Review Article

Vasoactive agents for the treatment of sepsis

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Abstract: The article describes some commonly used vasoactive agents in patients with septic shock. Depending on their distinct pharmacological properties, their effects on vascular bed and cardiac function are different. For example, dopamine has equivalent effect on heart and vasculature, which can result in increases in cardiac output, mean arterial pressure and heart rate. Dobutamine is considered as inodilator because it has potent effect on cardiac systole and vasculature. Patients with sepsis and septic shock sometimes have coexisting cardiac dysfunction that justifies the use of dobutamine. Levosimendan is a relatively new agent exerting its inodilator effect by increasing sensitivity of myocardium to calcium. Some preliminary studies showed a promising result of levosimendan on reducing mortality.

Keywords: Septic shock; sepsis; norepinephrine; dopamine

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Introduction

The cardiovascular system faces great challenge during systemic inflammatory response syndrome (i.e., although SIRS is no longer a diagnostic criteria for sepsis, it still reflects important characteristics of systemic response to infection), and the response of cardiovascular system (tachycardia and hypotension) has been used as important components in the list of diagnostic criteria for sepsis (1-4). Since it remains largely unknown whether such response is an adaptation to noxious stimulus or a mal-adaption to it, a variety of drugs have been used for the management of cardiovascular presentations of sepsis, severe sepsis or septic shock (5-7). In this review, we aimed to discuss vasoactive agents that can be used to treat sepsis. Vasoactive agents comprise broad categories of drugs that have vasoactive effects. These include but not limited to inotropes, vasopressors, vasodilators and inodilators. Literatures on the effectiveness of vasoactive agents in the treatment of sepsis were reviewed.

Methodology

We performed an electronic search of PubMed by using terms related to sepsis (sepsis, septic, bacteremia, septicemia) and vasoactive agents (vasoactive, inotrope, inodilator, dobutamine, dopamine, epinephrine, epinephrine, epinephrine, vasopressin, terlipressin, phenylephrine, esmolol, beta-blocker, levosimendan) from inception to January 2016. More recent evidence was added during revision. We restricted searching results to clinical studies using the filter function provided by PubMed. The article was a narrative review and no meta-analysis was performed.

Categories of vasoactive drugs

In this section, we have a general description of vasoactive drugs. Their pharmacological action sites, dosage and vasoactive effect will be described.

Vasoactive medications included inotropes, vasopressors,

Table 1 Pharmacological properties of vasoactive medications

Vasoactive agents	Heart	Vasculature		Other	Hemodynamic effect	Initial dose[¶]	Dose range[¶]
	β1	α1	α2				
Dopamine (dose >5 μg/kg/min)	0~3+	0~3+	0~2+	–	CO↑; MAP↑; HR↑↑	2–10	2–20
Dobutamine	4+	+	2+	–	CO↑↑; MAP↔; HR↑	2.5–5.0	2.5–10.0
Adrenalin	4+	2~4+	1~3+	–	CO↑↑; MAP↑↑; HR↑↑	0.020–0.050	0.005–0.200
Norepinephrine	2+	4+	1+	–	CO↔; MAP↑↑; HR↑	0.01–0.04	0.04–1.00
Phenylephrine	0	4+	0	–	CO↓; MAP↑; HR↔	0.1–0.3	0.1–1.5
Vasopressin/ terlipressin	0	0	0	Vasoconstriction via vasopressin receptor	CO↓; MAP↑; HR↔	0.01–0.04 U/min	0.01–0.04 U/min
Milrinone	0	0	0	Phosphodiesterase-3 inhibition	CO↑↑; MAP↓↔; HR↑	0.25	0.25–0.75

[¶], in the unit of μg/kg/min if not specified.

vasodilators and inodilators (8). Some agents have overlapping functions. *Table 1* lists commonly used vasoactive agents in the treatment of sepsis, as well as their action sites, hemodynamic effects and typical dosages. Dopamine and norepinephrine are the most commonly used vasoconstrictor in the initial phase of septic shock. Dopamine in a large dose activates α1 receptor and has potent vasoconstriction effects. Norepinephrine has great potency in increasing blood pressure via α1 receptor, but its inoconstriction effect is not so potent as dopamine. Epinephrine has equivalent effect on heart and vasculature and it is second line medication in resuscitation of septic shock. Phenylephrine is not a typical drug for use in septic shock.

Dopamine and norepinephrine

Dopamine and norepinephrine are probably the most widely investigated vasoconstrictors in the treatment of septic shock. Epidemiological surveys showed that norepinephrine was the most favored vasopressor in the treatment of septic shock (>70%), followed by dopamine (9). There are numerous head-to-head randomized controlled trials (RCTs) in this field (10-15). In a recent systematic review and meta-analysis, norepinephrine was found to be superior to dopamine in reduction of mortality rate [odds ratio (OR): 1.24; 95% confidence interval (CI): 1.01–1.53; norepinephrine as reference], adverse cardiac events (OR: 0.15; 95% CI: 0.05–0.43; dopamine as reference), heart rate [standardized mean difference (SMD): –2.10; 95% CI: –3.95 to –0.25; P=0.03], and cardiac index (SMD: –0.73; 95% CI: –1.14 to –0.03; P=0.004) (16). Norepinephrine increased systemic vascular resistance index (SVRI) more effectively than dopamine (SMD: 1.03; 95% CI: 0.61–1.45; P<0.0001). Similar results were replicated in other systematic reviews (17-19). Avni's study reported that norepinephrine as compared with dopamine was associated with reduced all-cause mortality (RR: 0.89; 95% CI: 0.81–0.98; I^2=0%), corresponding to an absolute risk reduction of 11% and number needed to treat (NNT) of 9. That means nine patients need to be treated to prevent one additional death (19). However, the Havel's review failed to identify beneficial effect of norepinephrine on mortality reduction over dopamine (20). Together with the marginal significant level in the Zhou's study, we conclude that the mortality reduction effect is still controversial that requires further investigations. However, in pediatric patients with septic shock, dopamine use was found to be associated with doubled mortality rate as compared with norepinephrine (14.2% *vs.* 7%; P=0.033). Furthermore, dopamine was strongly related to healthcare-associated infection (OR: 67.7; 95% CI: 5.0–910.8; P=0.001) (21). The great effect size in pediatric population may be explained by different responses of pediatric patients to vasopressors. Furthermore, the study used peripheral or intraosseous line for the administration of vasopressors. It remains to be investigated whether administration route has impact on the effects of vasopressors.

Epinephrine

Epinephrine has potent inoconstriction and vasoconstriction effect. It is less commonly used as the first line therapy for septic shock. But there are still many investigations on the effectiveness of epinephrine (14,15,22-26). Subjects in these trials were randomized to receive either epinephrine alone or norepinephrine plus dobutamine, because norepinephrine has only moderate effect on the cardiac β1 receptor. As compared to the norepinephrine plus dobutamine regimen, epinephrine has no significant effect on mortality reduction (OR: 0.86; 95% CI: 0.57–1.30) (16). However, epinephrine was associated with greater cardiac index than that in norepinephrine plus dobutamine group (MD: −0.87, 95% CI: −1.16 to −0.57 mL/min/m^2). Septic shock is typically associated with hyperdynamic circulation and thus epinephrine has no superiority in this regard. However, for some patients with compromised cardiac function, epinephrine can be a useful alternative medication. Currently, there is no evidence to recommend epinephrine as the first line vasopressor for the treatment of septic shock.

Dobutamine

Cardiac dysfunction is common in patients with sepsis and septic shock. Such cardiac dysfunction can be either chronic (i.e., preexisting cardiac dysfunction due to prevalence of cardiac diseases) or acute (i.e., induced by systemic inflammatory response). Irrespective of the causes, some experts recommend the use of dobutamine if there existing pump failure as manifested by elevated cardiac filling pressure and low cardiac output (27,28). Clinical studies yielded conflicting results with respect to the effect of dobutamine on left ventricular stroke work index, mean arterial pressure and mean pulmonary artery pressure (29-33). These results have been summarized in a recent systematic review (34). Collectively, dobutamine was able to increase stroke work index (SMD: 0.375±0.112; P=0.001) and pulmonary artery pressure (SMD: 0.085±0.114; P=0.458), but lower mean arterial pressure (SMD: −0.204±0.155; P=0.188). On the other hand, dobutamine appears to be effective in reducing heart rate (SMD: −0.714±0.083) and increasing cardiac index (SMD: 0.783±0.078). To strike a balance between oxygen demand and supply is an important end point during resuscitation and many clinical studies have explored this endpoint (35). In the same meta-analysis, the authors found that oxygen delivery was reduced by dobutamine (SMD: −0.89±0.083; P<0.001), whereas oxygen extraction was increased (SMD: 0.647±0.087; P<0.001). However, there is little evidence showing that the improvement in cardiac parameters can translate into more important patient outcomes. A large RCT randomized patients with septic shock to receive either epinephrine (n=161) or epinephrine plus dobutamine (n=169), and found there is no significant difference in mortality rate (50% *vs.* 52%), as well as other secondary outcomes (14). Other studies also failed to draw a definitive conclusion (15,23-25).

Vasopressin and terlipressin

Vasopressin, also known as arginine vasopressin, is a neurohypophysial that can be found in most mammals. Its physiological functions include water retention and vasoconstriction (36). In the treatment of septic shock, its potent vasoconstriction property is of great interest. The common practice is to use vasopressin in patients with refractory shock. In the well-known VASST study, patients were randomized to either vasopressin or norepinephrine group when they had septic shock and were at minimum dose of 5 μg/min of norepinephrine (37). Although vasopressin is regarded as a promising medication in the treatment of refractory septic shock, evidence from RCTs failed to identify beneficial effect on mortality outcome (37-40). In a systematic review, Zhou and colleagues found that there was no significant difference in mortality between norepinephrine and vasopressin groups (RR: 1.07; 95% CI: 0.97–1.20; P=0.19) (18). As compared with norepinephrine, vasopressin showed no significant effect on other secondary outcomes or intermediate variables including mean arterial pressure (SMD: 0.15; 95% CI: −0.15 to 0.44; P=0.33), heart rate (SMD: 0.21; 95% CI: −0.08 to 0.50; P=0.15), cardiac index (SMD: −0.10; 95% CI: −0.64 to 0.44; P=0.73), SVRI (SMD: 0.15; 95% CI: −0.39 to 0.70; P=0.58), oxygen delivery (SMD: −0.06; 95% CI: −0.62 to 0.49; P=0.82), oxygen consumption (VO_2) (SMD: 0.03; 95% CI: −0.52 to 0.59; P=0.91) or lactic acid (SMD: 0.07; 95% CI: −0.23 to 0.36; P=0.66). Adverse event of acute coronary syndrome should be suspected in patients with chest pain and elevated cardiac enzymes during treatment with vasopressin (38). In conclusion, vasopressin can be an alternative medication but is not recommended as a first line treatment of septic shock.

Terlipressin is an analogue of vasopressin and can be used as a vasoactive drug in the management of low blood pressure induced by septic shock. Similar to vasopressin, it

can be used as a rescue therapy for septic shock when shock is refractory to conventional treatment (41). Following Obrien's seminal paper describing the use of terlipressin in clinical practice, many investigators began to explore the effectiveness of terlipressin in standard way (19,39,42-44). Terlipressin was found to have equivalent effect on raising MAP, but it was associated with decreased cardiac index and oxygen consumption (42). In another study using terlipressin as the first line therapy, it reduced norepinephrine requirement and the rate of rebound hypotension was lower than the control group (39).

Phenylephrine

Phenylephrine is a potent vasoconstrictor without significant effect on cardiac function. The highly selective action site of phenylephrine makes it unique in all vasopressors. From hemodynamic perspective, it increases mean arterial pressure, but lowers cardiac output. There is no effect on heart rate. As compared with norepinephrine, phenylephrine has no additional beneficial effect on cardiopulmonary performance, global oxygen transport, and regional hemodynamics in the initial resuscitation of septic shock (45). In a small RCT, phenylephrine is superior to norepinephrine in reducing heart rate and increasing systemic vascular resistance (46). As compared to other vasopressors, phenylephrine receives fewer attentions in medical literature. Before new evidence emerges, we suggest use of phenylephrine in patients with prominent tachycardia and low systemic vascular resistance.

Beta-blockers

Sepsis or its severe form septic shock is always associated with tachycardia, and tachycardia *per se* is an item in the list of sepsis diagnostic criteria. Pathophysiologically, tachycardia is associated with more oxygen consumption, making oxygen debt more prominent in patients with severe sepsis and septic shock. Therefore, it is reasonable to rest heart by reducing its beating rate. This theoretical hypothesis has been verified in burn children (47).

While it is theoretically plausible, experimental and clinical studies yielded conflicting results (5-7,48,49). Observational studies showed that esmolol, the most commonly used beta-blocker in septic shock, was associated with economization of cardiac work and oxygen consumption. Such cardiac performance was characterized by reduced heart rate, maintained cardiac output and decreased dP/dt MAX (50,51). Also there are some evidence that esmolol administration was associated with reduced norepinephrine requirement (52). The most important clinical trial that has been published is probably the one performed by Morelli and colleagues. The study showed that esmolol reduced 28-day mortality rate by nearly 50% (80.5% *vs.* 49.4%; P<0.001) (53). This was a large effect size and if verified in large multi-center trials it can be a milestone in the history of the treatment of septic shock. Two main concerns have compromised the generalizability of the study. First, the mortality in the control group was exceedingly high as compared to general ICU patients with septic shock (80% *vs.* 40–60%) (50). Although the authors explained the high mortality by the presence of multidrug-resistant Gram-negative organisms, this is not convincing. However, we still suggest the use of short-acting beta-blockers to rest the heart in patients with severe sepsis and/or septic shock.

Concerns regarding the negative inotropic action of beta-blocks have been raised in septic shock. Therefore, some studies have investigated the combined use of beta-blockers and inotropes (milrinone) (51,54). Preliminary results suggested that the combination had positive effect on improving cardiac performance and mortality risk. This is an interesting area of research that warrants further trials to confirm or refute the current results.

Levosimendan

Levosimendan exerts its inotropic effect by increasing sensitivity of myocardium to calcium. The rationale for its use in septic patients is that myocardial depression is prevalent in these patients (55,56), and levosimendan is used to enhance myocardial contraction via mechanisms different from vasoactive agents discussed previously. Other therapeutic effects of levosimendan include reduction of oxidative burst activity of polymorphonuclear leucocytes (PMNs), immunomodulation and antiapoptotic properties (57). Experimental studies using animal models of septic shock showed that levosimendan was able to improve haemodynamic variables, attenuate metabolic acidosis, and ameliorate organ dysfunctions (i.e., liver, kidney and lung) (58,59). Similar beneficial effects were observed in human studies (60,61). However, there is also evidence that inotropic medication (15.6% of inotropes were levosimendan) was associated with increased risk of death (62).

RCTs are at the top of the pyramid of evidence grade (63-65). Therefore, this section focuses on RCTs in this

area, aiming to provide the highest evidence for clinical practice. Looking at the mortality outcome as the study endpoint is reasonable because it is the most important outcome in critically ill patients. Other therapeutic effects on intermediate variables may be of limited clinical significance if they cannot be translated into improvement in mortality outcome. To the best of our knowledge, there are seven RCTs investigated the effectiveness of levosimendan on mortality outcome (61,66-69). Results of these RCTs were combined in a recent meta-analysis, which showed that levosimendan was associated with significantly reduced risk of death as compared to the conventional inotropes (47% *vs*. 61%; risk difference =–0.14; risk ratio: 0.79; 95% CI: 0.63–0.98; P=0.03). The NNT was seven (70). However, because the effect size is not very large and levosimendan is very expensive, formal recommendation of levosimendan for severe sepsis and septic shock requires evidence from cost-effectiveness studies. Furthermore, potentially severe side effects of levosimendan (severe vasoplegia that might be difficult to control) should be noted in patients already presenting with severe vasoplegic shock.

Summary

Cardiovascular system is under great challenge in sepsis and septic shock. Therefore, various vasoactive agents and treatment strategies have been introduced and tested in clinical trials. Septic shock is characterized by vasoplegia, resulting in inadequate of effective circulatory volume. Vasopressors such as norepinephrine and dopamine are potentially beneficial to counteract inappropriate vasodilation during septic shock. However, their pharmacologically promising effect cannot be translated into mortality benefits and there are still controversies in the literature. Tachycardia is a hallmark of sepsis. There is evidence that tachycardia is a maladaptation to infection and heart rate reduction can rest the heart. Preliminary trial found that esmolol was effective in reducing 28-day mortality by reducing heart rate. Cardiac dysfunction is common in patients with sepsis and septic shock, which justifies the use of inotropes. Levosimendan is shown to be potentially beneficial in reducing mortality risk, but its high cost has limited its use in low-income and middle-income countries.

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Footnote

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