Vasopressin in traumatic hemorrhagic shock

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Purpose of review
Hemorrhage and subsequent development of therapy refractory shock are the major cause of death in potentially salvageable trauma victims. Recent scientific work recognizes that there is an urgent need to develop new life-support strategies. From a variety of interventions and drugs with the potential to prolong the compensation phase or to reverse the decompensation phase of shock, arginine vasopressin (AVP) is one of the most promising and best evaluated drugs. Nonetheless, the efficacy of AVP administration in hemorrhagic shock is still to be proven. Thus, this umbrella review summarizes the current evidence of AVP in hemorrhagic shock.

Recent findings
Fifteen short reviews, narrative reviews, systematic reviews and meta-analysis addressing AVP in traumatic hemorrhagic shock were identified and included in this umbrella review. There is robust evidence deriving form 23 animal studies that AVP administration is effective in hemorrhagic shock, resulting in hemodynamic stabilization and improved survival. This observation is supported by six case reports but not confirmed by two retrospective observational studies and two randomized control trials.

Summary
In uncontrolled hemorrhagic shock, arginine vasopressin might be considered as a therapy of last resort in shock patients not responding to conventional therapy. Further research is needed to determine the potential benefits and optimal dosage/timing of vasopressin use in hemorrhagic shock.

Keywords
exsanguination, hemorrhage, review, shock, trauma, vasopressin

INTRODUCTION

Although prehospital mortality from hemorrhage seems to decrease [1], exsanguination and brain injury are still the most common causes of trauma death, which results in many years of life lost. Traumatic hemorrhage is a complex illness and the most common cause of hypovolemic shock. It leads to a fall in systemic filling pressure and venous return. The resulting decrease in cardiac minute volume and, therefore, in oxygen and nutrient supply sets off a pathophysiologic cascade. Depending on the amount of blood lost and, on the organism's functional status before shock, hemorrhage can either be compensated by endogenous mechanisms, reversed by timely intervention, or ends in death. The key question, how to avoid cardiac arrest from exsanguination when fluid resuscitation fails and surgical intervention is not available in time, remains unanswered.

The potential role of vasopressors as first-line drugs for hemodynamic stabilization before, along with or instead of intravenous fluids and the appropriate rescue medication in the decompensation phase of shock is still to be defined. The rationale to use vasopressor drugs for cardiocirculatory stabilization in hemorrhage is based on our current knowledge of the physiologic response to hypovolemia, and the idea to support physiologic, endogenous mechanisms involved in the compensation phase of shock. Moreover, second-line drugs are needed to counteract pathomechanisms responsible for the development of irreversible vasoplegia.

MECHANISMS OF COMPENSATION AND DECOMPENSATION DURING HEMORRHAGIC SHOCK

A variety of different endocrine and neurohumoral compensatory mechanisms can temporarily ensure

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KEY POINTS

- This umbrella review identified robust evidence for the efficacy of AVP when administered for hemodynamic stabilization in hemorrhagic shock animal models.
- In multiple case reports, AVP effectively restored hemodynamics in fluid and catecholamine refractory shock.
- In two randomized control trials, AVP administration in hemorrhagic shock patients decreased fluid requirements after injury.
- Observational studies failed to demonstrate a survival benefit of AVP administration in hemorrhagic shock.
- The question when to administer AVP during the time course of fighting hemorrhagic shock is still unanswered.

cardiovascular stability during hypovolemia, and the compensatory mechanisms of the body responding to hypovolemic shock by vasoconstriction and redirection of blood flow to vital organs are key factors enabling survival. Accordingly, it seems reasonable to consider the role of vasopressor hormones when hypotension becomes life threatening. Baroreceptor stimulation activates an α-adrenergic reflex that leads to the release of epinephrine from the adrenal medulla and norepinephrine from sympathetic nerve endings within seconds. The vasoconstrictor effects of catecholamines are mediated via α-1 and extrasynaptic α-2 receptors. The stimulation of presynaptic α-2 receptors, which occurs at the same time, blocks the continuing release of norepinephrine from nerve endings. This feedback mechanism seems to be one of the causes of the vascular decompensation seen during the late stage of hemorrhagic shock [2].

Arginine vasopressin (AVP) is known as an endogenous stress hormone and significantly increased in trauma patients [3]. A drop in blood pressure induces the secretion of AVP resulting in levels up to the 40-fold of the physiologic concentrations, whereas at the same time, a 75% decrease of AVP clearance is noted [4]. Interestingly, patients in vasodilatory septic or hemorrhagic shock have also been identified to be deficient in AVP, a condition thought to be related to a defect in the baroreflex-mediated secretion of AVP and depletion of neurohypophyseal stores [5,6]. Thus, the importance of the secretion of AVP in humans in response to reductions in central blood volume may be underscored by the observation that maximal elevations in AVP and systemic vascular resistance are greater in individuals with high tolerance to hypovolemia compared with those with low tolerance [7]. Interestingly, the sensitivity to exogenously administrated AVP further seems to be regulated, just as is the AVP secretion, by volume and pressure stimuli. Accordingly, in AVP-depleted dogs, even low doses of AVP yield a hypersensitive pressure response, whereas AVP has little or no effect in normal animals or in hypotensive settings with appropriate AVP levels [8]. This may, in part, explain conflicting findings of animal experiments on the use of AVP in hemorrhagic shock.

This increase in AVP levels causes a rise in systemic vascular resistance and blood pressure. The main factor leading to hemodynamic stability after AVP is caused by the volume mobilization from venous capacitance vessels to the central circulation, resulting in a rise of central venous pressure, and subsequently cardiac output [8]. Vasopressin further leads to peripheral vasoconstriction via V1-receptors in the vasculature and does not cause β-mimetic increase in heart rate and myocardial oxygen consumption, which may further contribute to vital organ ischemia. As such, because vasopressin shifts blood primarily from the skeletal muscle, cutaneous, and splanchnic bed to the heart and brain, this effect will most likely be beneficial in hypovolemia [9]. Moreover, AVP is known to exert a significant vasoconstrictive effect even in the late or decompensation phase of shock. In an animal model of shock, Pieber *et al.* [10] found a significant decrease in angiotensin II-mediated and norepinephrine-mediated vasoconstriction after hemorrhage of 60 and 120 min, respectively, whereas AVP-mediated vasoconstriction was unchanged even during the late stages of shock. The authors suggested that this finding might be due to excessive nitric oxide (NO) formation during the decompensation phase of hypovolemic shock.

Taken together, three mechanisms have thus far been identified to be the involved in vasodilatation and resistance to vasopressors that occur in shock: First, activation of ATP-sensitive potassium channels (KATP channels) in the plasma membrane of vascular smooth muscle; second, activation of the inducible form of nitric oxide synthase; and third, deficiency of the hormone vasopressin [11].

Despite the potential benefits of AVP as a potent vasopressor drug, vasoconstriction in extreme hypovolemic situations will most likely result in tissue hypoperfusion and subsequently cell death, despite high blood pressure values [12,13].

Today, trauma guidelines and review papers recommend vasopressor use only in cases of severe hypotension refractory to fluid therapy [14–16]. Acknowledging the significant knowledge gap, we

performed an umbrella review of meta-analyses addressing the potential role of AVP in hemorrhagic shock.

RESEARCH QUESTIONS

The aim of this study was to summarize and assess the results from reviews, systematic reviews and meta-analyses, addressing the potential role of AVP in traumatic hemorrhagic shock.

The research questions of the umbrella review were as follows: first, does the data derived from currently available systematic reviews support the assumption that administration of AVP improves survival in trauma patients with hemorrhagic shock when compared with standard care? Second, is there reliable data about timing and dosage of AVP in life-threatening traumatic hemorrhage? And, third, are there significant side effects that may impair outcome?

The design of this umbrella review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

SEARCH STRATEGY

An electronic search was performed in the following databases: Medline, Scopus and Cochrane Library. Systematic reviews, with or without meta-analysis, evaluating randomized controlled trials, controlled trials or experimental trials with control groups, and narrative reviews with case reports or data derived from animal studies were included. Acknowledging that a search of AVP in trauma will not match with the research questions, data bases were screened employing the following search string for Medline: ('Vasopressins' [MeSH Terms] OR 'Arginine Vasopressin' [MeSH Terms]) AND ('Hemorrhage' [MeSH Terms] OR 'shock, traumatic' [MeSH Terms] OR 'shock, hemorrhagic' [MeSH Terms] OR shock [MeSH Terms] OR Trauma [MeSH Terms]); and Scopus: [TITLE-ABS-KEY (vasopressin) AND TITLE-ABS-KEY (haemorrhage) OR TITLE-ABS-KEY (hemorrhagic AND shock) OR TITLE-ABS-KEY (traumatic AND shock) AND TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (metaanlysis)].

Titles and abstracts were screened for eligibility. Articles matching the research question were exported to a reference management system (Papers 4.16, Digital Science Research & Solutions Inc.), and duplicate articles were removed.

FINDINGS

From a total of 816 citations, 15 short reviews, narrative reviews, systematic reviews and meta-analysis were identified and included in this umbrella review (Fig. 1, Flowchart). Two reviews focused on animal studies only [18,19], whereas the remaining 13 included experimental and clinical data. Primary studies cited in the manuscripts comprised 23 animal studies, 6 case reports, 2 retrospective observational trials, 1 multicenter prospective cohort study and 2 randomized control trials (Table 1). In total, 756 animals (388 rodents, 18 dogs and 350 pigs) were investigated in the animal studies. In case reports, 11 patients were presented. Within the two retrospective database analyses, 567 AVP patients were compared with 2095 controls. One prospective multicenter cohort study comprised 119 AVP patients vs. 802 controls. Finally, in two randomized control trials evaluating the 'Impact of Low-dose Vasopressin on Trauma Outcome' and the 'Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock', 87 patients were treated with AVP and compared with 91controls (38 vs. 40; and 49 vs. 51, respectively; Table 2).

There is ample experimental and, in part, clinical data addressing the potential value of AVP in distributive and septic shock, in cardiopulmonary resuscitation after cardiac arrest, in the impact of the AVP analogue Desmopressin on platelet function and coagulation management, the hemostatic properties of AVP and Terlipressin in esophageal variceal bleeding, and in the obstetric setting. Moreover, the physiology of AVP and its role in the maintenance of hemostasis, as well as its pharmacologic properties has been extensively studied. Based on the remarkable vasoconstrictive properties of AVP, the assumption that a pharmacologic intervention in traumatic hemorrhagic shock might be a promising therapeutic option is more than justified. Given the fact, that death due to exsanguination and traumatic brain injury are still the leading causes of death after trauma, new therapeutic options are eagerly awaited. Unfortunately, design of experimental models reflecting the impact of trauma on the physiology in a standardized, reproducible and comparable way is difficult. Moreover, inclusion of severely injured patients in clinical trials is also a major challenge. Administration of a study drug along with a bundle of interventions at a precisely defined time point during advanced care is challenging. Accomplishment of surrogate or outcome parameters such as an increase in blood pressure, sustained survival or ultimately hospital discharge in good health due to a single pharmacologic intervention is most likely influenced by may confounders. This might explain why the Vasopressin In TRaumatIc Shock Trial (VITRIS) [20] failed and never got published.

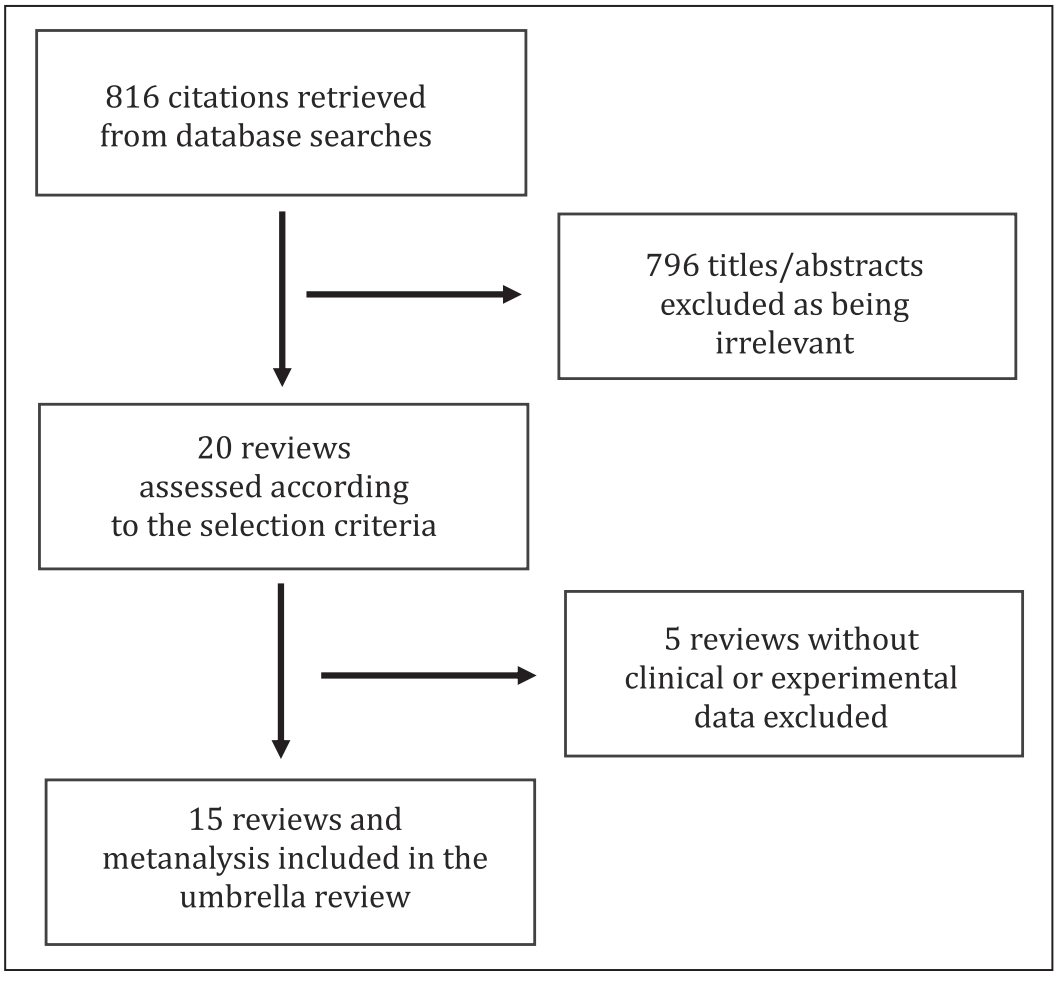

FIGURE 1. Prisma flow chart.

Does the data derived from currently available systematic reviews support the assumption that administration of arginine vasopressin improves survival in trauma patients with hemorrhagic shock when compared with standard care?

The quality of the review articles varies significantly. Eight short or narrative reviews provide no data about the search strategy [21–23,24▪,25–28]. Five systematic reviews [29–32,33] and one meta-analysis [18] detail the search strategy employed for the systematic review process. The three most elaborated reviews, comprising 21 primary studies, also assessed the risk of bias and estimated the pooled risk ratios along with their 95% confidence interval [18,32,34▪▪]. Data and conclusions acquired from eight of the analyzed reviews suggest scientific evidence for the efficacy of AVP when administered to treat hemorrhagic shock in animal models. Acknowledging the low number and methodologic quality of available clinical trials (two randomized control trials [35,36], and three observational database cohort studies [12,13,37]), there was no statistically significant survival benefit observed for patients who received AVP in hemorrhagic shock when compared with those who did not. This is in stark contrast with the case reports cited in eight review articles, comprising 11 patients. Each of them showed at least a temporary AVP effect on hemodynamic stabilization in traumatic shock patients.

Is there reliable data about timing and dosage of arginine vasopressin in life-threatening traumatic hemorrhage?

The value of vasopressors when administered in the early stages of hemorrhagic shock is still a controversy and has no universal acceptance [30]. It has been postulated that vasopressor administration in the bleeding trauma patient must be exercised with caution and in concert with appropriate intravascular resuscitation [38]. One review refers to two retrospective studies addressing an early exposure to

Table 1. Review articles enclosed in the umbrella review, number and type of primary studies cited, outcomes and conclusion

First author [ref]	Year	Number of experimental studies and aninmals included	Number of clinical studies and patients included	Outcome	Conclusion
Anand [29]	2012	Seven Pigs = 100 [41–45] Rodents = 61 [46,47]	Three case reports 7 patients [22,40,48]	Meaningful and sustained increase in blood pressure after major hemorrhage	AVP is linked to improved outcome
Beloncle [25]	2013	Eight Pigs = 200 [41–45,49,50]	Three studies [12,13,35] One retrospective database analysis [13] (351 AVP patients vs. 1349 controls) One multicenter prospective cohort study [12] (119 AVP patients vs. 802 controls) One RCT [35] (38 AVP patients vs. 40 controls)	Hemodynamic and side effects	Insufficient clinical evidence for AVP in hemorrhagic shock Vasopressors cannot replace fluid loading
Cossu [18]	2014	Fifteen Pigs = 282 Rodents = 151 [51–53]		Reduction of mortality	AVP seems more effective to improve survival in hemorrhagic shock when compared with all other treatments
Fage [24▪]	2023	Two Pigs = 39 [44,54]	One RCT [36] (49 vs. 51)	Renal hemodynamics	Not enough data to conclude the impact of vasopressin on kidney hemodynamics and/or function
Forrest [31]	2001	Two Pigs = 18 [54] Dogs = 7 [55]	One case report 2 patients [55]	Outcome of hypovolemic cardiac arrest and irreversible hypovolemic shock	Vasopressin may be useful in hypovolemic cardiac arrest. Limited, though tantalizing evidence that vasopressin may reverse irreversible hypovolemic shock
Haas [21]	2004	Two Pigs = 18 [54] Dogs = 7 [55]	One case report 1 patient	Outcome of cardiac arrest in hypovolemic shock	In one case of cardiac arrest in hypovolemic shock, vasopressin was helpful restoring spontaneous circulation
Hylands [32]	2017		One RCT, $N = 78$ [35] One prospective cohort study (119 AVP patients vs. 802 controls) [12] One retrospective observational trial (225 AVP patients vs. 746 controls) [37]	Mortality, adverse events, ICU days, RBC and FFP requirements	Lack of reliable data on patient outcomes when vasopressors are administered in the early phase of traumatic resuscitation
Gupta [30]	2017	Five Pigs = 73 [42,44,49,50,54]	One case report 3 patients [22] One case report 2 patients [40] One retrospective database analysis [13] (351 AVP patients vs. 1349 controls) One RCT [35] (38 AVP patients vs. 40 controls)	Mortality in uncontrolled bleeding	Vasopressor use in hemorrhagic shock is controversial due to the paucity if human data

Table 1 (*Continued*)

First author [ref]	Year	Number of experimental studies and aninmals included	Number of clinical studies and patients included	Outcome	Conclusion
Krismer [22]	2004		Case report 3 patients	Mortality	Vasopressin was helpful to restore spontaneous circulation as an adjunct vasopressor to catecholamines in uncontrolled traumatic hemorrhagic shock
Laou [34▪▪]	2023	Twelve Pigs = 68 [43,50,56–58] Dogs = 23 [59,60] Rodents = 490 [52,53,61–63]	One RCT [35] (38 AVP patients vs. 40controls) One RCT [36] (49 AVP patients vs. 51controls)	Mortality within 24 h Impact of vasopressin on hemodynamic parameters during resuscitation of hemorrhagic shock	Safe conclusions from animal studies are challenging due to heterogeneity in terms of species and dosage of vasopressin among studies. The risk of mortality between patients who received vasopressin and those who did not was statistically significant
Nistor [19]	2017	Three, Pigs = 60 [56,64,65]		Vital parameters Brain-specific parameters	Neuroprotective therapies in hemorrhagic shock revealed only few animal studies. Vasopressors showed a neuroprotective effect
Raab [26]	2008	Seven Pigs = 145 [42,44,45, 49,50,54,55] Dogs = 7 [55]	Four case reports 7 patients [21,22,55,66]	Blood flow, blood loss, survival	Employment of vasopressin in experimental models of uncontrolled hemorrhagic shock has decreased blood loss and improved vital organ blood flow and survival. Observation confirmed by several case reports
Voelckel [28]	2010	Twelve Pigs =183 [39,41–45,50,54,55,60,67] Dogs =7 [55,60]	Four case reports 8 patients [21,22,48,55] One prospective cohort study (119 AVP patients vs. 802 controls) [12]	Survival, blood loss	It seems reasonable to suggest that AVP might provide a life-saving therapy for use in the treatment of hemorrhagic shock
Wenzel [27]	2008	Ten Pigs = 185 [42,44,45, 49,50,54,56,62] Dogs = 7 [55,60]	Five case reports 9 patients [21,22,48,55,66]	Effect of AVP on hemodynamics, blood loss and outcome	AVP can only be considered as a rescue therapy in hemorrhagic shock, which is resistant to conventional therapy

AVP, arginine vasopressin.

Table 2. Overlapping of primary studies included in reviews and meta-analysis

Primary studies	Systematic reviews that included the primary studies	Number of animals or patients included in the primary study
Bayram, B., *et al.* Effects of terlipressin in a rat model of severe uncontrolled hemorrhage via liver injury. *Am. J. Emerg. Med.* 30, 1176–1182 (2012).	Cossu *et al.* [18]	21 rats
Cavus, E. *et al.* Cerebral effects of three resuscitation protocols in uncontrolled haemorrhagic shock: A randomised controlled experimental study. *Resuscitation* 80, 567–572 (2009).	Anand *et al.* [29]; Beloncle *et al.* [25]	24 pigs
Dickson, J. M. *et al.* Damage Control Resuscitation Supplemented with Vasopressin in a Severe Polytrauma Model with Traumatic Brain Injury and Uncontrolled Internal Hemorrhage. *Mil. Med.* 183, e460–e466 (2018).	Laou *et al.* [34▪▪]	15 pigs
Indrambarya, T., Boyd, J. H., Wang, Y., McConechy, M., & Walley, K. R. Low-dose vasopressin infusion results in increased mortality and cardiac dysfunction following ischemia-reperfusion injury in mice. *Crit. Care* 13, R98–R98 (2009).	Anand *et al.* [29]	29 mice
Feinstein, A. J. *et al.* Resuscitation with Pressors after Traumatic Brain Injury. *J. Am. Coll. Surg.* 201, 536–545 (2005).	Beloncle *et al.* [25]	39 pigs
Feinstein, A. J., Cohn, S. M., King, D. R., Sanui, M. & Proctor, K. G. Early Vasopressin Improves Short-Term Survival after Pulmonary Contusion. *J. Trauma* 59, 876–883 (2005).	Voelckel *et al.* [28]	35 pigs
Gil-Anton, J. *et al.* Addition of terlipressin to initial volume resuscitation in a pediatric model of hemorrhagic shock improves hemodynamics and cerebral perfusion. *PLoS One* 15, e0235084 (2020).	Laou *et al.* [34▪▪]	17 pigs
Jochem, J. Central histamine-induced reversal of critical haemorrhagic hypotension in rats – a comparison with the pressor effect of arginine vasopressin. *Inflamm. Res.* 53, S61–S62 (2004).	Laou *et al.* [34▪▪]	48 rats
Johnson, K. B., Pearce, F. J., Jeffreys, N., McJames, S. W. & Cluff, M. Impact of Vasopressin on Hemodynamic and Metabolic Function in the Decompensatory Phase of Hemorrhagic Shock. *J. Cardiothorac. Vasc. Anesthesia* 20, 167–172 (2006).	Laou *et al.* [34▪▪]; Wenzel *et al.* [27]	16 pigs
Lima, R., Villela, N. R., & Bouskela, E. Microcirculatory effects of selective receptor blockade during hemorrhagic shock treatment with vasopressin: experimental study in the hamster dorsal chamber. *Shock* 38, 493–8 (2012).	Laou *et al.* [34▪▪]	30 hamster
Meybohm P., *et al.* Small Volume; A Randomized Controlled Trial With Either Norepinephrine or Vasopressin During Severe Hemorrhage. *J. Trauma* 62, 640–646 (2007).	Laou *et al.* [34▪▪]	14 pigs
Meybohm, P. *et al.* Release of protein S100B in haemorrhagic shock: Effects of small volume resuscitation combined with arginine vasopressin. *Resuscitation* 76, 449–456 (2008).	Nistor *et al.* [19]	30 pigs
Liu, L. *et al.* Small Doses of Arginine Vasopressin in Combination With Norepinephrine "Buy" Time for Definitive Treatment for Uncontrolled Hemorrhagic Shock in Rats. *Shock* 40, 398–406 (2013).	Cossu *et al.* [18]	260 rats
Morales, D. *et al.* Reversal by Vasopressin of Intractable Hypotension in the Late Phase of Hemorrhagic Shock. *Circulation* 100, 226–229 (1999).	Forrest *et al.* [31]	7 dogs
Raedler, C. *et al.* Treatment of Uncontrolled Hemorrhagic Shock After Liver Trauma: Fatal Effects of Fluid Resuscitation Versus Improved Outcome After Vasopressin. *Anesthesia Analg.* 98, 1759–1766 (2004).	Anand *et al.* [29]	21 pigs

Table 2 (*Continued*)

Primary studies	Systematic reviews that included the primary studies	Number of animals or patients included in the primary study
Sanui, M. *et al.* Effects of arginine vasopressin during resuscitation from hemorrhagic hypotension after traumatic brain injury* *Crit. Care Med.* 34, 433–438 (2006).	Anand *et al.* [29]	35 pigs
Stadlbauer, K. H. *et al.* Vasopressin improves survival in a porcine model of abdominal vascular injury. *Crit. Care* 11, R81 (2007).	Beloncle *et al.* [25]	19 pigs
Stadlbauer, K. H. *et al.* An observational study of vasopressin infusion during uncontrolled haemorrhagic shock in a porcine trauma model: Effects on bowel function. *Resuscitation* 72, 145–148 (2007).	Voelckel *et al.* [28]	23 pigs
Stadlbauer, K. H. *et al.* Vasopressin, but Not Fluid Resuscitation, Enhances Survival in a Liver Trauma Model with Uncontrolled and Otherwise Lethal Hemorrhagic Shock in Pigs. *Anesthesiology* 98, 699–704 (2003).	Beloncle *et al.* [25]	23 pigs
Voelckel, W. G. *et al.* Vasopressin Improves Survival After Cardiac Arrest in Hypovolemic Shock. *Anesthesia Analg.* 91, 627–634 (2000).	Gupta *et al.* [30]	18 pigs
Voelckel, W. G. *et al.* Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. *Crit. Care Med.* 31, 1160–1165 (2003).	Anand *et al.* [29]	21 pigs
Truse, R. *et al.* Exogenous vasopressin dose-dependently modulates gastric microcirculatory oxygenation in dogs via V1A receptor. *Crit. Care* 23, 353 (2019).	Laou *et al.* [34▪▪]	6 dogs
YOO, J.-H., KIM, M.-S. & PARK, H.-M. Hemodynamic Characteristics of Vasopressin in Dogs with Severe Hemorrhagic Shock. J. Vet. Med. Sci. 68, 967 (2006).	Laou *et al.* [34▪▪]	5 dogs
Cohn, S. M. *et al.* Impact of Low-dose Vasopressin on Trauma Outcome: Prospective Randomized Study. *World J. Surg.* 35, 430–439 (2011).	Beloncle *et al.* [25]	RCT 38 AVP patients vs. 40 controls)
Haas, T., Voelckel, W. G., Wiedermann, F., Wenzel, V. & Lindner, K. H. Successful Resuscitation of a Traumatic Cardiac Arrest Victim in Hemorrhagic Shock with Vasopressin: A Case Report and Brief Review of the Literature. *J. Trauma* 57, 177–179 (2004).	Haas *et al.* [21]	1 patient
Haren, R. M. V. *et al.* Vasopressor Use during Emergency Trauma Surgery. *Am. Surg.* 80, 472–478 (2014).	Hylands *et al.* [32]	Retrospective observational trial (225 AVP patients vs. 746 controls) [37]
Krismer, A. C. *et al.* Employing vasopressin as an adjunct vasopressor in uncontrolled traumatic hemorrhagic shock. Three cases and a brief analysis of the literature. *Anaesthesist* 54, 220–4 (2004).	Anand *et al.* [29]	3 patients
Morales, D. *et al.* Reversal by Vasopressin of Intractable Hypotension in the Late Phase of Hemorrhagic Shock. *Circulation* 100, 226–229 (1999).	Forrest *et al.* [25]; Haas *et al.* [21]; Laou *et al.* [34▪▪]; Raab [26]; Voelckel *et al.* [28]; Wenzel *et al.* [27]	2 patients
Plurad, D. S. *et al.* Early Vasopressor Use in Critical Injury Is Associated With Mortality Independent From Volume Status. *J. Trauma* 71, 565–572 (2011).	Beloncle [25]; Gupta [30]	Retrospective database analysis (351 AVP patients vs. 1349 controls)
Sharma, R. M. & Setlur, R. Vasopressin in Hemorrhagic Shock. *Anesthesia Analg.* 101, 833–834 (2005).	Anand *et al.* [29]; Wenzel V [27]	2 patients

Table 2 (*Continued*)

Primary studies	Systematic reviews that included the primary studies	Number of animals or patients included in the primary study
Sims, C. A. *et al.* Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock: A Randomized Clinical Trial. *JAMA Surg.* 154, 994 (2019).	Fage [24▪]; Laou [34▪▪]	One RCT (49 AVP patients vs. 51controls)
Sperry, J. L. *et al.* Early use of vasopressors after injury: caution before constriction. *J. Trauma* 64, 9–14 (2008).	Beloncle [25]; Hylands M [32] Voelckel W [28]	One multicenter prospective cohort study (119 vasopressor patients vs. 802 controls)
Tsuneyoshi, I., Onomoto, M., Yonetani, A. & Kanmura, Y. Low-dose vasopressin infusion in patients with severe vasodilatory hypotension after prolonged hemorrhage during general anesthesia. *J. Anesthesia* 19, 170–173 (2005).	Gupta *et al.* [30]	2 patients
Yeh, C.-C., Wu, C.-T., Lu, C.-H., Yang, C.-P. & Wong, C.-S. Early Use of Small-Dose Vasopressin for Unstable Hemodynamics in an Acute Brain Injury Patient Refractory to Catecholamine Treatment; A Case Report. *Anesthesia Analg.* 97, 577–579 (2003).	Raab [26]; Wenzel V [27]	1 patient

vasopressors after critical injuries observing an increased mortality [12,13,25]. Administration of vasopressors in general prior or instead fluid resuscitation might be considered potentially harmful due to hypoperfusion caused by vasoconstriction. In one randomized control trial, AVP was administered within 1 h after the patient's SBP fell below 90 mmHg. Although mortality rates did not differ significantly between the study and control group, AVP patients required significantly lower volume of resuscitation fluid [35]. Richards *et al.* [38] argue that multiple clinical scenarios exist, which may warrant early administration of AVP or NOREPI, along with appropriately titrated volume administration and resuscitation. When AVP was given late during the time course of trauma management, as a therapy of last resort in therapy refractory shock, or in hypovolemic cardiac arrest, at least temporary hemodynamic stabilization was observed in the case reports and animal studies cited in the reviews.

Are there significant side effects that may impair outcome?

Possible side effects and major complications produced by AVP have been summarized in one review and comprise severe gastrointestinal tract ischemia possibly leading to bowel necrosis, peripheral vasoconstriction leading to cutaneous gangrene, and severe hypertension causing cardiac complications such as myocardial ischemia, infarction or ventricular arrhythmias, including tachycardia and asystole [31]. AVP given during uncontrolled hemorrhagic shock shifts blood from the periphery towards the heart, lungs and brain, which may increase vital organ perfusion pressure, and decrease bleeding. In a porcine model of severe thoracic trauma accompanied by hemorrhagic shock, arginine vasopressin stabilized arterial blood pressure most likely because of the aforementioned effects, reduced the amount of fluid resuscitation, improved pulmonary function, and subsequently decreased mortality [39]. Further beneficial effects of AVP administration in prolonged and severe hemorrhage are the potent increase in filling pressures, and the decreasing need for exogenous catecholamines [40]. AVP pharmacodynamics induce a blood shifting away from a subdiaphragmatic bleeding site towards the heart and brain [20]. When AVP is administered in hypovolemic shock states, the possible negative side effects must be balanced against the net gain in perfusion pressure and subsequently blood flow, which is redistributed primarily towards vital organs, such as the heart and brain [41]. However, Fage *et al.* [24▪] detailed the AVP effects on kidney blood flow in shock states when compared with epinephrine and found a rather favorable AVP effect with improved renal blood flow and urine production due to specific vasoconstrictive properties of AVP. Moreover, assessment of bowel mucus membrane 7 days after AVP administration in hemorrhagic shock revealed no histopathological changes [67]. Noteworthy, most of the experimental models addressed in the analyzed reviews were not designed to detect possible negative side effects but rather to demonstrate that AVP can facilitate survival in otherwise lethal conditions.

CURRENT GUIDELINES

The European guideline on management of major bleeding and coagulopathy following trauma (sixth edition) recommends (No 14) the administration of noradrenaline in addition to fluids to maintain target arterial pressure when a restricted volume replacement strategy does not achieve the target blood pressure (Grade 1C) [14]. Although the potential benefits of AVP are detailed in the publication, there is no recommendation made for AVP. In the Level 3 guideline on the treatment of patients with severe/multiple injuries, as well as in the current ATLS guidelines, there is no recommendation for the use of vasopressors to correct hypotension in uncontrolled bleeding [15].

LIMITATIONS

Some limitations of this umbrella review must be noted. First, some important data might be missed because of the search strategy chosen. Moreover, given the number of purely narrative reviews (6/15) drafted aside with case reports detailing the lifesaving effect of AVP administration in critical conditions, there is a significant risk of bias. Design and execution of experimental and clinical studies are challenging. Accordingly, interpretation of study data and generalization of the findings is difficult because of the limited comparability.

CONCLUSION

In uncontrolled hemorrhagic shock, AVP might be considered as a therapy of last resort in shock patients not responding to conventional therapy. Further research is needed to determine the potential benefits and optimal dosage/timing of vasopressin use in hemorrhagic shock.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- ■■ of outstanding interest

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