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(Research Article)

The Effects of Vasopressin in the Critically ill Patient

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ABSTRACT

Introduction: Vasopressin has had a major impact on the evolution of the clinical situation of critically ill patients and on the choice of treatment. It acts on vasopressinergic receptors to maintain osmotic and baroreceptor homeostasis. It has complex and variable effects depending on serum levels, comorbidities and organs involved. **Objective:** The aim of this study is to clarify the role of vasopressin in critically ill patients with septic shock. **Material and Methods:** A systematic review of the literature by mobilising the descriptors "therapeutic vasopressin", "sepsis" and "critically ill patients", using the PICO method, in databases conceivable between 2018 and 2023 was selected, and seven articles were included in the analysis. **Results and discussion:** The majority of trials found that vasopressin has beneficial effects when used early in treatment as an adjunct to norepinephrine, but most trials reported secondary effects and small reductions in hospital length of stay and

mortality. It should be noted that one trial showed more beneficial effects in less severe septic shock. This effect was not seen in severe septic shock. Most trials mention the need for larger samples.
Conclusions: It can be concluded that vasopressin has widespread effects throughout the body and has several important clinical applications in the critically ill patient with septic shock. However, some aspects need to be considered and further studies with larger samples are always recommended.

Keywords: Vasopressin, critically ill adult patients, septic shock.

1. INTRODUCTION

The critically ill patient is a heterogeneous group of individuals who require complex care and constant monitoring, usually requiring hospitalisation in an intensive care unit (ICU). Critically ill patients are often haemodynamically unstable (or at risk of becoming unstable) due to hypovolemia, cardiac dysfunction or altered vasomotor function, leading to organ dysfunction, deterioration to multi-organ failure and ultimately death (Russell, 2019; Huygh et al, 2016). Under resting and normal conditions, approximately 25% of cardiac output is in the splanchnic circulation. Shock is characterised by redistribution of blood flow with vasoconstriction in the splanchnic circulation and peripheral tissues in an attempt to maintain perfusion of vital organs. Patients with haemodynamic instability require rapid and intensive treatment to restore homeostasis. Therapeutic measures may include fluid resuscitation, vasopressors and inotropic agents. These drugs are used to increase blood pressure to match organ and tissue perfusion (Ostinini et al, 2018; Ivie et al, 2017).
Septic shock, defined by the need to use vasopressors to maintain mean arterial pressure (MAP) above 65 mmHg after adequate fluid resuscitation and associated with a serum lactate level above 2 mmol/L, is the most common type of shock in hospitalised patients and an important cause of morbidity and mortality worldwide (Rocha et al, 2015; Takala et al, 2010). Septic shock, characterised by severe haemodynamic failure, remains a major challenge, associated with an in-hospital mortality of 30% to 40%, despite important therapeutic advances over the past decades (Girbes, 2020; Vicent et al, 2019). Fluid resuscitation is the first-line therapy to correct hypotension and low perfusion associated with both relative and absolute hypovolemia. However, as hypotension is also induced by sepsis-related systemic vasodilatation, vasopressor therapy is fundamental in septic shock, aiming to correct the depression of vascular tone and subsequently improve organ perfusion pressure (Rhodes et al, 2016; Russel et al, 2008; Krejci, et al, 2006).
Vasopressin (AVP) is a posterior pituitary hormone originally known for its antidiuretic effects. Currently, its main indication in intensive care is vasoplegic shock due to its vasopressor properties (Russell, 2019; Gamper, 2016). This potent vasopressor activity is related to the activation of V1 receptors located in vascular smooth muscle (Levy et all, 2011). This article reviews the scientific evidence for AVP therapy and its potential benefits as an adjunct to norepinephrine (NE) in vasoplegic shock.
NE is the first-line vasopressor recommended by the Surviving Sepsis Campaign Guidelines (SSCG) when fluid resuscitation alone is insufficient to raise MAP in critically ill patients with septic shock. Are catecholamines that activate alpha1 and beta1 adrenergic receptors and have a minimal effect on heart rate (Evans et al. 2021).

2. MATERIALS AND METHODS

A systematic review of the literature is one of the research methods used in evidence-based practice and its purpose is to gather and summarise the results of research on a particular topic in a systematic and orderly way, thereby contributing to knowledge about the topic (Mendes et al., 2008; Benefield, 2003). The methodology used is based on the PICO strategy (PICO stands for patient, intervention, comparison and outcomes). This maximises the inclusion of relevant information in different databases, focusing on the research object and avoiding unnecessary searches (Santos, Pimenta and Nobre, 2007).
Taking into account all the steps required to use this method, a protocol was developed to identify the studies of interest for this work, which consisted of a search in the search engines between August and November 2023: Ebsco and B-ONline, and in the following databases: CINAHL Plus, PubMed/ MEDLINE, LILACS, Scielo, Web of Science, ScienceDirect, Cengage Learning, Academia Search Complete, Psychology and Behavioural Sciences

Collection, John Wiley & Sons, Sport Discus, The Joanna Briggs Institute, U.S. National Library of Medicine, Directory of Open Access Journals, Springer Science & Business Media and Repository of Scientific Open Access of Portugal.

A search strategy using the following descriptors was used to identify relevant studies: vasopressin AND critically ill adults AND septic shock. Once all these protocol requirements were met, some articles that did not meet the requirements were eliminated using a methodical reductive process.

3. RESULTS

Seven articles were selected for the study, presented in Table 1.

Table 1: Description of selected studies and main results of investigations

Study (S)	Author(s)/ Year	Main Results
S1: "Cardiovascular Management in Sepsis: Improving Cardiac and Vascular Functions"	Lourenço, Lieber, Bach, Marlot and Pinto; 2023.	-AVP has been shown to be an important therapy to ensure that both the vascular and cardiac systems are as close to optimal as possible during septic shock. - AVP has been shown to improve the vascular response in catecholamine refractory patients, leading to improved patient outcomes. -It was concluded that by improving the cardiovascular management of septic shock, a further step can be taken towards improving the overall management of septic shock.
S2: "Timing of vasopressin initiation and mortality in patients with septic shock: analysis of the MIMIC-III and MIMIC-IV databases"	Xu, Cai and Zheng; 2023.	-This study was designed to investigate when the initiation of AVP may be beneficial for 28-day mortality in patients with septic shock. -The results of this study showed that AVP is commonly used as a second-line vasopressor in patients with septic shock, but the optimal timing of its initiation is uncertain. However, the study showed that high doses of NE (NE≥0.25 µg/kg/min) when AVP is initiated in septic shock led to excessive catecholamine exposure, more fluid overload, prolonged recovery of renal function, and poor outcome. -This study concluded that in adults with septic shock, AVP initiation with low-dose (NE<0.25µg/kg/min) NE was associated with an improvement in 28-day mortality. This demonstrates that AVP can be initiated earlier than recommended by guidelines. -The authors suggest further randomised controlled trials to confirm these results.
S3: "Vasopressin Response and Clinical Trajectory in Septic Shock Patients"	Bauer, Sacha, Siuba, Wang, Wang, Scheraga and Vachharajani; 2022.	-The study concluded that patients diagnosed with septic shock who received AVP treatment were more likely to have a better clinical outcome, with faster recovery and a lower likelihood of early death, compared to patients who did not receive AVP treatment.

		-The study suggests that AVP has emerged as a new prognostic marker for short-term clinical outcome.
S4: "Association of Catecholamine Dose, Lactate, and Shock Duration at Vasopressin Initiation with Mortality in Patients with Septic Shock"	Sacha, Lam, Wang, Duggal, Reddy, and Bauer; 2022.	-The study showed that early administration of AVP was associated with lower in-hospital mortality compared with later administration. -It concluded that lower mortality was associated with starting AVP administration at a dose equivalent to 10ug/min of norepinephrine or at a lactate concentration below 2.3mmol/L, i.e. when the patient was less hypoperfused.
S5: "Vasopressin Loading for Refractory Septic Shock: A Preliminary Analysis of a Case Series"	Nakamura, Nakano, Naraba, Mochizuki, Takahashi, Sonoo, Hashimoto, Abe, Hayakawa and Yamakawa; 2021.	-Twenty-one consecutive cases were analysed in this study, including 14 responders and 7 non-responders. Consecutive cases of septic shock in which AVP was initiated with loading under norepinephrine at >0.2 µg/kg/min during the study period were analysed. -The study shows that the primary outcome (patients with a negative change in catecholamine index (CAI) 6 h after AVP induction) accounted for 71.4% of responders and 0% of non-responders (those with a change in mean arterial pressure <18 mmHg 1 min after AVP induction, of whom none had a change in CAI <0), with a significant difference ($p = 0.0039$). Median changes in CAI at 2, 4 and 6 h after AVP administration were 0, -5 and -10 in responders and +20, +10 and +10 in non-responders, respectively. CAI was not reduced in any of the non-responders. -Outcomes, including mortality, were not significantly different between responders and non-responders. -Digital ischaemia (1/21) and mesenteric ischaemia (1/21) were also observed.
S6: "Vasopressors in septic shock: which, when, and how much?"	Shi, Hamzaoui, De Vita, Monnet and Teboul, 2020.	-Research shows that NE is now the first-line vasopressor for septic shock, with epinephrine and AVP remaining second-line therapy for refractory shock. -Studies in patients with distributive shock have shown a lower incidence of atrial fibrillation when AVP was added to norepinephrine compared with the use of norepinephrine alone. -It appears that early administration of NE is recommended to achieve the initial mean arterial pressure (MAP) goal of 65 mmHg more rapidly and to reduce the risk of fluid overload.

		-cautions that the optimal MAP target should be individualised, as it depends on several factors, and in cases of refractory hypotension, increasing NE at high doses (≥1 µg/kg/min) may be an option, although there is a current consensus in favour of adding other vasopressors such as AVP.
S7: "Predictors of response to fixed-dose vasopressin in adult patients with septic shock"	Sacha, Lam, Duggal, Torbic, Bass, Welch, Butler and Bauer; 2018.	-Retrospective cohort study to determine factors associated with haemodynamic response to fixed-dose AVP in patients with septic shock. -It was observed that at a mean initial dose of arginine AVP of 0.03 units/min, non-responders had higher rates of liver failure (19.3 vs. 14.3%), lower MAP values (65 vs. 69 mmHg) and higher lactate concentrations (5.4 ± 4.8 vs. 4.0 ± 3.6 mmol/L). -It was concluded that patients with less severe forms of septic shock seemed to benefit more from AVP than those with more severe forms, and responders had better outcomes with lower hospitalisation (57 vs. 72%) and ICU mortality (50 vs. 68%).

4. DISCUSSION

The studies found on this topic, since the majority of them (S1, S2, S3, S4, S6, S7) recognise that it was possible to verify vasopressin as a critical therapy to ensure that both the vascular and cardiac systems are as close as possible to optimal conditions during septic shock, facts that corroborate with Bahvesh et al, 2002; Bittainy et al, 2018; Russel, 2001 and Cuda et al, 2020. Only S5 showed that outcomes, including mortality, were not significantly different between responders and non-responders, facts that corroborate with Russel (2019).

The timing of AVP initiation still raises some questions. Studies 1, 3, 4 and 6 advocate a short-term initiation of AVP, as early administration was associated with lower in-hospital mortality compared to later initiation (Bittainy et al, 2018; Russel, 2001 and Cuda et al, 2020). On the other hand, the results of S2 showed that AVP is commonly used as a second-line vasopressor in patients with septic shock, but the optimal timing of its initiation is uncertain, facts that corroborate with Patel et al (2020) who report that the results show variability in the supporting literature on the optimal timing of AVP administration, as the correlation between the start of administration and improvement in clinical outcomes such as mortality or length of ICU stay is unclear. However, the majority support starting as soon as possible.

Studies 2 and 6 mention the SSCG 2021, which suggests adding AVP instead of escalating the dose of NE when it is in the range of 0.25-0.5 µg/kg/min. (Evans, et al (2021)). They also used it to define low and high doses of NE. Both conclude that the introduction of AVP at low doses of NE avoids the adverse consequences of excessive adrenergic load and point out that the addition of AVP to catecholamine vasopressors was associated with a lower risk of atrial fibrillation compared with catecholamines alone.

In a study by Kny et al, 2018, they reported high mortality in the first 72 hours of treatment with AVP in the sample evaluated. The use of AVP in NE-refractory patients had little or no effect on mortality (however, it could not be excluded that the high mortality in the study was related to the relatively late start of AVP after NE refractoriness had been established). These findings are consistent with those reported in studies S4 and S5.

Study 5 mentions that digital ischaemia was observed, a fact that Yao R, et al, (2020) conclude in a systematic review and meta-analysis study, pointing out that "an increased incidence of digital ischaemia should be noted in patients receiving agonists for AVP receptors". In addition, the study by Demiselle et al (2020) states that

the administration of AVP reduces the need for NE, but so far no improvement in survival has been reported and side effects are frequent, especially ischaemic events.
It appears that early administration of NE is recommended to achieve the initial MAP target of 65 mmHg more rapidly and reduce the risk of fluid overload, although there is a current consensus in favour of adding other vasopressors such as AVP. This is in line with Cuda et al, 2020; Russel, 2011 and Bhavesh et al, 2002.
The same line of thought is clarified by Demisell et al, 2020, when they state that in the presence of refractory hypotension, increasing the dose of NE (≥1 µg/kg/min) may be an option, but the addition of other vasopressors, such as AVP, is currently consensual but not entirely satisfactory.
However, S1 points in the opposite direction, stating that AVP ensures an improvement in the vascular response in catecholamine refractory patients and leads to better patient outcomes regardless of the time of onset, facts that are in line with Bhavesh et al, 2002.
With regard to shock severity, S7 states that it was concluded that patients with less severe forms of septic shock appeared to benefit more from AVP than those with more severe forms, and those who responded had better outcomes with lower rates of ICU admission and mortality, and S3 states that "it was possible to conclude that patients diagnosed with less severe septic shock who were treated with AVP were more likely to develop a better clinical course, with faster recovery and less likelihood of early death, compared with patients who were not treated with AVP. These facts are in line with the findings of Russel, 2011 and Cuda et al.

5. CONCLUSION

The diversity of problems faced by critically ill patients, due to the physiological changes of the pathological process, challenges healthcare professionals to adopt a holistic approach. A traditional and/or conventional approach to the problems of critically ill patients does not always meet their needs. We must therefore constantly update and evolve in order to reduce mortality and morbidity in these patients.
In relation to the results of the studies analysed, it can be noted that the justifications for the use of AVP in septic shock, according to most studies, are as follows: a deficiency of AVP in septic shock; secondly, low-dose AVP infusion improves blood pressure, reduces the need for NE and improves renal function; and recent studies that conclude and suggest AVP versus NE suggest that low-dose AVP may reduce mortality in less severe septic shock. However, some studies show that the use of AVP in patients refractory to NE has little or no effect on mortality.
In conclusion, most evidence suggests that it should be given as early as possible, even at low doses, as an adjunct to NE because of its benefits. It is more effective in less severe forms of shock, but not very effective when NE is already refractory. The possibility of hypoperfusion associated with NE should be noted. Few studies contradict these facts, so further studies with larger samples are often recommended.

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