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Masterthesis / Review

Insights into haemorrhagic shock: A narrative review of pathophysiology and vasopressor options

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Abstract

Haemorrhagic shock is a critical condition characterised by decreased circulating blood volume due to significant fluid or blood loss, resulting in impaired tissue perfusion and oxygen delivery. The management of haemorrhagic shock requires an understanding of its complex pathophysiology and the implementation of appropriate treatment strategies. This review focuses on the role of vasopressors in the management of haemorrhagic shock, addressing the current understanding of its pathophysiology and the use of vasopressors. The review evaluates the use of different vasopressors, including norepinephrine, epinephrine, phenylephrine and vasopressin, in the context of different studies that examined their impact on mortality and patient outcomes. While some studies suggest a potential benefit from the use of vasopressors, others suggest an increased mortality associated with their use. However, studies of vasopressin show conflicting results, suggesting its potential efficacy in reducing blood product transfusion and mortality.

Further research is needed to clarify the role of vasopressors in the management of haemorrhagic shock. This review highlights the need for further research, including prospective clinical trials, to elucidate the optimal use of vasopressors in the management of haemorrhagic shock. Understanding the pathophysiology and taking into account individual patient factors is essential to guide vasopressor therapy to improve outcomes in patients with haemorrhagic shock.

Keywords: **Haemorrhagic shock, vasopressor, norepinephrine, epinephrine, vasopressin, phenylephrine.**

Introduction

Shock is a life-threatening medical condition that occurs when the body has an imbalance between oxygen delivery and supply, leading to cellular dysfunction and possibly organ failure. Several types of shock are recognised, such as hypovolemic, distributive, cardiogenic and obstructive shock. Each category has a different pathophysiology and requires specific management strategies. Haemorrhagic shock, a subtype of hypovolemic shock, is characterised by reduced circulating blood volume due to significant fluid or blood loss. This volume loss severely compromises tissue perfusion and oxygen delivery, triggering a cascade of physiological responses to restore homeostasis. The intricate interplay between neurohormonal responses, vascular reactivity, and endothelial dysfunction underscores the complexity of managing haemorrhagic shock. Understanding these pathophysiological mechanisms is essential for guiding and implementing appropriate treatment strategies. This is especially important in the sympatho-inhibitory phase, where arterial vasodilation, bradycardia and endothelial dysfunction play a critical role in microvascular dysfunction, contributing to the progress of haemorrhagic shock.

Standardised approaches to blood product resuscitation have been established, with guidelines advocating a more limited use of intravenous (IV) crystalloids. While vasopressors such as norepinephrine, epinephrine, phenylephrine, and vasopressin aim to counteract vasodilation and maintain adequate perfusion pressure, their efficacy and safety remain debatable. The current manuscript addresses the available knowledge on the pathophysiology of haemorrhagic shock, specifically focusing on using vasopressor agents to manage haemorrhagic shock. By synthesising existing

knowledge and outlining areas of uncertainty, this narrative review attempts to provide clinicians with valuable insights into the management of haemorrhagic shock, aiding informed decision-making and potentially improving patient outcomes.

Methods

Search Approach

In the present article, we did a systematic literature search concerning the ideal vasopressor use in haemorrhagic shock. We searched five databases: MEDLINE (PubMed), Embase, Web of Science, Scopus, and Cochrane Library. We followed the PICO model:

P: Patient with age < 18, in haemorrhagic shock

I: Use of vasopressors

C: no vasopressors

O: In-hospital mortality and morbidity, including hospital and intensive care length of stay

We added the following terms to our search since we were particularly interested in norepinephrine, epinephrine, phenylephrine, and vasopressin. The investigation strategy and keywords are mentioned in Appendix A.

Titles and abstracts were screened for relevance. Following this screening, articles deemed applicable to the scope of this review underwent full text analysis, and their references were examined for additional related studies (Figure 1).

Inclusion and exclusion criteria

The inclusion criteria for potentially relevant studies were those concerning adult patients with haemorrhagic shock in the last five years (starting from 2018). Exclusion criteria were duplicate publications, animal studies, case reports, comments or narrative reviews, paediatric cases, and articles written in languages other than English. Moreover, papers with no full texts available were also excluded (Figure 1).

The quality of the included RCT studies was examined using The Jadad Scale. The quality of cohort studies and systematic reviews were assessed using The Newcastle-Ottawa Scale and AMSTAR Checklist. No useful systematic reviews were found about using vasopressors in haemorrhagic shock (Appendix B). Moreover, a summary of the investigated studies along with their respective outcomes is presented in Table I.

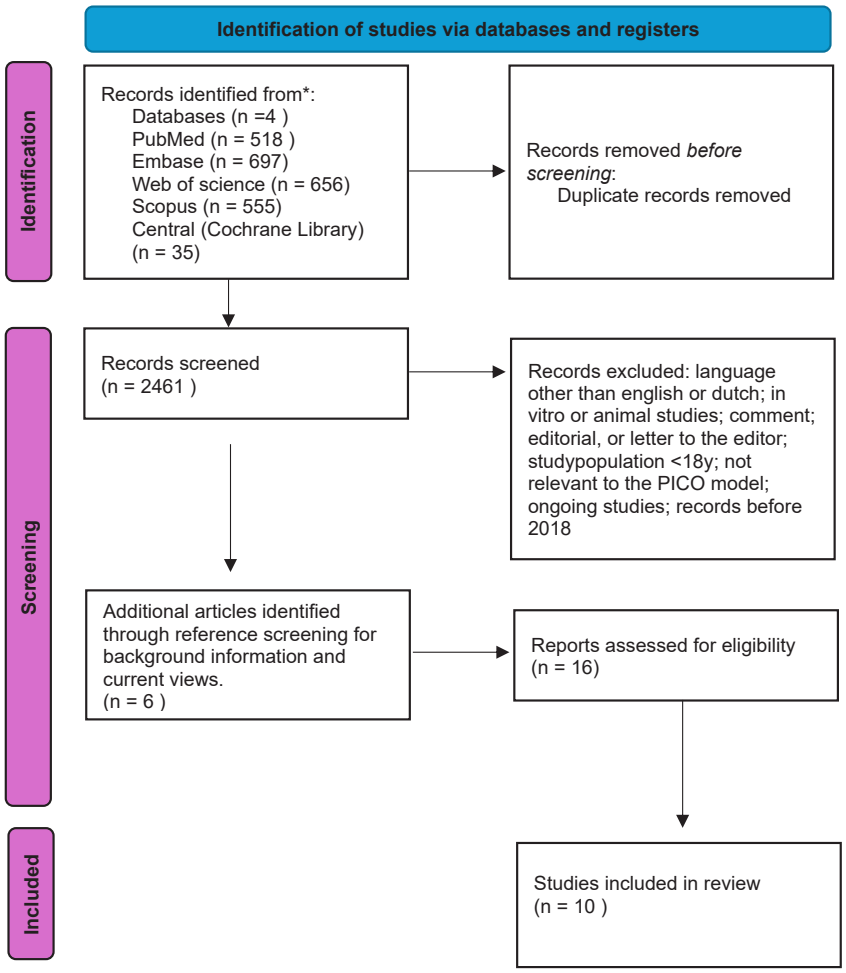

Fig. 1 — PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Table I. — Summary of Available Evidence on Vasopressor Use for Hemorrhagic Shock Management: Studies from the Last Five Years.

Author	Years	Study design and Sample size	Key findings
Sims C.	2019	RCT, N = 100	• Low-dose supplementation of AVP significantly reduced the use of all blood products and improved fluid balance at 48 hours without increasing overall complications. • Gauss T. et al. AVP supplementation was associated with fewer DVT events.
Haan B. et al.	2020	Retrospective cohort Study N = 160 (vasopressin) N = 85 (norepinephrine)	• Time to shock reversal was significantly shorter in the vasopressin group compared to the norepinephrine group (58.32 hours vs. 74.64 hours, P = 0.004). • 28-day all-cause mortality was lower in the vasopressin group compared to the norepinephrine group (25% vs. 41%, P = 0.01). • Hospital and ICU lengths of stay were similar between groups.
Fisher AD. et al.	2020	Retrospective cohort study N = 124	• Mortality was higher in the vasopressor group; univariable analysis (OR 0.09, 0.06-0.13) and multivariate logistic regression model (OR 0.32, 0.18-0.56). • Survival was lower in the vasopressor group (71.3%) compared to the propensity-matched cohort (94.3%), p < 0.001 • Prehospital maximum heart rate was higher in the vasopressor group, and systolic blood pressure was lower compared to the control group. • The total units of blood products transfused were significantly higher in the vasopressor group. (58.5, 95% CI 25.8–91.2 versus 6.0, 95% CI 5.8–6.3).
Gauss T. et al.	2022	Retrospective cohort study N = 2164 (total) N = 1498 (norepinephrine)	• The overall 24-hour mortality was 18%, and in-hospital mortality was 36%. • Early norepinephrine administration was not significantly associated with 24-hour or in-hospital mortality among patients with blunt trauma, hypotension, and hemorrhagic shock.
Makoto et al.	2018	Retrospective cohort study N = 3551	• Vasopressor use was associated with increased in-hospital mortality but was not significantly related to in-emergency department mortality (OR, 1.391; 95% CI, 0.802–2.413).
Ushida K. et al.	2020	Retrospective cohort study N = 2164	• The maximum catecholamine index was significantly higher in non-survivors compared to survivors (2 [0–4] vs 14 [10–18]; p = 0.008). • Mortality rate was significantly higher in the early vasopressor group. • The total amount of blood transfused within 24 hours after admission was significantly higher in survivors.
Beni C. et al.	2021	Retrospective observational study N = 337	• Median time to lactate normalization was 15 hours (IQR, 7-25 hours) • Median Intravenous fluid volume was 3.7 L (IQR, 1.5-6.4 L) • Larger volumes were associated with longer ICU length of stay and duration of mechanical ventilation, as well as acute kidney injury (37%). • Median of 20 ICU-free days (IQR, 6–24 days). • Median of 24 ventilator-free days (IQR, 10–26 days). • Mortality rate is 20%, with a 12% mortality rate during the first 48 hours of ICU admission.
Abbas M. et al.	2019	Randomized Controlled Trial N = 84	••Mean (SD) amount of intra-operative blood loss: *Terlipressingroup: 1351 (887) *Placebogroup: 1892 (889) mL in the placebo group (P = 0.006). • Blood transfusions: 30% terlipressin group, 64.2% placebo group (P = 0.002) • Duration of hospital stay longer in the control group (p = 0.003).
Barmparas et al.	2018	Retrospective observational study N = 120	• Overall mortality: 49% • Vasopressors group has a higher overall mortality compared to those without vasopressors (60% vs. 34% p = 0.03). Nevertheless, the study could not determine whether the use of vasopressors itself increases mortality or whether it serves as a marker of poor outcomes.
Gauss T. et al.	2018	Observational Study N = 518 (total) N = 201 (norepinephrine)	• Hazard-ratio mortality was 0.95 (95% confidence interval: 0.45-2.01; P=0.69). • Noradrenaline use in the early phase of traumatic HS does not seem to affect mortality adversely.

AVP: arginine vasopressin, DVT: Deep venous thrombosis, ICU: intensive care unit, N= number of patients.

Pathophysiology of haemorrhagic shock

The progression of haemorrhagic shock involves two distinct phases, each one marked by complex physiological responses. The initial sympatho-excitatory phase is characterised by vasoconstriction and increased systemic vascular resistance. The sympathetic nervous system takes centre stage, orchestrating a symphony of responses to maintain blood pressure and perfusion. The release of neurohormones such as angiotensin-II (as a consequence of the renin-angiotensin system and a lesser relative increase in arginine vasopressin), epinephrine and norepinephrine, contributes to vasoconstriction and increased heart rate[1,2].

As the shock progresses, the sympatho-inhibitory phase occurs. In this phase, vascular hypo-reactivity takes over, resulting in arterial vasodilation and bradycardia. Despite the increased production of epinephrine and norepinephrine by the adrenal medulla, vasodilation occurs. The complexity of this phase is compounded by the involvement of neurohormones such as angiotensin II and vasopressin, which play a role in restoring arterial blood pressure. However, prolonged and significant blood loss can lead to the depletion of these critical mediators, ultimately contributing to the loss of vascular tone[1,2].

Endothelial dysfunction, an aspect of haemorrhagic shock, serves as a linchpin in the cascade of events leading to post-traumatic complications. The endothelium, a vast network of cells lining blood and lymphatic vessels, orchestrates critical functions such as regulation of vascular permeability, fluid homeostasis and control of vasomotor tone. When the endothelium is compromised due to trauma-induced coagulopathy, microvascular dysfunction ensues, setting the stage for the development of multiple organ dysfunction syndrome[3].

Vasopressor Hyporesponsiveness in Haemorrhagic Shock

Due to several mechanisms, there is a reduced response to vasopressors in haemorrhagic shock. Three levels of interaction are highlighted, namely, central (neuro-immune communication), cellular (G protein-coupled receptors or GPCRs) and intracellular (alterations in second messenger pathways)[4].

Neuro-immune communication during shock involves a complex interplay between the sympathetic system and the hypothalamic-pituitary-adrenal axis, driven by baro- and chemoreceptors and inflammatory cytokines. The release of norepinephrine, epinephrine, cortisol and vasopressin and their interactions contribute to vascular reactivity during the initial shock phase. However, prolonged sympathetic activation leads to dysautonomia, tachycardia, adrenoceptor desensitisation and pro-inflammatory states, all contributing to vascular hyporesponsiveness to vasopressors[4,5].

G-protein coupled receptors (GPCRs), including adrenergic, vasopressin 1 (V1) and angiotensin type 1 (AT1) receptors, play a central role in the regulation of vascular tone. Haemorrhagic shock induces a process of receptor desensitisation characterised by the phosphorylation of GPCRs. This process, activated even after transient agonist stimulation, contributes significantly to vascular hyporesponsiveness to major vasopressors[4,5].

Alterations in second messenger pathways further accentuate vascular hyporesponsiveness to vasopressors. Inducible nitric oxide synthase (iNOS) expression is enhanced during shock, leading to increased NO production and subsequent activation of several pathways that cause vasodilation. Other mechanisms, such as the prostacyclin and cyclo-oxygenase-2 (COX2) pathways, contribute to vasodilation. Critical illness-related corticosteroid insufficiency also plays a pivotal role, affecting vascular responsiveness through various mechanisms, including cortisol synthesis insufficiency and excessive pro-inflammatory response[4,5].

Haemodynamic Changes in Haemorrhagic Shock

Understanding cardiac haemodynamics is crucial for effective shock management. Key concepts include the relation between preload and stroke volume as demonstrated by the Frank-Starling law[6]. In haemorrhagic shock, reduced blood volume led to decreased preload and stroke volume and ended with drops in cardiac output. Administering vasoconstrictors could compensate for this effect but could potentially reduce oxygen delivery. Severe bleeding shifts metabolism from aerobic to anaerobic causing lactate production. Furthermore, if shock persists and this compensation mechanism fail, cellular damage takes place[1].

Clinical manifestations of haemorrhagic shock

The clinical presentation of haemorrhagic shock is classic and instructive. Initially, the body's compensatory mechanisms strive to maintain blood pressure and cardiac output, resulting in increased heart rate, decreased pulse pressure, and increased respiratory rate. Later, when management is not yet started, or the patient is not responsive, a new sympatho-inhibitory phase kicks in. Monitoring

certain parameters provides valuable insight into the patient's physiological state. However, it is essential to recognise that relying solely on blood pressure and heart rate may miss occult hypoperfusion in many patients. Therefore, the integration of tissue perfusion parameters such as base excess and lactate levels could be valuable[4,7].

Resuscitation Strategies in Haemorrhagic Shock

Recent advances in damage-control surgery and blood transfusion practices have changed initial trauma care, leading to fewer deaths from haemorrhage and subsequent organ failure. Standardised approaches to blood product resuscitation have been established, with a more limited use of intravenous (IV) crystalloid advocated in the guidelines.

Although there is still some variability in volume and timing of IV crystalloid administration during the Intensive Care Unit (ICU) phase, larger volumes of IV crystalloids are associated with worse outcomes, including longer ICU stays, longer mechanical ventilation duration, and increased incidence of acute kidney injury. Vasopressor usage increases during this phase and is associated with longer ICU stays. However, there was no significant difference in mortality or discharge rates to home based on the volume of IV crystalloid administered.

Some study confirmed that vasopressors are used in trauma resuscitation after the initial stabilisation of the patient. commonly in subjects who died during resuscitation.

Vasopressors administered at the end of this phase is associated with longer ICU length of stay, possibly indicating volume unresponsiveness. However, the study could not directly attribute poor outcomes solely to vasopressor use[6,8].

Vasopressor options in haemorrhagic shock

Several vasopressor agents have been used in the management of haemorrhagic shock. In the current article, we focus mainly on the following drugs: norepinephrine, epinephrine, phenylephrine, and vasopressin.

Norepinephrine

Norepinephrine is a potent stimulant of alpha and beta-1 receptors, with minimal effect on beta-2 receptors. The activation of alpha-1 receptors leads to vasoconstriction and increases blood pressure, while stimulation of beta-1 receptors increases cardiac contractility and heart rate. Blood pressure is reliably increased, but the effect on cardiac output is variable. It is commonly used as a vasopressor in the treatment of hypotension and shock, particularly septic shock.

The use of vasopressors in the management of haemorrhagic shock has not been extensively studied, with many articles mentioning vasopressors in general and not comparing norepinephrine with other vasopressors. However, a few retrospective cohort studies have compared the efficacy and outcomes of norepinephrine administration during haemorrhagic shock or major bleeding.

For instance, a comparison between norepinephrine and vasopressin, as first-line vasopressors in distributive and haemorrhagic shock, suggested that vasopressin may lead to faster shock reversal and lower mortality than norepinephrine monotherapy. It is important to note that, baseline differences and treatment patterns are likely to have influenced these results[9].

Another study assessed the use of pre-hospital norepinephrine in hypotensive trauma patients and found that norepinephrine administration was associated with lower odds of survival. However, this study did not specifically compare different vasopressors[6].

Likewise, data from the Japan Trauma Bank shows an association between vasopressor use and higher in-hospital mortality in patients with traumatic haemorrhagic shock. However, it did not differentiate between vasopressor types[10].

Another study highlighted the potential association between early vasopressor administration and increased mortality in severe blunt trauma patients, emphasising the need for further research[11].

In contrast, a multicentre study challenged the notion that vasopressors, including norepinephrine, should be avoided after traumatic injury[12]. It found no increased mortality with early administration of norepinephrine in patients with blunt trauma and haemorrhagic shock.

Massively transfused trauma patients often require vasopressors during initial resuscitation, particularly in traumatic brain injury, but less commonly in penetrating trauma. However, their use is associated with significantly increased mortality, with deaths occurring later than in those who did not receive them and with mortality increasing with the number of vasopressors used. While norepinephrine use is often considered as a marker of inadequate resuscitation, its specific role remains unclear, with some studies suggesting a potential delay in mortality rather than a direct increase. Overall, although norepinephrine is commonly used in the management of haemorrhagic shock, comparative studies specifically focusing on norepinephrine are limited[13].

Epinephrine

The use of or epinephrine (adrenaline) in certain types of shock management is characterised by its dual action on alpha and beta receptors, resulting in vasoconstriction and increased cardiac output, respectively. Studies evaluating the prehospital administration of vasopressors, including epinephrine, to trauma patients have shown decreased survival rates compared to control groups, even after adjustment for confounding factors, suggesting potential risks and challenges associated with the administration of vasopressors in combat casualties[6]. In addition, trauma patients who received vasopressors during massive transfusion had higher mortality rates, with mortality increasing proportionally with the number of vasopressors used[13]. The study did not specifically break down outcomes based on individual vasopressors, including adrenaline. The results presented were aggregated for all vasopressors used collectively. Therefore, the study does not provide specific information about the comparative effects of adrenaline versus other vasopressors in the given context. Despite these limitations, the findings highlight the association between vasopressor use and increased mortality in trauma patients; it may serve as a marker of poor outcomes rather than a direct cause.

Phenylephrine

Phenylephrine, primarily activating alpha-1 adrenergic receptors, induces vasoconstriction and elevates blood pressure, making it valuable in managing hypotension or shock. Unlike other sympathomimetic drugs, phenylephrine has minimal direct impact on heart rate but may induce reflex bradycardia as a compensatory response to increased blood pressure.

Findings suggest that the use of phenylephrine and other vasopressors in hypotensive trauma patients may be associated with worse outcomes, including decreased survival[6]. The study emphasises the need for further evaluation of vasopressor use in combat casualties, especially considering the resource-constrained environment of pre-hospital care.

Another study states that theoretically norepinephrine, being both a β-1 and α-1 agonist, should be superior to phenylephrine, which is a pure α-1 agonist, in maintaining regional blood flow in patients at risk of bleeding and hypoperfusion14. No clear conclusion about phenylephrine specifically was made here. Some studies pooled various vasopressors, including phenylephrine, dopamine, vasopressin, and norepinephrine, without specifying criteria or timing for their administration.

Although phenylephrine's impact on mortality is not directly compared with other vasopressors, its common utilisation in trauma patients undergoing massive transfusion, particularly in traumatic brain injury cases, is highlighted[13]. Despite its frequent use, vasopressors, including phenylephrine, are linked to increased mortality, posing questions about their optimal application in trauma resuscitation.

Vasopressin

Vasopressin, a peptide hormone released from the posterior pituitary in response to an increase in serum osmolarity or hypovolemia, also known as antidiuretic hormone (ADH), acts primarily on V1 receptors in vascular smooth muscle cells, leading to vasoconstriction and an increase in peripheral vascular resistance. This constriction narrows the blood vessels and increases blood pressure. In addition, vasopressin acts on V2 receptors in the kidneys to promote water reabsorption and reduce urine output, helping to maintain blood volume and further support blood pressure. Acting on the blood vessels and the kidneys, vasopressin is crucial in regulating blood pressure and fluid balance. An additional action is the increase of the release of the von Willebrand factor from the vascular endothelium, which increases platelet aggregation.

Vasopressin and its derivatives have been investigated for their efficacy in managing haemorrhagic shock and trauma-induced hypotension. Studies evaluating low-dose arginine vasopressin supplementation in trauma patients demonstrated decreased blood product transfusion requirements and potentially reduced risk of deep venous thrombosis[15]. When compared with norepinephrine for the efficacy and safety of vasopressin as first-line therapy for distributive and haemorrhagic shock states in a retrospective cohort study at a level I academic medical centre including adult patients admitted to the intensive care unit between 1 June 2012 and 30 June 2017, the unadjusted analysis showed a statistically significant shorter time to shock reversal in the vasopressin group compared with the norepinephrine group[9]. The incidence of needing an additional vasopressor and the number of additional vasopressors given were similar between the two groups. However, when an additional vasopressor was required, it was started more quickly in the vasopressin group than in the norepinephrine group. There was a statistically significant difference in 28-day all-cause mortality in favour of the vasopressin group (25% vs 41%). All safety data, including the incidence of adverse

events such as acute kidney injury, ischaemia, new arrhythmias, hyponatraemia, extravasation, acute myocardial infarction and cardiac arrest, were similar between the two groups. However, the study had several limitations, including its retrospective design, potential confounding variables, reliance on documentation accuracy, prescriber bias, and practice variability. The bottom line is that while vasopressin showed promise as a first-line vasopressor for circulatory shock reversal in the univariate analysis, it failed to maintain this difference in the multivariable analysis.

Trauma resuscitation strategies, including the use of massive transfusion protocols to decrease mortality from blood exsanguination showed that despite adequate resuscitation with fluids and blood products, some trauma patients still require vasopressors to maintain blood pressure[13].

A Nationwide Cohort Study in Japan studied the association between vasopressor use and mortality in traumatic haemorrhagic shock patients[10]. It suggested that while vasopressor administration might initially improve survival beyond the emergency department phase, it could eventually lead to increased fluid resuscitation needs and higher in-hospital mortality rates. Vasopressor use was not associated with mortality in the emergency department (ED), suggesting that the disadvantages of vasopressor use may not be apparent within the first 24 hours.

This finding was confirmed in another randomised controlled trial, where patients receiving vasopressors tended to die at a later time interval from admission[13]. Vasopressor use may be a marker of poor outcomes rather than a direct cause of mortality.

Detailed information on the dose, type, and duration of vasopressor use was unavailable in these studies, limiting the ability to assess the specific effects of different vasopressors, including vasopressin. The study may also be subject to indication bias, as vasopressors may have been used in the more severe cases of haemorrhage.

In liver resection surgery, terlipressin infusion (a vasopressin derivative) significantly reduced intraoperative bleeding and transfusion requirements, highlighting its potential benefit in surgical contexts[16]. Despite promising results, further research is warranted to assess the applicability and effectiveness of vasopressin analogues like terlipressin across different clinical scenarios. Overall, while vasopressors play a crucial role in trauma resuscitation, their specific impact on patient outcomes, particularly with regard to vasopressin and terlipressin, requires more targeted investigation.

Limitations

We acknowledge that the current review may have several limitations. Firstly, it focuses on recent studies published within the last five years and excludes relevant older research that could offer valuable insights. Additionally, excluding non-English articles may lead to language bias, potentially limiting the scope of our analysis. Moreover, variability in study design and patient populations among the included studies makes it challenging to get definitive conclusions. Even though quality assessment tools like the Jadad Scale and Newcastle-Ottawa Scale offer some insight, they do not completely eliminate bias.

Last, some studies lack detailed information on specific vasopressor administration, limiting their interpretability. Despite the limitations mentioned above, our review highlights the need for further research, particularly prospective trials, to address these gaps in knowledge and provide more explicit guidance for the optimal management of haemorrhagic shock with vasopressors.

Conclusion

Haemorrhagic shock is a critical condition resulting from significant fluid or blood loss, presents a complex challenge and requires a nuanced approach to clinical management. Although various vasopressors such as norepinephrine, epinephrine, phenylephrine and vasopressin have been studied, their efficacy in managing haemorrhagic shock remains uncertain. While some studies suggest a potential benefit, others raise concerns about increased mortality risk. Notably, vasopressin shows promise in reducing blood transfusion and mortality. Yet more research is needed to determine its optimal use. Despite these complexities, a comprehensive understanding of the pathophysiology and individual patient factors is essential to guide vasopressor therapy to improve outcomes in haemorrhagic shock.

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