VIEWPOINT

Squeeze the Pipes in Septic Shock

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Abstract

Rationale for fluid resuscitation is to increase mean systemic filling pressure, venous return, and cardiac output by increasing circulatory stressed volume. However, several conditions must be fulfilled to achieve desirable outcomes from fluid resuscitation. Vasopressors are also important components of resuscitation in septic shock (SS) and can potentially supplement the beneficial effects of fluid. However, the potential benefits of vasopressors must be weighed against several harms associated with vasopressors. Risks associated with vasopressors are more pronounced with underfilling of circulation and in higher doses. Current physiological and clinical evidence support intravenous fluids as the first-line resuscitation agent in SS with vasopressor infusion as a supplement to the same.

Keywords: Intravenous fluid, Septic shock, Vasopressors.

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Introduction

Akin to other forms of shock, SS leads to inadequate delivery of oxygen to tissues. This result in end-organ damage and an increase in mortality.[1] One of the unique features of SS is that the hemodynamic aberration is associated with an exaggerated decrease in vascular tone. The dogma of early fluid resuscitation in SS is based on the theory that SS is a state of relative hypovolemia caused due to systemic vasodilation and increased capillary permeability. Incessant fluid resuscitation results in extravascular fluid accumulation and pulmonary edema which further compromises the oxygenation of tissues. Current evidence about the management of SS indicates that uncorrected hypotension even for a short duration may lead to adverse outcomes.[2] Therefore, investigating the appropriate time for initiating vasopressors is essential to improve clinical outcomes.

Pathology of Septic Shock—Beyond Just Fluids

As alluded above, SS is associated with reduced vascular tone and relative/absolute hypovolemia which leads to a decrease in mean arterial pressure (MAP). If MAP reduces below a critical level, there is a decrease in organ perfusion. Precisely for this reason MAP should be targeted >65 mm Hg in patients with SS by early fluid resuscitation and timely initiation of vasopressors as recommended by Surviving Sepsis Campaign (SSC) 2021 guidelines. Fluid resuscitation restores intravascular volume and thus improves cardiac output; however, fluid overload may occur due to excessive fluid resuscitation and has been shown to worsen clinical outcomes. Approximately, only half the subset of patients in SS responds to fluid administration and there is no improvement in cardiac output by fluid resuscitation in the other half of patients. Intravenous fluid administered may extravasate to extracellular compartment in about 30–60 minutes. Thus, even in the early phase, simultaneous targeting of hypovolemia through fluid resuscitation and restoring vascular tone by using vasopressors (norepinephrine being the first choice) is important to ensure organ perfusion.

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How "Squeezing the Veins" May Help?

In the absence of evident loss of fluid, systemic pathological vasodilation results in a decrease in venous return and thus cardiac output. This brings back the argument that how likely fluid resuscitation is going to reverse vasodilation and hypotension. Vasopressors by changing venous capacitance increase mean systemic filling pressure. This mobilizes nonstressed blood volume back to circulation, increasing preload and cardiac output. Secondly, early initiation of vasopressors decreases both the duration and severity of hypotension and improve clinical outcome.[2] Third, vasopressors may additionally increase cardiac output by increasing cardiac contractility through improving ventriculoarterial coupling. Fourthly, coronary artery perfusion is improved due to improved diastolic blood pressure leading to improvement in cardiac function in SS. Fifthly, norepinephrine might increase microcirculatory perfusion in SS, especially when initial microcirculatory blood flow is abnormal. Sixthly, the use of norepinephrine in SS has been shown to be associated with improved MAP, sustained mesenteric blood flow, and better tissue oxygenation when compared with fluid resuscitation alone.[3]

Evidence over the Last Decade is Supportive of Squeezing the Pipes Rather Than Filling!

Bai et al., in a retrospective study of 213 patients, concluded that the time of initiation of vasopressors to the time of onset of SS plays a

vital role in the survival of patients. Mortality was high for a delay in vasopressors initiation within 6 hours of the onset of SS. Each hour delay in initiation increased mortality by 5.3%. Another significant finding in this study was that those patients, who were initiated with vasopressors within 2 hours of the onset of SS, received less intravenous fluids. A much more recent study of over 5,600 patients again demonstrated that distributive shock leads to prolonged episodes of hypotension. In this study, 62.0% of patients had a MAP of <65 mm Hg and 17.2% of patients had a MAP of <55 mm Hg for at least 2 hours of intensive care units admission. Application of step ladder resuscitation practices of 2004 SSC guidelines (fluid first then vasopressors) did not reduce the frequency of hypotensive episodes. Duration of MAP <65 mm Hg was strong predictor of mortality. Unlike clinical trials, which have stringent inclusion and exclusion criteria, this dataset included almost all patients with distributive shock in a real-world resuscitation setting.[1]

Any doubts regarding interpretation of results of these studies due to their retrospective nature, were put aside by the randomised control CENSER trial (Early Use of Norepinephrine in Septic Shock Resuscitation) which got published in 2019. The CENSER trial was a single-center prospective, double-blind, placebo-controlled trial. It evaluated shock control rate in patients randomized to early low-dose norepinephrine administration or placebo; shock control rate was defined as a sustained MAP of at least 65 mm Hg along with good tissue perfusion defined as either urine output >0.5 mL/kg/minute or a lactate decline >10% from baseline. The early vasopressor group received norepinephrine at 1.5 hours compared to 3 hours in the standard treatment group. Shock control at 6 hours was achieved in 76.1% of patients in the vasopressor group as compared to 48.4% in the standard group ($p < 0.001$). Arrhythmias were common in the norepinephrine group, with a lower rate of cardiogenic pulmonary edema in the norepinephrine group.[4,5]

Conclusion

In SS the predominant mechanism responsible for hypotension may be different in different patients. Some patients are hypovolemic, but some others have myocardial depression as a predominant manifestation. The therapeutic approach must be personalized as there is no single approach suitable for all patients. Early administration of vasopressors during SS improves cardiac output, preload, cardiac contractility, microcirculation, and limits volume overload.[6] The current evidence suggests that vasopressors should be initiated ideally within 1 hour of shock onset and postinitiation of fluid resuscitation.[7]

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