Vasoactive drugs in the intensive care unit

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Purpose of the review

Vasoactive drugs are the mainstay of hemodynamic management of vasodilatory shock when fluids fail to restore tissue perfusion. In this review, studies published during the past year that increase our understanding of the use of vasoactive drugs in the intensive care unit are discussed.

Recent findings

In septic shock, there is no benefit in increasing mean arterial pressure from 65 to 85 mmHg. Norepinephrine did not worsen renal function. Epinephrine induced visceral hypoperfusion and hyperlactatemia, and worsened organ function and survival compared with norepinephrine and vasopressin. There are a number of reports of the safety and efficacy of vasopressin but it is not currently recommended as first line therapy, and if used, should be given as a continuous low dose infusion. Terlipressin is showing promise but decreases cardiac output. Metaraminol is being investigated as an alternative to norepinephrine. Dopamine may improve splanchnic flow mainly by increasing cardiac output. Dobutamine improves oxygen delivery and may improve mesenteric blood flow.

Summary

Over the last 40 years, there have been few controlled clinical trials to guide clinicians on the use of vasoactive drugs of treating shock states. It is not known whether the currently favored combination of norepinephrine and dobutamine is superior to traditional therapy with dopamine. Epinephrine is not recommended as the first-line therapy. The role of vasopressin and terlipressin remains unknown. Three large ongoing clinical trials will be completed soon and the results should clarify the role of these various agents.

Keywords

dobutamine, dopamine, epinephrine, metaraminol, norepinephrine, sepsis syndrome, septic shock, terlipressin, vasopressin

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Abbreviations

GMP gastric mucosal perfusion
ICU intensive care unit
MAP mean arterial pressure

1070-5295

Introduction

The purpose of vasoactive drug therapy in the intensive care unit (ICU) setting is to restore tissue perfusion in shock states. Hypovolemic, cardiogenic, and obstructive forms of shock are characterized by decreased cardiac output, arterial pressure, and profound vasoconstriction in the peripheral circulation. In vasodilatory shock there is a complex interaction between pathologic vasodilation, relative and absolute hypovolemia, myocardial depression, and altered blood flow distribution, which occur as a consequence of the inflammatory responsive to injury [1••]. Sepsis is the most frequent cause of vasodilatory shock; however, vasodilatory shock is also the final common pathway for prolonged and severe shock of any cause [2].

The hemodynamic management of shock is aimed at maintaining oxygen delivery above a critical threshold and increasing mean arterial pressure (MAP) to a level that allows appropriate distribution of cardiac output for adequate organ perfusion. Vasoactive drug therapy in the treatment of shock states aims to increase oxygen delivery or increase organ perfusion pressure or both.

Vasopressor agents increase MAP, which increases organ perfusion pressure and preserves distribution of cardiac output to the organs. Maintenance of an adequate systemic pressure is essential for adequate tissue perfusion. When MAP falls below the autoregulatory range of an organ, blood flow decreases, resulting in tissue ischemia and organ failure. Vasopressor agents also improve cardiac output and oxygen delivery by decreasing the compliance of the venous compartment and thus augmenting venous return.

Ventricular function can also be decreased in vasodilatory shock states either from a previous condition, or from myocardial depression due to sepsis. Because oxygen delivery is dependent on cardiac output, the successful resuscitation of these patients depends on identifying left ventricular dysfunction and correcting it by the use of inotropic agents [3].

Vasopressor and inotropic support in vasodilatory shock

Although many vasopressors have been used since the 1940s, few controlled clinical trials have directly compared these agents or documented improved outcomes due to their use [4••]. Thus, the manner in which these agents are commonly used largely reflects expert opinion, animal data, and the use of surrogate endpoints such as tissue oxygenation as a proxy for decreased morbidity and mortality.

An evidence-based consensus of vasopressor and inotropic support in septic shock was recently published by a subcommittee of the Surviving Sepsis Campaign [1••,5••]. The authors acknowledge 'making recommendations about the choice of individual vasopressor agents in septic shock is made difficult by the paucity of controlled trials and by the clinical reality that agents are frequently used in combination' [1••]. Based on the available evidence they make the following recommendations:

(1) Vasopressor therapy should be started when an appropriate fluid challenge fails to restore an adequate arterial blood pressure (Grade E).
(2) Low dose dopamine should not be used for renal protection (Grade B).
(3) Epinephrine and phenylephrine should not be used as first-line vasopressors in septic shock (Grade D).
(4) Dobutamine is the agent of choice to increase cardiac output in septic shock (Grade E).
(5) Inotropic agents should not be used to increase cardiac output above physiologic levels (Grade A).

Two areas of uncertainty are described: (a) Whether the combination of norepinephrine and dobutamine is superior to dopamine in the treatment of septic shock, and (b) whether vasopressin should be administered as vasopressor therapy in septic shock when conventional vasopressor therapy fails. Three large continuing trials in patients with septic shock are comparing epinephrine to combined dobutamine and norepinephrine, dopamine to norepinephrine [6•], and vasopressin to norepinephrine.

Mean arterial pressure goals

MAP is commonly used as a surrogate of organ perfusion in shock states; however, the recommended endpoints with regard to MAP remain controversial. Increasing MAP with vasopressor therapy improves tissue perfusion pressure but carries the inherent risk of regional vasoconstriction. In a prospective randomized controlled trial, increasing MAP from 65 to 85 mmHg through increasing doses of norepinephrine was accompanied by a significant increase in cardiac index and left and right ventricular stroke work indices; however, oxygen consumption and lactate levels were not affected [7]. Renal variables were also not improved by increasing MAP >65. This study demonstrates that there is no benefit from increasing MAP >65 mmHg in septic shock patients.

Specific vasoactive agents

The vasopressor agents effective in raising blood pressure in vasodilatory shock states are norepinephrine, epinephrine, dopamine, and vasopressin. Recently, terlipressin and metaraminol have been investigated for their vasopressors properties. Dopamine, dobutamine, and the phosphodiesterase inhibitors, milrinone and amrinone are considered inotropic agents. Phosphodiesterase inhibitors have fallen out of favor in the treatment of vasodilatory shock due to their long half-life and vasodilatory properties [1••,8••].

Norepinephrine

Norepinephrine is a potent α-adrenergic agonist and less potent β-adrenergic agonist and is considered first-line therapy for the maintenance of blood pressure and tissue perfusion in septic shock [8••]. Traditionally, dogma recommended that norepinephrine be avoided at all cost, as this agent caused severe vasoconstriction. However, data suggest that this is incorrect [9].

The renal effects of norepinephrine were investigated in 14 patients with septic shock and compared with 12 uninfected patients with head trauma in whom norepinephrine was infused to maintain cerebral perfusion pressure [10•]. Norepinephrine reestablished urine flow in 12 of the 14 septic patients with a decrease in serum creatinine levels and an increase in creatinine clearance rate after 24 hours. Urine parameters were not affected in the head trauma group. This study demonstrates the beneficial effects on renal function that accompany norepinephrine-induced vasoconstriction in septic shock.

Epinephrine

Epinephrine is a potent α and β-adrenergic agent that is not considered first-line therapy for septic shock because of its detrimental effects on regional circulation and blood lactate levels [1••]. It should be used for cases of extreme hemodynamic collapse.

In a hyperdynamic animal model of sepsis, the effect of epinephrine on regional circulation was studied [11]. Although epinephrine increased cardiac output, blood pressure, and myocardial performance, it was also associated with potent metabolic effects, decreased mesenteric, coronary, and renal conductance, and a significant reduction in renal blood flow.

The effect of epinephrine versus norepinephrine in a porcine model of prolonged shock induced by endotoxin infusion was investigated [12]. Epinephrine caused systemic hyperlactatemia and acidosis, induced a marked increase in lactate-to-pyruvate ratio in various visceral tissues, and was associated with decreased portal blood flow despite apparently maintained total splanchnic blood flow. Epinephrine increased gastric venous-to-arterial Pco2 gradients, indicating a visceral perfusion defect, as opposed to norepinephrine infusion. It also induced intraperitoneal lactate and glycerol release. These adverse hemodynamic and metabolic changes were not observed when norepinephrine was administered with the same arterial pressure goal.

Epinephrine was compared with vasopressin and norepinephrine in a canine model of septic shock [13••]. Epinephrine had a harmful effect on 28-day survival that was

significantly related to drug dose but not bacterial dose. Norepinephrine and vasopressin had beneficial effects on survival that were similar at all drug and bacteria doses. Compared with concurrent infected controls, epinephrine caused greater decreases in cardiac index, ejection fraction, and pH, and greater increases in systemic vascular resistance and serum creatinine than norepinephrine and vasopressin. These epinephrine-induced changes were significantly related to the dose of epinephrine administered. In this study, epinephrine adversely affected organ function, systemic perfusion, and survival compared with norepinephrine and vasopressin.

Vasopressin

Vasopressin is an endogenously released stress hormone that is important during shock. The rationale for its use in the ICU is that there is a vasopressin deficiency in vasodilatory shock and that exogenously administered vasopressin can restore vascular tone [2]. Vasopressin restores vascular tone in vasoplegic (catecholamine-resistant) shock states by at least four known mechanisms; through activation of V_1R's, modulation of K_{ATP} channels, modulation of nitric oxide, and potentiation of adrenergic and other vasoconstrictor agents [14,15••]. A recent review of the current studies of vasopressin in the ICU highlighted the evidence and rationale for use of vasopressin [16••]. There is growing evidence that vasopressin infusion in septic shock is safe and effective, and several studies support the hypothesis that vasopressin should be used as a continuous low-dose infusion (between 0.01 and 0.04 U/min in adults) in conjunction with other agents, and not titrated as a single vasopressor agent. However, multiple studies highlight the uncertainty that exists regarding the use of vasopressin in vasodilatory shock. The ongoing Vasopressin and Septic Shock Trial (VASST) [17] is a randomized controlled clinical trial that compares conventional vasopressor therapy (norepinephrine) versus vasopressin in septic shock with 28-day mortality as the primary outcome. This trial will complete enrollment in 2006 and will contribute to our understanding of the role of vasopressin in the treatment of septic shock.

Terlipressin

Terlipressin, an analog of vasopressin with a longer duration of action, is under investigation for the treatment of hypotension not responsive to conventional vasopressor therapy. The half-life of terlipressin is 6 hours, and the duration of action is 2 to 10 hours, compared with the short half-life of vasopressin (6 minutes) and duration of action (30 to 60 minutes). The disadvantage of terlipressin over vasopressin is that once a bolus of terlipressin is given its effects cannot be reversed easily, as with a continuous infusion of vasopressin. However, vasopressin is not available in every country. There have been several published studies in the last year investigating the effects of terlipressin in vasodilatory shock states.

A prospective open-label study of the physiologic effects of terlipressin in 17 adults with norepinephrine-resistant septic shock was reported [18]. Patients received either one or two 1 mg boluses of terlipressin and this therapy was associated with significant increases in MAP accompanied by significant decreases in cardiac index, heart rate, and oxygen delivery index. Mesenteric circulation was not evaluated, but liver function was affected with increases in bilirubin and hepatic transaminases. Renal function was improved with a significant increase in urine flow and creatinine clearance. Serum lactate was significantly decreased. Conventional catecholamines were able to be weaned.

The effect of 1 mg bolus terlipressin in 15 adult septic shock patients resistant to norepinephrine was studied in a prospective open-label study [19]. Terlipressin produced a decrease in cardiac output (all patients had an elevated cardiac output at baseline), a progressive increase in MAP ($P < 0.05$) and an increase in gastric mucosal perfusion (GMP), as detected by laser-Doppler flowmetry over 30 minutes. This effect was sustained for at least 24 hours. Terlipressin significantly increased urine output compared with baseline, associated with a significantly increased creatinine clearance. Terlipressin administration allowed the reduction of the high-dose norepinephrine in all patients. The main finding of this study was the significant increase in GMP, despite the fall in cardiac output, and a lack of effect on mucosal hypercarbia after an intravenous bolus dose of terlipressin, suggesting positive redistribution of cardiac output on the hepatosplanchnic macro- and microcirculation, resulting in an increase of blood flow toward the gut mucosa.

A retrospective review of 14 children with septic shock who were treated with terlipressin was conducted, evaluating the differences between those who succumbed and those who died [20]. All children were in advanced vasodilatory shock, unresponsive to increasing doses of dopamine, epinephrine, and milrinone. Six of the 14 study patients survived: there were eight successful terlipressin treatments for 16 episodes of septic shock. In these patients, terlipressin was associated with a significant improvement in hemodynamics and an increase in urine output and a decrease in serum creatinine. An important benefit was the ability to wean catecholamine agents, especially epinephrine, which probably accounted for the significant decrease in serum lactate levels. Terlipressin was also reported to be of benefit as rescue therapy in an 8-day-old infant with intractable hypotension due to septic shock after heart surgery [21]. Another group also reported a beneficial effect of terlipressin as rescue therapy in four pediatric patients with catecholamine-resistant septic shock [22]. These small physiologic observational studies suggest the use of terlipressin in pediatric septic shock clearly merits further study.

Metaraminol

Metaraminol is a sympathomimetic drug with a direct effect on vascular–adrenergic receptors and an indirect mechanism of action related to the stimulation of norepinephrine release. The effect of norepinephrine versus metaraminol on global hemodynamics, oxygen delivery and consumption, and gas exchange was studied in 10 patients with septic shock when both drugs were targeted to maintain the same value of MAP [23]. Both norepinephrine and metaraminol maintained MAP in septic shock patients without significant differences in global hemodynamics. There was no correlation between metaraminol and norepinephrine doses, suggesting that metaraminol does not act mainly by inducing norepinephrine delivery or by an identical stimulation on adrenergic receptors as norepinephrine. These findings suggest that further investigations are merited on the mechanism of action and the effect of metaraminol on regional perfusion and organ dysfunction in vasodilatory shock patients.

Dopamine

Dopamine is the immediate precursor of both norepinephrine and epinephrine. In healthy humans, there is a different receptor interaction with increasing doses. At low doses (0–5 μg/kg/min), dopaminergic receptors are activated leading to vasodilation of renal and mesenteric vascular beds. At midrange doses (5–10 μg/kg/min), β-adrenergic receptors are activated leading to positive inotropic and chronotropic effects on the myocardium. At higher doses (10–20 μg/kg/min), α-adrenergic receptors are activated leading to systemic vasoconstriction. The disadvantage of the 'dose-approach' is that the exact effect of a given dose of dopamine administered to critically ill humans is not known [24].

Theoretically, dopamine should be advantageous in the treatment of septic shock, as it leads to increased MAP through its mechanism of increasing cardiac output and peripheral resistance. However, the current approach to the hemodynamic treatment of septic shock is based on a pivotal randomized controlled trial of early goal-directed therapy in septic shock [3]. In this trial, oxygen delivery was inferred by measuring the central venous oxygen saturation and treated with red blood cell transfusions and/or dobutamine. MAP below 65 mmHg was increased with norepinephrine. This trial demonstrated a 16% absolute mortality reduction using agents that predictably act either as inotropic or vasopressor agents and treating to predetermined goals.

Dopamine has been investigated in two small trials in the last year because of its potentially beneficial vasodilatory effect on the splanchnic circulation. The effects of dopamine versus dobutamine versus dopexamine on systemic, on regional and local blood flow was studied in a porcine septic shock study [25•]. All three drugs significantly increased cardiac index compared with baseline: dopamine by 18%, dobutamine by 48%, and dopexamine by 35%. Microcirculatory blood flow did not change significantly in any of the organs studied with any of the drugs tested, despite this increase in cardiac index.

The effects of dopamine and norepinephrine on systemic and splanchnic hemodynamics and energy metabolism was investigated in 12 patients with hyperdynamic sepsis [26•]. Maintaining an adequate MAP, hepatosplanchnic blood flow, and oxygen exchange with dopamine required a consequent increased cardiac output, which was responsible for an increased global oxygen demand when compared with norepinephrine. Dopamine also impaired hepatic energy balance. The results of this small, uncontrolled observational study suggest that in vasoplegic septic patients, preferential treatment with dopamine compared with norepinephrine had no advantage.

Dobutamine

Dobutamine is a β-adrenergic agent that remains the 'gold standard' inotropic agent in the treatment of septic shock. In a consensus conference evaluating the evidence for early goal-directed therapy [27], the following Grade B recommendation is made:

> During the first 6 hrs of resuscitation of severe sepsis or septic shock, if a central venous oxygen saturation (Scvo2) of 70% is not achieved with fluid resuscitation to a central venous pressure of 8–12 mm Hg, then transfuse packed red blood cells to achieve a hematocrit of ≥30% or administer a dobutamine infusion (up to a maximum of 20 ug/kg/min) to achieve this goal.

The Rivers study [3] used dobutamine as the inotropic agent, and, along with the other aspects of the protocol, demonstrated a significant mortality difference.

A porcine endotoxic shock study compared the effects of vasopressin alone and in combination with dobutamine on systemic and splanchnic circulation and metabolism [28]. Vasopressin as a monotherapy decreased portal venous blood flow, and this effect was prevented by dobutamine titrated to maintain cardiac output. Vasopressin also induced splanchnic lactate release and arterial hyperlactatemia, which were not observed when dobutamine was combined with vasopressin. This study demonstrated that dobutamine prevented the adverse hemodynamic and metabolic effects of vasopressin in this model of septic shock.

Conclusion

The hemodynamic management of vasodilatory shock often requires use of vasoactive agents, after adequate fluid resuscitation, to preserve tissue perfusion. Vasoactive drugs should be used judiciously, with a goal-directed approach. The traditional agent of choice has been

dopamine. A more recent strategy is to titrate norepinephrine to a MAP goal of 60–70 mmHg and to titrate dobutamine to a central venous oxygen saturation goal of 70%. Currently, it is not known whether this strategy is advantageous over monotherapy with dopamine. Epinephrine has undesirable vasoconstriction, induces metabolic acidosis, and should be reserved for catastrophic shock. Vasopressin and terlipressin have favorable effects on systemic pressure in catecholamine-resistant shock; however, their survival advantage over norepinephrine remains to be substantiated.

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