EDITORIAL

Vasopressors in Septic Shock: The Quest for Refinement

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Fluid resuscitation and vasopressor therapy have been the bedrock of the treatment of septic shock. The objective of this treatment is to quickly restore tissue perfusion and organ function. These two modalities target the two key pathophysiological pillars of septic shock: relative hypovolemia and systemic vasodilation. The amount of research interest in fluid resuscitation, as evidenced by the large number of published trials in that domain, far outweighs research into vasopressor therapy. However, studies looking at vasopressor therapy in septic shock have focused on three main areas.

The first area of research has been to determine the ideal target blood pressure of vasopressor therapy. A mean arterial pressure (MAP) of 65 mm Hg has traditionally been used based on autoregulatory physiology of organ perfusion. A higher MAP of 85 mm Hg has been seen to lead to better recruitment of the microcirculation.[1] Large randomized controlled trials (RCTs) have proven, however, that targeting an MAP higher than 65–70 mm Hg has not shown to improve clinically significant outcomes in the majority of patients.[2] There remain a few subgroups of patients who may benefit from higher MAP targets. The first of these is that with chronic hypertension who seem to have less renal injury when a higher MAP target of 75–80 mm Hg was used.[2] The next group includes those with high central venous pressures (CVPs) where an MAP-CVP target of 60 mm Hg is more appropriate than an MAP target alone.[3] Patients with raised intra-abdominal or intracranial pressure also need an MAP sufficient to produce an adequate abdominal or cerebral perfusion pressure.

Another important research question is related to the timing of initiation of vasopressors. Typically, guidelines state that vasopressors ought to be started only if hypotension persists after fluid resuscitation with 30 mL/kg of crystalloids. On the contrary, starting vasopressors early, at the same time as fluid therapy, is a novel concept being explored by some. This may entail vasopressor administration through a peripheral venous access as a central venous access may not be available at such an early point in the patient's resuscitation.[4] It is well known that the duration of hypotension in the initial phase of septic shock strongly influences outcomes.[5] RCTs have demonstrated earlier termination of hypotension, better urine output, and enhanced lactate clearance in the early vasopressor groups.[6] Data regarding the influence of this approach on mortality, however, are conflicting.[6,7] Early vasopressor use also obviates the need for excessive fluid administration and seems to prevent harmful fluid overload.[8]

The choice of vasopressor for septic shock has also been another bone of contention. Noradrenaline is the recommended vasopressor for septic shock because of its predominantly vasoconstrictive effect with a good safety profile. The use of dopamine has been discontinued after RCTs, and a meta-analysis revealed more adverse effects and an increased risk of death with dopamine.[9] Adrenaline is a second-line agent most suited to patients who have a concomitant cardiac systolic dysfunction. It has been shown to be equivalent to a combination of noradrenaline and dobutamine in efficacy and safety.[10] However, at higher doses, it may contribute to tachyarrhythmias and hyperlactatemia. Vasopressin is a recommended second-line agent in septic shock. It has the advantage of being a nonadrenergic vasopressor. When used in combination with noradrenaline, it has been shown to help reach target MAP faster while reducing the noradrenaline dose requirement.[11] Digital ischemia seems to be more common in patients managed with vasopressin.[12] Related drugs, terlipressin, and selepressin have also been studied for similar usage. Angiotensin-II is another emerging vasopressor being investigated.[13]

In this issue of the journal, Sahoo et al.[14] have reported the results of a comparison of a combination of noradrenaline with terlipressin and noradrenaline alone in the management of the early phase of septic shock. Hemodynamic parameters were tracked for a period of 12 hours. They discovered that addition of terlipressin led to faster resolution of shock, with lower noradrenaline requirements, better urine output, and faster lactate clearance, compared to noradrenaline alone. Conducting a RCT in this domain in unstable patients is technically and logistically challenging, and the authors should be commended for it. However, there are a number of limitations of this study which need to be considered while interpreting the results. Firstly, the intervention period was only 12 hours. This is a too short duration to judge the effect of vasopressor choice on clinically significant outcomes. Second, terlipressin has a long half-life of 50 minutes, and additionally, because of its active metabolite, the duration of effect is approximately 6 hours. This makes it difficult to use as a continuous infusion, like it was done in this study. It is disturbing to note that 28% of patients in the terlipressin with noradrenaline group developed digital ischemia even with the short duration of the infusion. More study on the safety of longer

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duration infusions of terlipressin is warranted. Lastly, an important drawback of the study design is that equipressor doses were not used in the two arms. The noradrenaline plus terlipressin arm started with higher noradrenaline equivalents of vasopressors compared with the noradrenaline-alone arm. This may have led to a faster achievement of target MAP and translated to better organ function, urine output and lactate clearance. In other words, just starting with a higher noradrenaline dose may have led to all the beneficial effects that have now been attributed to the addition of terlipressin. The present study does not allow us to clarify this hypothesis.

So where do we go from here? We need large, well-designed trials to help determine the best vasopressor combination, the best time to initiate pressor therapy, and the ideal personalized MAP targets for different patient populations.

We also need to think outside the box in our quest to improve the efficacy of vasopressor therapy. An example of this is automated closed-loop control of vasopressor infusions.[15] This emerging technology promises to reduce time to achieve target MAP and maintain the MAP in the target range consistently resulting in better patient outcomes.

I am confident that in the coming years, this established modality of therapy is going to be transformed and become more precise, personalized, and automated, much to the benefit of our patients.

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