CHAPTER 5

Vasopressors in Septic Shock: Why, When, Which One, How Much?

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INTRODUCTION

Septic shock is a state of vasodilatory shock as a result of decreased vascular tone. Hypovolemia is also one of the common pathophysiological alteration in septic patients. Multiple factors contribute to hypovolemia including fever, gastrointestinal losses, and capillary leak. Persistent hypovolemia can lead to hemodynamic instability, hypoperfusion, and multiorgan dysfunction. This can be counteracted by hemodynamic optimization with fluid resuscitation and vasopressor therapy. The objective of this chapter is to throw a light on why we need vasopressors, which is to be used as a preferred one, appropriate time to initiate them, and what is the maximum dose limit.

WHY DO WE NEED AND WHEN SHOULD WE INITIATE VASOPRESSORS?

Besides relative and absolute hypovolemia, decreased vascular tone is a major phenomenon in septic shock causing hypotension. For decades, resuscitation in septic shock used substantial fluid loading before initiation of vasopressors. The vasopressors were used only after fluid therapy was unable to restore targeted mean arterial pressure (MAP). During the initial resuscitation of septic shock, the MAP target is currently recommended to be at least 65 mm Hg by the Surviving Sepsis Campaign (SSC).[1] But, as in septic shock, hypotension occurs mainly because of decreased vascular tone, it is unlikely that administering fluid alone is sufficient to correct the targeted MAP. Moreover, overzealous fluid administration has its own adverse effects. In this regard, positive cumulative fluid balance is an independent predictor of mortality in septic shock patients.[2] A meta-analysis of 11 studies has recently shown that in patients with sepsis or acute respiratory distress syndrome (ARDS), conservative fluid strategy results in increased number of ventilator-free days and decreased length of intensive care unit (ICU) stay as compared to liberal fluid strategy.[3] A recent cohort study of 23,513 patients with sepsis and septic shock showed that administration of more than 5 liters of fluid during the first day is associated with significantly increased risk of death.[4]

Vasopressors are used when decreased arterial tone is assumed to be a major cause of hypotension in septic shock. It also prevents potential risk of fluid overload. Data from the recent literature favors early initiation of vasopressors during septic shock in order to prevent hypoperfusion and organ dysfunction, which is independently associated with increased mortality. However, starting vasopressors to counteract the depression of vascular tone does not mean to stop or not to initiate fluid administration. Fluid management must be individualized during septic shock by assessing preload responsiveness in order to avoid too conservative strategy in patients who are preload responsive and too liberal strategy in those who are preload unresponsive. The question of initiating a vasopressor needs to be separated from that of initiating (and continuing) fluid initiation as these two interventions reflect two different mechanisms of circulatory shock in sepsis that vary among patients. We thus need relevant markers for decreased vascular tone which are easy to obtain and interpret. Diastolic arterial blood pressure (DAP) is the simplest bedside marker especially in patients with tachycardia. In these patients, the diastolic time is reduced in such a way that DAP should be higher than normal for a normal vascular tone. Hence a low DAP (< 40 mm Hg) will suggest a decreased vascular tone, which should trigger initiation of vasopressors. Another potential marker called dynamic elastance (Eadyn), which is the ratio of pulse pressure variation (PPV)/stroke volume variation (SVV), can also be used to identify patients who will not increase their MAP after fluid challenge.[5] But, this method requires to obtain PPV and SVV from two independent signals which are poorly feasible in clinical practice.

NOREPINEPHRINE

This agent carries certain advantages to consider it as first-line vasopressor. Firstly, norepinephrine through its alpha-1 adrenergic effects, increases cardiac preload and systemic venous return in patients who are preload responsive, a condition that is quite common in early sepsis. *In this regard,* recent clinical studies show that early norepinephrine initiation was associated with a significant increase in cardiac output. In a series of 105 patients with septic shock who were severely hypotensive, it was found that early norepinephrine administration aimed at achieving a sufficient perfusion pressure, resulted in increase in stroke volume and cardiac output, which were attributed to increase in cardiac preload since global end-diastolic volume (marker of cardiac preload) increased and PPV (marker of volume responsiveness) decreased.[6] It is likely that norepinephrine increases cardiac preload and venous return by increasing the mean systemic pressure due to blood redistribution from the unstressed to the stressed blood volume,[7] a mechanism which is important in septic patients as their unstressed blood volume is abnormally increased and can be overfilled by excessive fluid administration. Secondly, norepinephrine has beneficial effects on microcirculation if initiated early in septic shock. One of the most common fears of initiation of norepinephrine, while correction of hypovolemia has not yet been completed, is worsening of microcirculation due to excessive vasoconstriction of the precapillary network. A clinical study investigated the effects of early norepinephrine initiation on microcirculation assessed by near-infrared spectroscopy at the level of thenar eminence in septic shock patients.[8] Norepinephrine was added to fluid therapy

in cases of hypotension with a low DAP. The MAP increased from 54 mm Hg to 77 mm Hg whereas the average tissue oxygen saturation (StO_2) increased from 75% to 78% (normal values around 80%). Vascular occlusion tests were performed to evaluate the hyperemic response to a local hypoxia, a stimulus which was created by a transient ischemia of the vascular bed of the thenar eminence (after pneumatic cuff inflation of the upper arm). Increasing MAP with norepinephrine caused a significant increase in StO_2 recovery slope,[8] a parameter that reflects capacity of the microvessels to be recruited in response to the local hypoxic stimulus and that represents a prognostic factor in septic shock patients. Hence, it was postulated that increasing the MAP in severely hypotensive patients, improves microcirculation in pressure-dependent vascular beds.[8] Thirdly, early initiation of norepinephrine also prevents adverse consequences of fluid overload, an effect that can be considered favorable as positive cumulative fluid balance is an independent predictor of mortality in septic shock.[2] In this regard, a retrospective study in septic shock patients shows that those in whom norepinephrine was administered within the first 2 hours of resuscitation received less fluid than those who received a delayed norepinephrine administration.[9]

How Much?

The SSC recommends to target a MAP of at least 65 mm Hg during the initial resuscitation of septic shock[1] assuming that 65 mm Hg is higher than the lower level of the autoregulation part of the organ blood flow/organ perfusion pressure relationship and that increasing MAP above 65 mm Hg would not result in further benefits in terms of organ perfusion. In patients with history of chronic hypertension, higher values of MAP are suggested to be targeted.[10,11] It is likely but not formally proven that in cases of increased central venous pressure or increased intra-abdominal pressure, the downstream pressure of organ perfusion is abnormally increased so that a higher upstream pressure (MAP) can be necessary for the organ perfusion pressure to be maintained. To summarize, the key message is that there is no universal MAP target and that individualization of the target in function of the context is necessary.

Patients with severe septic shock often require a high dose of norepinephrine to achieve the targeted MAP as a result of downregulation of alpha-1 adrenergic receptors. The dosage of norepinephrine usually ranges from 0.1 mcg/kg/min to 1.5 mcg/kg/min knowing that there is no fixed dose protocol that is recommended. It is usually titrated up to meet the target MAP. A patient is considered to have high norepinephrine requirements or refractory shock when the dosage exceeds 1 mcg/kg/min. There is an increased risk of mortality in these patients as possibly a consequence of the severity of the septic abnormalities. Serious adverse effects such as myocardial ischemia, mesenteric ischemia, digital ischemia, and necrosis have also been reported at doses above 1 mcg/kg/min in about 5–10% of patients.[12] In addition, increasing the dose of norepinephrine may cause oxidative stress and can alter the immunomodulatory response associated with sepsis.[13]

When the dose of norepinephrine is increasing rapidly and the MAP target not yet reached, administration of steroids can be considered, knowing that outcome can be improved with steroids in very severe septic shock patients[14] as opposed to less severe septic shock patients in

whom no benefit is expected.[15] In case of no or insufficient MAP response or when the dose of norepinephrine is judged to be too high, adding other vasopressors is suggested by the SSC.[1]

VASOPRESSIN

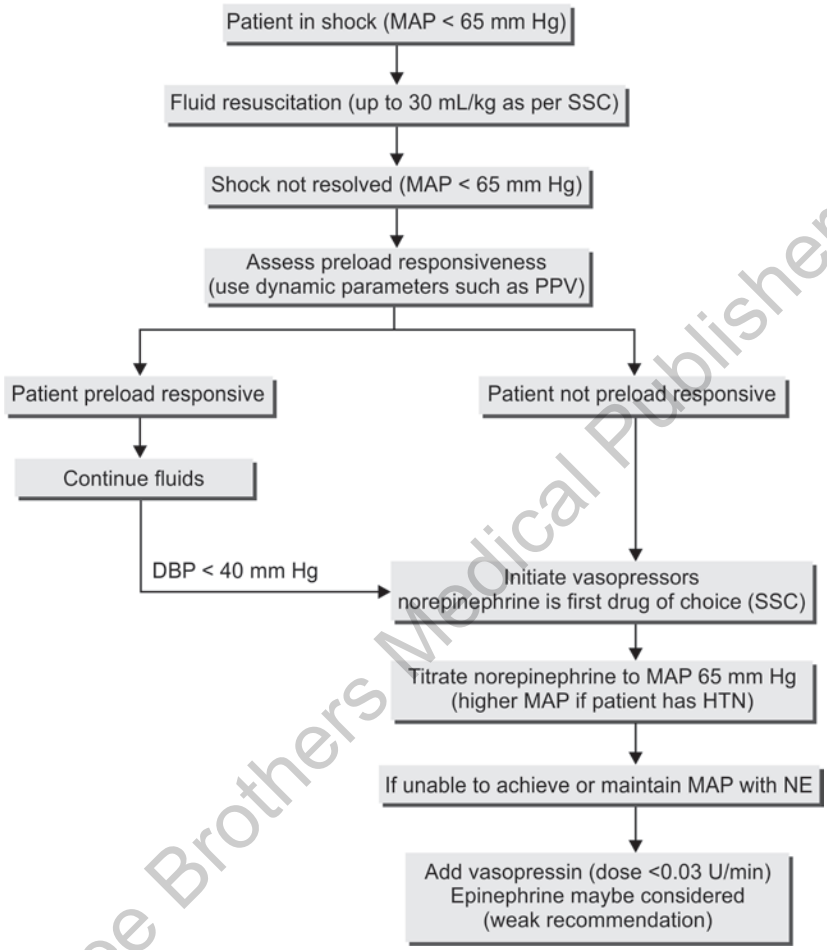
Vasopressin infusion can be used as an adjunct to norepinephrine to maintain adequate MAP and to reduce the norepinephrine requirements.[1] The rationale behind this attitude is that there is a relative vasopressin deficiency in septic shock. Exogenous vasopressin through its action on V_1 receptors helps in restoring vascular tone, increasing blood pressure, and reducing norepinephrine requirements. In a large multicentric randomized controlled trial (RCT), vasopressin decreased mortality compared with norepinephrine in patients with less severe septic shock, although the overall mortality was not different.[16] The VANISH trial, which compared in a RCT, vasopressin and norepinephrine found no difference in rates of acute kidney injury, the primary endpoint.[17] Vasopressin is currently recommended as a second-line vasopressor for septic shock by the SSC[1] at a dose not exceeding 0.03 U/min to avoid serious adverse events such as mesenteric, digital, and cardiac ischemia. The SSC also weakly suggests adding epinephrine to norepinephrine in case of refractory hypotension but compared to adding vasopressin, adding epinephrine to norepinephrine seems less logical. Indeed, epinephrine exerts vasoconstricting effects through the same alpha-1 adrenergic pathway as norepinephrine and also has deleterious side effects like tachyarrhythmia through beta-1 receptor activity. In septic shock, there is a relative angiotensin II (AT II) deficiency due to loss of pulmonary angiotensin-converting enzyme. Hence, AT II has also been proposed as a vasopressor in vasodilatory shock. A multicentric RCT found that AT II increased MAP more than placebo in early septic shock without increasing adverse events.[18]

It cannot be excluded that combination of multiple vasopressors acting on different vascular receptors would be the best vasopressive therapy in the future,[19] the dose of each one being selected in function of biomarkers evaluating the degree of alteration of each receptor.[19] Such a therapeutic approach could result in minimizing the dose of each agent and thus in increasing safety (Flowchart 5.1).

KEY POINTS

- Norepinephrine is the first vasopressor of choice as recommended by the SSC.
- Low DAP may serve as a guide to identify patients who can benefit from early initiation of norepinephrine. Initiation of norepinephrine before complete completion of hypovolemia has many advantages.
- Norepinephrine is titrated to achieve a target MAP of 65 mm Hg, a higher MAP maybe needed in patients with chronic hypertension. Individualization of the target MAP is a key issue in the resuscitation of septic shock patients.
- Vasopressin can be added to norepinephrine in patients with refractory shock at a dose not exceeding 0.03 U/min.
- Combination of various vasopressors acting on different deficient vascular receptors could represent the best therapeutic option in the future, mostly if biomarkers help to identify the most severely deficient vascular receptors.

Flowchart 5.1: Stepwise algorithm in septic shock



(MAP: Mean arterial pressure; DBP: Diastolic blood pressure; SSC: Surviving sepsis campaign; PPV: Pulse pressure variation)

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