.[24] Renal perfusion is also increased with an improvement in creatinine clearance.

In an animal study by Poloujadoff *et al.*, 100 rats were subjected to uncontrolled hemorrhagic shock and randomly assigned to either no resuscitation group or saline infusion group or resuscitation with different doses of norepinephrine in combination with saline infusion.[25] The authors concluded that norepinephrine infusion decreased the volume of fluid requirement to achieve a target arterial pressure and demonstrated lower blood loss and significantly improved survival. Norepinephrine group was also found to have a better hematocrit than the fluid-treated group in this study. In another study conducted by Meier *et al.*, pigs were subjected to normovolemic hemorrhage and received hemodilution until death. The MAP was maintained more than 60 mmHg by norepinephrine infusion, thus allowing the exchange of a significantly higher volume of blood.[26]

Few argue against the use of vasopressor agents as it may compromise microcirculation and cause tissue ischemia due to excessive arteriolar vasoconstriction during hemorrhagic shock. A recently published study by Harrois *et al.* disproved the above argument.[27] In this study, 42 mice were subjected to uncontrolled hemorrhage and were then randomly allocated into various groups treated with no fluids, fluids alone, or fluids and norepinephrine infusion. The MAP was maintained between 50 and 60 mmHg, and the intestinal microcirculation was observed by intravital microscopy. It was observed that norepinephrine decreased blood loss and the fluid requirements, while the intestinal microcirculation was preserved to the same extent in fluid resuscitated groups without norepinephrine as well as fluid resuscitated groups with norepinephrine.

Arginine vasopressin

Arginine vasopressin is another drug studied widely in the experimental models of hemorrhagic shock. It is an endogenous neurohypophyseal hormone, which acts on v1 receptors in blood vessels and shunts blood from skin, splanchnic, and skeletal areas to heart and brain thus maintaining perfusion of vital organs. It also restores blood to kidney and liver and decreases the mesenteric and portal blood flow.[28] Vasopressin may specially be useful in patients with intra-abdominal bleed due to its property of decreasing mesenteric perfusion, thus limiting the blood flow to the injured gut.

The effects of vasopressin and fluid resuscitation on survival in a hemorrhagic shock (by inflicting liver trauma) model were compared in a study by Stadlbauer *et al.*[29] The animals were randomly assigned to receive either saline placebo or fluid resuscitation or 0.4 U/kg vasopressin followed by 0.08 U/kg infusion. The authors observed significantly higher MAP and survival with full recovery in the vasopressin-treated group than in the fluid resuscitation with saline or placebo groups. Their results were consistent with another similar study conducted by Raedler *et al.*[30] In this model of severe liver trauma with uncontrolled hemorrhagic shock in pigs, the authors observed higher MAP and improved organ blood flow without aggravating further blood loss in vasopressin-treated group as compared to fluid resuscitation or saline placebo. The authors concluded that vasopressin significantly improves short-term survival during hemorrhagic shock. In yet another study by Voelckel *et al.*, the potential benefits of large dose of

epinephrine versus vasopressin were compared in hemorrhagic shock and cardiac arrest in pigs.[31] All the pigs resuscitated with epinephrine died by 60 min whereas all the vasopressin-treated pigs survived. Treatment of hypovolemic cardiac arrest with vasopressin also showed sustained vital organ perfusion despite low blood pressure, less metabolic acidosis, and better survival than epinephrine-treated group. Although this study evaluated the effects in a hypovolemic cardiac arrest situation, the beneficial effects of vasopressin in hemorrhagic shock need to be highlighted from the study results. A meta-analysis of 15 randomized animal trials conducted by Cossu *et al*. concluded that arginine and its analog, terlipressin improves survival in the early phases of hemorrhagic shock and hence seems to be more effective than other treatment modalities, including other vasopressor drugs.[32] However, the meta-analysis needs to be interpreted with caution, before suggesting their clinical application. The dosages used in animal trials were much higher than the dosages used in human studies. Moreover, the survival times varied considerably; hence, no conclusion could be drawn for the long-term survival effect of vasopressin.

Phenylephrine

Phenylephrine is an α1 adrenergic receptor agonist used as a vasopressor in shock states. Alspaugh *et al.* used the pig model and subjected them to splenic laceration and cranial trauma causing uncontrolled hemorrhage, simulating the real trauma situation.[33] The authors observed that early administration of isolated phenylephrine showed a higher survival rate as compared to crystalloid resuscitation alone, although phenylephrine group had decreased cardiac output. Feinstein *et al.* used a similar model and compared the administration of crystalloid only versus crystalloid + vasopressin or phenylephrine.[34] It was observed that the use of vasopressor support decreased the rise in intracranial pressure while limiting the volume of perfused solutions.

Clinical Studies

Although many experimental studies have been done focusing on the use of vasopressors in hemorrhagic shock, there is a paucity of clinical studies in this group of patients. Moreover, the animal studies cannot fully reflect human responses. There is some basic difference in the structure of the vasopressin receptors in humans and pigs; vasopressin receptor in pigs is lysine vasopressin receptor whereas in humans, it is arginine vasopressin. This may result in a difference of response to arginine vasopressin administration. Thus, it may not be correct to apply the results of animal studies to humans, and prospective randomized controlled clinical studies are required to draw future conclusion and give recommendations. The sparse literature available in human subjects is described below.

In a retrospective analysis, vasopressor therapy in the early stages of resuscitation was analyzed in a multivariate analysis.[35] It was observed that vasopressor therapy was associated with a higher mortality than crystalloid alone group. However, the major limitation of the study was that early deaths (<24 h) were excluded from the analysis, whereas this group may be more likely to benefit the most from vasopressor therapy. In a multicenter, prospective, cohort study, early use of vasopressors versus aggressive early crystalloid resuscitation and their association with mortality was evaluated in severely injured adults in hemorrhagic shock.[4] The crude mortality rate for patients who received early vasopressor therapy was significantly higher than those who did not (34.5% vs. 8.9%, $P = 0.001$). Cox proportional hazard regression revealed an 80% increase in mortality at 12 h and a 2-fold increased risk of mortality within 12 h in the early vasopressor group, independent of the amount of crystalloid resuscitation a patient received. This increase in mortality was observed irrespective of the type of vasopressor (vasopressin, phenylephrine, dopamine, or norepinephrine) used. Aggressive early crystalloid resuscitation was independently associated with a 40% decrease in mortality ($P = 0.030$). However, the study was based on a secondary data analysis and could only provide associations and causality. The study excluded all the patients who died within 48 h. Moreover, the data were collected only till 24 h after injury and the effect of vasopressors on long-term survival benefit was not studied. All the above study results were refuted by a double-blind randomized controlled trial, wherein the control group ($n = 40$) received only fluids whereas the treatment group received vasopressin therapy ($n = 38$; 4 IU bolus followed by 2.4 IU/h for 5 h).[36] The vasopressin treatment group required lower fluid resuscitation volume over 5 days ($P = 0.04$) and also had lower mortality at day 5 (13%) as compared to 25% in crystalloid group ($P = 0.19$).

Current Recommendations

Giving vasopressors in the early stages of hemorrhagic shock is thus still a controversy and has no universal acceptance. However, in the presence of insufficient vasoconstrictive response or vasoplegia, it may be justified to use vasopressors to prevent circulatory arrest. An updated European guideline formulated by multidisciplinary Task Force for Advanced Bleeding Care in Trauma recommends the administration of vasopressors to maintain the target arterial pressures in the absence of response to fluid therapy.[37] Norepinephrine has been suggested as a first-line vasopressor in hemorrhagic shock. Norepinephrine being a sympathomimetic agent with predominant vasoconstrictive effect seems to be reasonable in hemorrhagic shock. Inotropic agent infusion of dobutamine

or epinephrine is advocated in the presence of myocardial dysfunction.[37] In the event of inability to evaluate for myocardial dysfunction, as it would be in the majority of trauma situations, cardiac dysfunction must be suspected if the patient fails to respond to adequate fluid therapy and norepinephrine infusion. In hemorrhage, a small dose of vasopressin maintains the blood pressure which is not possible even after volume replacement or catecholamine infusion. It reduces the overall fluid requirement in the shock state and can be used as an adjunct to fluid therapy. In the recently published guidelines formulated by the Critical Care Practice Committee of the Association of Emergency Physicians, recommendations for the use of vasopressors and inotropes in various shock states were given.[38] It was suggested that vasopressin may be administered in hemorrhagic shock if deemed necessary; however, routine use of vasopressor was not recommended.

Although vasopressors may have beneficial effects in the resuscitation of hemorrhagic shock, one should not undermine the fact that balanced fluid resuscitation and blood products administration remain the first priority in the management of hemorrhagic shock. Thus, vasopressor administration in the absence of adequate volume resuscitation may, in fact, worsen the outcome by increasing mortality.[39,40]

Summary

Fluid and blood products administration remains the mainstay of initial resuscitation in hemorrhagic shock. Vasopressors have a role in resuscitation when vasoplegic shock ensues and blood pressure cannot be maintained by fluids and blood products administration alone. Among vasopressors, norepinephrine and vasopressin have been used in the majority of the trials, although not many studies compare the effect of these two on long-term survival in trauma patients. Inotropic agent infusion of dobutamine or epinephrine is recommended in the presence of myocardial dysfunction. Due to the paucity of human data on this topic, it is still controversial as to when to use vasopressor in hemorrhagic shock and whether their use offers any decrease in mortality in uncontrolled bleeding patients. Further prospective randomized control studies are required to elucidate the beneficial effects of vasopressors in hemorrhagic shock. Results of a recently completed prospective European study conducted to evaluate the impact of vasopressin infusion as a salvage therapy in prehospital hemorrhagic shock persisting despite fluid resuscitation (Vasopressin in Traumatic Shock (VITRIS.at) trial, NCT00379522) are yet to be analyzed and published. Hopefully, the study may provide future directives and recommendations of stabilizing hemodynamic function in uncontrolled traumatic hemorrhagic shock states.

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Conflicts of interest

There are no conflicts of interest.

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