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REVIEW

Inotropic drugs in septic shock

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ABSTRACT:

Septic shock is a life-threatening condition characterized by a complex underlying mechanism that requires a multidimensional treatment approach. Sepsis-induced cardiomyopathy plays a significant role in the development of multiple organ failure. The focus of this review is to determine the evidence-based data of the commonly used inotropic drugs in the management of septic shock during clinical hypoperfusion and reduced myocardial performance. Current guidelines recommend adding dobutamine to norepinephrine or using epinephrine alone in septic-induced cardiomyopathy, while suggesting against the use of levosimendan. Although dobutamine increases cardiac contractility and heart rate, it also decreases systemic vascular resistance. Epinephrine has a greater potency than dobutamine but does not demonstrate a clinical difference in hemodynamic improvement. Milrinone is preferred for cases involving pulmonary hypertension and right ventricular failure but should be avoided in the presence of renal dysfunction. Levosimendan improves cardiac performance and promotes coronary blood flow, but later evidence mentioned significant arrhythmia compared to other inotropic agents. Due to the narrow therapeutic window of these agents, precise therapeutic targets are crucial.

Keywords: Septic shock; Inotropic drugs; Dobutamine; Epinephrine; Phosphodiesterase III inhibitor; Levosimendan

INTRODUCTION

Septic shock is defined as a dysregulated host response to infection in which underlying circulatory and cellular metabolism abnormalities result in inadequate oxygen delivery to tissues, leading to systemic inflammation and organ dysfunction [1]. Septic shock is a subset of sepsis with a greater risk of mortality. Globally, septic shock stands as a significant contributor to morbidity and mortality in the intensive care units (ICUs), leading to substantial economic burdens [2]. Common causes of death from septic shock are refractory shock and multi-organ failure. Around 10-20% of individuals experiencing refractory hypotension (need for dopamine >15 mg/kg/min or norepinephrine >0.25 mg/kg/min to maintain mean arterial pressure (MAP) above 60 mmHg or 80 mmHg if previous hypertension) may have a significant likelihood of reduced cardiac output due to severe myocardial dysfunction [3]. In several studies, sepsis-induced cardiomyopathy is present in more than 40% of cases with sepsis.

PATHOPHYSIOLOGY OF SEPSIS-INDUCED CARDIOMYOPATHY

The pathophysiology of sepsis-induced cardiac dysfunction can be induced by many factors. Some suggested mechanisms include impaired myocardial circulation, direct myocardial depression, and mitochondrial dysfunction. During sep-

tic shock, blood flow to the systemic and myocardial areas is reduced, causing macro-circulatory and micro-circulatory dysfunction. Moreover, multiple cytokines released during septic shock, causing endothelial dysfunction and fluid maldistribution, resulted in myocardial circulatory impairment. One of the key mechanisms behind direct myocardial depression is a decreased beta (β)-adrenergic receptor component, so called down regulation of β-adrenoceptors, which impairs the response of catecholamines or reduces the production of catecholamines during septic shock. The process is mediated by various pro-inflammatory substances, mainly cytokines and nitric oxide. Other mechanisms causing myocardial injury are toxin, complements, and apoptosis of cardiac myocytes. Mitochondrial dysfunction is another key mechanism associated with cardiac dysfunction during septic shock through abnormal calcium transport, mitochondrial damage, and injury-causing energy depletion [4]. During these processes, both ventricles have the potential to dilate and reduce theirejection fraction, resulting in a lessened response to fluid resuscitation and catecholamine infusion.

Pre-existing coronary artery disease also contributes to insufficient myocardial perfusion during sepsis-induced hypotension, which aggravates the vicious cycle of impaired left ventricular ejection fraction, leading to decreased cardiac output.

Apart from initial fluid management, antimicrobial administration, and infectious source control, a vasopressor is recommended as an initial add on treatment for adults with septic shock to maintain a target MAP over 65 mmHg. While norepinephrine is recommended as the first-line vasopressor, there are still patients with septic shock who have not achieved targeted MAP levels despite the high dose of norepinephrine. Therefore, adding vasopressin or other inotropic drugs to maintain adequate MAP is suggested [2]. However, aggressive use of vasopressor treatment can lead to an uneven increase in systemic vascular resistance (SVR) when compared to the enhancement of cardiac contractility through B1 receptor stimulation.

Typically, inotropic drugs are indicated when myocardial function is depressed with adequate left ventricular filling pressure and adequate MAP, yet persistent clinical hypoperfusion. Inotropes, including inodilators and inoconstrictor aim to enhance cardiac output through increased contractility. The mechanism of inodilators like dobutamine, milrinone, and levosimendan, in addition to enhancing cardiac contractility, involves reducing afterload through systemic vasodilation. In contrast, inoconstrictors such as adrenaline, dopamine, or high-dose norepinephrine increase afterload. Surviving Sepsis Campaign (SSC) Guidelines 2016 recommended dobutamine as the first-choice inotrope in septic shock with cardiac dysfunction, whereas epinephrine, phosphodiesterase III inhibitors, and levosimendan are alternative drugs. In 2021, SSC guidelines suggested adding dobutamine to norepinephrine or using epinephrine alone in patients with septic shock and cardiac dysfunction and, none the less, against the use of levosimendan.

The objective of this review is to provide a comprehensive overview of the current evidence regarding the usage of inotropic drugs in patients with septic shock. This review will focus on both inodilators and inoconstrictors mentioned earlier (Dobutamine, Epinephrine, Phosphodiesterase III inhibitor (milrinone), and Levosimendan).

KEY MESSAGES:

Inotropic drugs are indicated for septic shock patients when there is reduced myocardial function despite sufficient left ventricular filling pressure and adequate MAP, coupled with ongoing clinical signs of hypoperfusion. A comprehensive understanding of the mechanism of action and clinical evidence of each drug contributes to the improvement of the care and management of critically ill patients.

Dobutamine

Dobutamine is an exogenous catecholamine that has both inotropic and chronotropic effects, depending on the dosage of the drug. Through stimulation of the myocardium through the binding of the β_1 receptor, dobutamine increases intracellular calcium levels, leading to enhanced cardiac contractility, increased stroke volume, and increased cardiac output with weaker chronotropic activity. Dobutamine also has mild to moderate β_2 receptor activity via nitric oxide production, which contributes to the reduction of systemic vascular resistance (SVR). Another effect of dobutamine is an action through Alpha (α)1 activity on vasoconstriction effects. Thus, dobutamine at a mild to moderate dose (≤ 5 mcg/kg/min) increases contractility and heart rate while lowering the systemic vascular resistance, except at a high dose (>10-15 mcg/kg/min), when dose dependent α1 receptor agonism may become more prominent [5]. Vasoconstriction progressively dominates at higher infusion rates. The half-life of dobutamine is short, at 2 minutes. Cardiac output (CO) and systemic vascular resistance (SVR) outcomes of dobutamine infusions can be uncertain and unproportionate. While an elevation of CO might lead to an increase in MAP, conversely, it could induce significant vasodilation, potentially leading to a reduction in MAP. Additionally, the inotropic response may be blunt in sepsis with a preserved chronotropic effect by causing tachycardia without a corresponding rise in stroke volume [6]. The reason for this phenomenon is that as the heart rate increases, diastolic filling time becomes shorter. This leads to a reduction in left ventricular end-diastolic volume (LVEDV) but an increase in left ventricular end-diastolic pressure (LVEDP), resulting in a decrease in stroke volume during each cardiac cycle.

The guideline recommendations are based mainly on the randomized controlled trial involving early goal-directed therapy to optimize factors such as cardiac preload, afterload, and contractility. This approach aims to balance oxygen delivery with oxygen demand. In this trial, the treatment group with gold-directed therapy demonstrated a statistically significant reduction in

mortality. Notably, only 14% of the patients in the trial received dobutamine as the first-line inotrope [7].

In 2012, Enrico et al. conducted a study aimed at characterizing the cardiovascular responses to dobutamine and their predictors in septic shock patients. The results showed that dobutamine had variable hemodynamic effects. It increases heart rate, cardiac index, and stroke volume index, while mean blood pressure remains unchanged and systemic vascular resistance decreases. In the group where stroke volume index increased, there were lower changes in mean blood pressure and a higher rise in cardiac index. These changes significantly correlate with echocardiographic left ventricular ejection fraction. However, the capillary density of the sublingual microcirculation remains unchanged. [8]

Another study conducted early in 2013 aimed to assess the potential benefits of dobutamine on hemodynamic, metabolic, peripheral, hepatosplanchnic, and microcirculatory perfusion parameters during the initial resuscitation of septic shock. The findings were discouraging, as dobutamine did not yield positive results in terms of enhancement of microcirculatory perfusion parameters, even though it significantly increased systemic hemodynamic variables in septic shock patients who do not have low cardiac output but are experiencing persistent hypoperfusion. [9]

Later in 2013, a retrospective analysis involving 420 patients with septic shock revealed an independent correlation between the administration of inotropic agents, particularly dobutamine (utilized by 90% of the participants), and the increment of 90-day mortality. This association persisted even after adjustment with a propensity score [10]. In 2021, the European Society of Intensive Care Medicine (ESICM) published an anonymous web-based survey on the use of cardiovascular drugs. The survey revealed that two-thirds (66%) of respondents initiated the use of inotropic drugs when there were persistent clinical signs of inadequate tissue perfusion or persistent elevated lactate levels, despite an adequate administration of fluids and vasopressor agents. Dobutamine was the first line for 84% [11].

Recent randomized controlled trials determine the effects of dobutamine and placebo on clinical outcomes, but no conclusive evidence is still awaiting. The latest randomized controlled multi-center trial of adjunctive dobutamine in septic cardiomyopathy with tissue hypoperfusion (ADAPT trial) is still in the process (estimated completion in December 2024, ClinicalTrials.gov Identifier: NCT04166331).

Epinephrine

Epinephrine is a sympathomimetic catecholamine that has pharmacologic effects on both alpha and beta-adrenergic receptors. The effect on the α_1 receptor induces increased vascular smooth muscle contraction, causing increased SVR. Epinephrine also enhances cardiac output by binding to myocardial β_1 receptors to increase heart rate (chronotropy) and cardiac contractility (inotropy). Coronary blood flow is enhanced through stimulation of myocytes to release local vasodilators, which counterbalance direct α_1 mediated coronary vasoconstriction. β_2 effects of epinephrine produce bronchodilation, which may be useful as an adjunctive treatment of acute asthmatic exacerbations, and vasodilation and tocolysis. Epinephrine's inotropic potency is approximately 100 times greater than that of dobutamine or dopamine. Consequently, a lower dose of epinephrine is used to achieve a therapeutic augmentation of CO and/or heart rate through strong receptor stimulation. When administered parenterally, epinephrine has a rapid onset but a short duration of action. Its half-life is less than 5 minutes. The use of epinephrine could be restricted due to its tendency to promote the occurrence of atrial and ventricular arrhythmia, elevate myocardial oxygen consumption, and decrease splanchnic blood flow. An additional effect of epinephrine is its ability to cause a rise in glucose level and lactate production by stimulating hepatic β_2 receptors to provide fuel for muscle metabolism [5,12].

In 2007, an evaluation of the effect of a combination of dobutamine plus norepinephrine was found to be equivalent to epinephrine alone in one large RCT on septic shock patients targeting MAP at 70 mmHg or more (28-day all-cause mortality in the norepinephrine plus dobutamine group was 64 (40%) and the epinephrine group was 58 (34%), p=0.31; relative risk 0.86, 95% CI 0.65-1.14). There was no significant difference between both groups regarding mortality rates at discharge, time to hemodynamic success, time to vasopressor withdrawal, and the time course of the SOFA score. Besides, the rate of serious adverse events was also similar [13].

A study comparing epinephrine to norepinephrine in patients with septic shock (CAT study, 2008) showed no difference in time to achieve MAP gaol > 24 h without a vasopressor. No difference in mortality or the number of vasopressor-free days was observed. Moreover, a higher incidence of lactic acidosis and arrhythmia was found in the epinephrine-treated group [14]. A network meta-analysis in 2016 indirectly comparing dobutamine and epinephrine on mortality in patients with severe sepsis and septic shock showed no clear benefit on mortality (OR 1.18; 95% CI 0.47-3.97) [15].

To date, no evidence supports the superiority of dobutamine over epinephrine. The 2021 version of the SSC Guideline proposes that in septic shock patients with cardiac dysfunction and persistent hypoperfusion, one can consider adding dobutamine to norepinephrine or using epinephrine alone. It is best to evaluate the favorable and unfavorable outcomes of both medications. Discontinue either one if there is no improvement in clinical hypoperfusion or if adverse effects are observed.

Phosphodiesterase III inhibitor (Milrinone)

A phosphodiesterase III (PDE3) inhibitor, or Milrinone, mimics β-adrenergic receptor activation by increasing intracellular cyclic AMP breakdown. This, in turn, enhances the activity of protein kinase A, resulting in the phosphorylation of calcium ion channels in sarcoplasmic reticulum. Consequently, there is an increase in the availability of intracellular calcium. This mechanism operates independently of β-adrenergic receptors, augmenting cardiac contractility. The inotropic effect of milrinone inhibitors remains effective even in patients with desensitized or

down regulated β_1 receptors, or those under pharmacologically blocked conditions, e.g., concurrent betablocker use [12]. Therefore, milrinone is an alternative inotropic agent used to enhance cardiac output. In addition to its inotropic characteristics, milrinone can also reduce SVR and induce pulmonary artery vasodilatation. Milrinone has a longer half-life of 2-2.5 hours when compared to the majority of other inotropic agents. It undergoes hepatic metabolism and is eliminated through urinary excretion. The presence of kidney dysfunction significantly prolongs the half-life of milrinone, resulting in two-to-three-fold longer effects of the medication. The use of milrinone should be approached with caution in individuals with low SVR or experiencing hypovolemia, as its administration could potentially lead to excessive hypotension.

However, there are a limited number of studies of milrinone in patients with septic shock. Considering both milrinone and dobutamine produce similar improvements in cardiac output, dobutamine is advisable for septic shock patients with myocardial dysfunction and severe renal failure, while milrinone should be used with caution. On the other hand, milrinone is preferred when dealing with the presence of pulmonary hypertension and right ventricular failure due to its greater effect on reducing pulmonary vascular resistance (PVR) [16], as well as for patients with simultaneous use of betablockers.

A small randomized controlled trial in 1996 involving 12 pediatric patients with non-hyperdynamic septic shock demonstrated that, despite the administration of catecholamines in patients with signs of inadequate tissue perfusion, milrinone displays a significant increase in cardiac output. However, the trial's sample size was insufficient to adequately assess the outcomes [17]. In 2015, a study of combination therapy with milrinone and esmolol for heart protection in patients with severe sepsis was conducted. The results revealed an increase in cardiac index within both the milrinone monotherapy and the combination of milrinone and esmolol groups (1.8±0.4 to 3.6±0.8, and 3.5±0.6 respectively) [18]. In the study comparing dobutamine and milrinone, dobutamine produced more tachycardia, arrhythmias, hypertension, and myocardial ischemia than milrinone, while milrinone is more likely to cause hypotension [19]. The SSC Guideline 2016 recommended dobutamine as the first-choice inotrope for patients with cardiac dysfunction, while milrinone is considered an alternative inotrope.

The recent study from 2019 regards the evidence on the effects of inotropes, including epinephrine, dobutamine, and milrinone, on the in-hospital mortality of patients with septic shock and myocardial dysfunction. Among a total of 417 patients with septic shock, the use of both epinephrine and dobutamine was associated with significantly higher in-hospital mortality (epinephrine HR 4.79, 95% CI 2.12-10.82, dobutamine HR 2.53, 95% CI 1.30-4.95). The effect was time and dose dependent. On the other hand, the use of milrinone was not associated with increased mortality (HR 1.07, 95% CI 1.05-13.59) [20].

Table 1. Inotropic drug names, clinical indication, dose range, half-life, receptor binding, and major side effects.

Drug	Clinical Indication	Dose Range	Half-life	Receptor Binding				Major Side Effects
				Alpha-1	Beta-1	Beta-2	Other	
Dobutamine	Low cardiac output	2.0-20 mcg/kg/min (max 40 mcg/kg/min)	2 mins	+	+++++	+++	N/A	Tachycardia Ventricular arrhythmias Cardiac ischemia Hypotension
Epinephrine	Shock Cardiac arrest Bronchospasm/anaphylaxis Symptomatic bradycardia or heart block unresponsive to atropine or pacing Severe acidosis	Infusion: 0.01-0.1 mcg/kg/min Bolus: 1 mg IV every 3 -5 min (max 0.2 mg/kg)	< 5 mins	+++++	++++	+++	N/A	Ventricular arrhythmia Severe hypertension resulting in cerebrovascular hemorrhage Cardiac ischemia Lactic acidosis Hyperglycemia
Milrinone	Low cardiac output Beta-blocker use High pulmonary vascular resistance	Bolus: 50 mcg/kg over 10-30 min Infusion: 0.375-0.75 mcg/kg/min (dose adjustment for renal impairment)	2-2.5 hours	N/A	N/A	N/A	PDE III-I	Ventricular arrhythmias Hypotension Cardiac ischemia Torsade des pointes
Levosimendan	Decompensate heart failure	Loading: 12-24 mcg/kg over 10 min Infusion: 0.05-0.2 mcg/kg/min	1 hour	N/A	N/A	N/A	Ca sensitizer	Tachycardia Hypotension

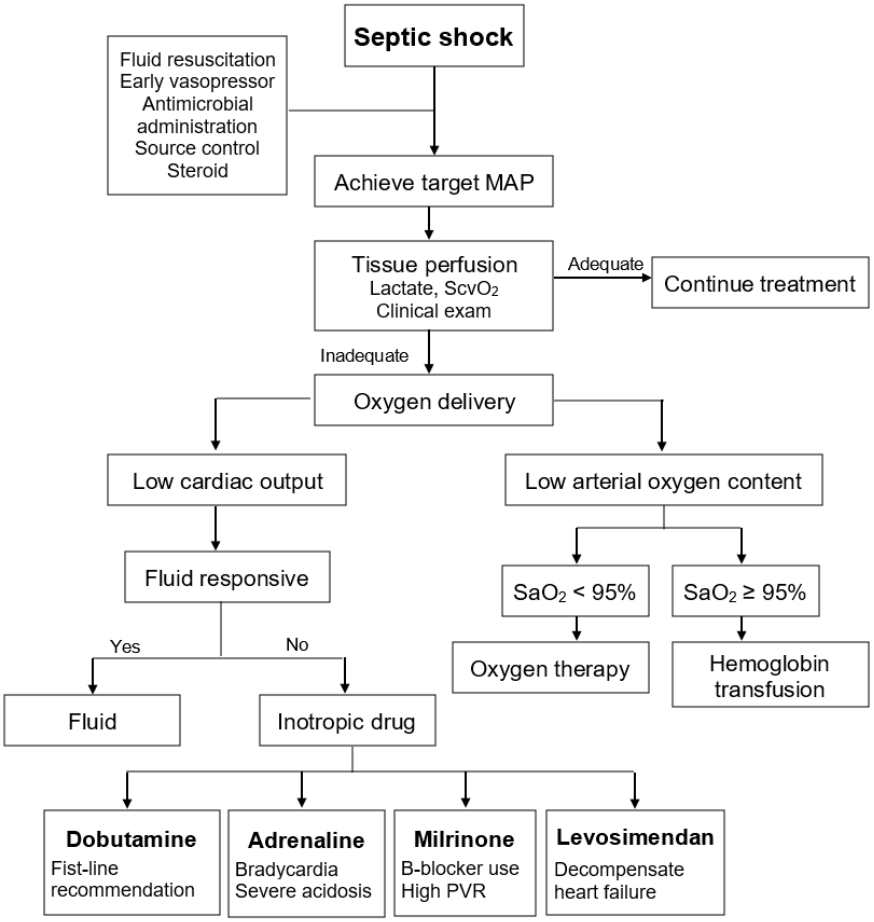

Figure 1. Algorithm for septic shock management that have clinical of inadequate tissue perfusion.
Abbreviations: $ScvO_2$: Central venous oxygen saturation; SaO_2: Arterial oxygen saturation; B-blocker: Beta-blocker; PVR: Pulmonary vascular resistance.

Levosimendan

Levosimendan sensitizes troponin C to calcium independently of the calcium concentration, increasing the effect of calcium on cardiac myocytes and improving contraction at a low energy cost. Unlike other inotropic agents, levosimendan does not cause cardiac myocyte dysfunction, arrhythmia, or an increase in energy consumption. In addition, levosimendan opens ATP-dependent potassium channels in myocytes and vascular smooth muscle cells, giving the drug both inotropic and vasodilatory properties. The drug's ability to decrease afterload and increase contractility promotes an augmentation in coronary and other organ blood flow [21]. Levosimendan has a rapid onset of action, but it has a short half-life of only 1 hour, whereas its metabolites can persist for up to 80 hours. As abnormal intracellular calcium transportation during septic shock is one of the mechanisms leading to cardiac dysfunction and impaired micro-circulatory function, the use of levosimendan has been proposed in patients with refractory septic shock during SSC guidelines 2016.

The trial of 35 patients with septic shock and acute respiratory distress syndrome (ARDS) in 2006, randomized to receive levosimendan or placebo, demonstrated improved right ventricular performance (increased cardiac index, decreased mean pulmonary artery pressure, and pulmonary vascular resistance) through pulmonary vasodilator effects. Levosimendan also increased right ventricular ejection fraction and mixed venous oxygen saturation compared to placebo [22]. A meta-analysis of RCTs on the use of inotropes in the treatment of severe sepsis and septic shock published in 2015 compared the use of levosimendan to standard inotropic therapy (e.g., dobutamine) and showed that levosimendan was associated with significantly reduced mortality compared with standard inotropic therapy (59/125 [47%] and 74/121 [61%]; risk difference = -0.14, risk ratio = 0.79 [0.63-0.98], p for effect = .03, I2 = 0%, NNT = 7). Blood lactate was significantly reduced, whereas cardiac index and total fluid infused were significantly higher in the levosimendan group. No difference in mean arterial pressure and norepinephrine usage was noted. Due to the small size, a larger randomized trial will have to confirm the findings. [23]

Trials comparing levosimendan with other inotropic agents are limited, but later evidence shows no clear benefit compared to dobutamine in patients with sepsis [24]. An RCT published in 2016 enrolled 516 patients with septic shock to receive either levosimendan or placebo. there was no difference in mortally; however, more patients in the levosimendan group had a significantly higher risk of supra-ventricular tachy-arrhythmia than placebo (absolute difference 2.7%; 95% CI 0.1-5.3%) [25]. The meta-analysis of seven RCTs comparing levosimendan with dobutamine showed that, in adults with sepsis, levosimendan did not demonstrate superiority over dobutamine in terms of mortality outcomes. Given the drug's lack of benefit, in addition to its safety profile, cost, and limited

availability, the SSC guideline 2021 advises against the use of levosimendan.

CONCLUSION

Septic shock is a critical, life-threatening condition that contributes to the majority of morbidity and mortality in ICUs. Sepsis-induced myocardial dysfunction is one of the common causes of refractory shock, leading to insufficient tissue perfusion and multi-organ dysfunction. Subsequent recommendations suggest the addition of inotropic drugs to norepinephrine in patients with septic shock with cardiac dysfunction and persistently inadequate tissue perfusion. Current guidelines support the use of dobutamine, epinephrine, and milrinone while cautioning against the use of levosimendan. Epinephrine has greater potency than dobutamine; however, subsequent findings have indicated that dobutamine doesn't exhibit superiority over epinephrine. A retrospective cohort study indicated that both epinephrine and dobutamine were associated with elevated in-hospital mortality, whereas milrinone did not show the same association. Milrinone is preferred for cases involving pulmonary hypertension and right ventricular failure, while it should be avoided in the presence of renal dysfunction. Given the heterogeneous quality of evidence supporting the use of these inotropic drugs, clinical correlation is necessary. Nonetheless, all these agents have a narrow therapeutic spectrum and expose patients to potentially lethal complications. As a result, precise therapeutic targets are necessary, along with close monitoring and dose titration, to achieve the minimally efficacious dose. It is advisable to discontinue these agents as promptly as possible [26].

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