Editorial Commentary

Terlipressin as a first choice in septic shock—not yet

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Sepsis, a dysregulated host response to infection leading to organ dysfunction, and septic shock, a subset of patients with sepsis, cardiovascular collapse and cellular and metabolic dysfunction, are still major healthcare problems (1). Despite significant progresses in intensive care medicine, septic shock remains associated with high morbidity and mortality (1), and all efforts should be made to improve the outcomes of this group of patients. Patients presenting to the intensive care unit (ICU) with septic shock are frequently treated with vasopressors in addition to other supportive therapies (1,2).

Together with fluid resuscitation, early introduction of antibiotics and treatment of the infection source (when necessary), the use of norepinephrine as the first line vasopressor agent in septic shock which is unresponsive to fluid resuscitation is well established (2,3). The aim of the introduction of a vasopressor agent is to promote macro and microvascular coupling and achieve hemodynamic stabilization, reestablishing adequate tissue perfusion (4). Norepinephrine is a catecholamine classified as a sympathomimetic drug, and its effects include an increase in heart rate and myocardial contractility, and vasoconstriction, making it very useful for treating conditions involving hypotension (2,3).

In some cases, achieving the arterial blood pressure target may require high doses of norepinephrine, which may result in myocardial injury and alter the sepsis-associated immunomodulation (2,3). In addition, there is increased evidence that high doses of adrenergic agents can worsen tissue damage, and induce cardiac, immunologic, metabolic, and coagulation dysfunction (5). The need of high doses of norepinephrine is usually accompanied by reduced responsiveness to vasopressor therapy, and vasopressin deficiency (5,6).

Vasopressin, also called antidiuretic hormone, is produced in the hypothalamus, stored in the posterior pituitary, and released from vesicles into the circulation in response to extracellular fluid hypertonicity (6). It has two mainly functions: (I) increases the amount of solute-free water reabsorbed back into the circulation from the filtrate in the kidney tubules of the nephrons; and (II) constricts arterioles, which increases peripheral vascular resistance and raises arterial blood pressure (6). It acts classically by binding to three types of transmembrane G-protein receptors, namely: V1, V2 and V3 receptors. While the V1 receptor is responsible for most of the hemodynamic effects of vasopressin, and predominantly found in the smooth muscles of the vasculature and in cardiac myocytes, the V2 receptor is responsible for the osmoregulatory and antidiuretic effects. The V3 receptor is found in the pituitary gland and is related to the stimulation of corticotropin secretion (6).

The rationale for vasopressin use in patients with septic shock is the relative deficiency and the hypothesis that exogenously administered vasopressin can restore vascular tone and blood pressure, thereby reducing the need for the

use of catecholamines in these patients (6,7). Terlipressin, a synthetic long-acting vasopressin analog with potent vasoconstriction activity through highly selective binding to V1 receptor, has been shown to effectively reduce the need of norepinephrine in patients with septic shock (8). However, no randomized clinical trial powered enough to evaluate the effect of terlipressin on mortality, organ dysfunction or safety in patients with septic shock has been done until now.

Recently, a multicenter, randomized, double-blind clinical trial involving 21 intensive care units in China was conducted to determine the efficacy of terlipressin versus norepinephrine in patients with septic shock (9). In this study, septic shock was defined according to the old definition of the American College of Chest Physicians/Society of Critical Care Medicine Conference definition (10). Patients were randomized to receive either terlipressin (20–160 μg/h with maximum infusion rate of 4 mg/day) or norepinephrine (4–30 μg/min) before open-label vasopressors targeting an initial mean arterial pressure of 65–75 mmHg. The primary outcome was 28-day mortality and secondary outcomes included changes in the Sequential Organ Failure Assessment (SOFA) scores on day 7, days alive and free of vasopressor during 28 days and the incidence of adverse events.

The trial was well designed, and its selection criteria were clear and appropriate to the clinical question. In addition, the randomization procedure and adherence to the intervention was adequate. The trial was stopped early, after the second interim analysis due to futility. There was no significant difference in 28-day mortality between groups. Yet, no differences were observed in the secondary outcomes of changes in the SOFA score or vasopressor-free days at day 7. However, an important increase in adverse events was observed in the terlipressin group. The overall incidence of adverse events was 30% in the terlipressin group, as opposed to 11.6% in the norepinephrine group ($P<0.01$), and 33 patients (12.6%) in the terlipressin group had digital ischemia compared to one (0.35%) in the norepinephrine group ($P<0.0001$). In conclusion, in the present study, no difference in 28-day mortality between terlipressin and norepinephrine infusion in patients with septic shock was observed, and patients in the terlipressin group had a higher incidence of serious adverse events. The authors suggest that the early association of terlipressin and open-label norepinephrine in the terlipressin group and doses up to 4 mg/day (higher than reported in previous studies) could have had an important contribution to the adverse events found in the study.

As a criticism, the trial results could have been impaired by the early stopping, despite being interrupted according to predefined rules, and the fact that the observed mortality was lower than the considered for the sample size calculation, resulting in an underpowered study. Also, the relatively high number of exclusions after randomization in the modified intention-to-treat population might decrease the internal validity of the study.

A systematic review and meta-analysis which included nine randomized clinical trials comparing norepinephrine to vasopressin or to terlipressin demonstrated a reduction in mortality and an important sparing-norepinephrine effect with vasopressin use, avoiding potential adrenergic adverse effects of the catecholamine infusion in patients with septic shock (11). It is noteworthy that such benefits were not shown when considering only studies using terlipressin. Indeed, mortality reduction was not shown in other systematic reviews. Avni *et al.* did not demonstrate a decrease in mortality when comparing norepinephrine to epinephrine, dopamine, phenylephrine, or vasopressin/terlipressin in patients with septic shock (2). A recent Cochrane systematic review also failed to demonstrate a difference in mortality in hypotensive shock when different vasopressors were used, catecholaminergic or non-catecholaminergic (12).

Previous studies comparing the effects of norepinephrine and vasopressin were also negative for their primary outcome. Russell *et al.* compared the infusion of norepinephrine combined with vasopressin with norepinephrine alone in patients with septic shock (13). In the study, low-dose vasopressin did not reduce mortality rate or changed any secondary outcome, including adverse events. However, the rate of norepinephrine infusion was significantly lower in the vasopressin group than in the norepinephrine group. The VANISH trial was a factorial trial comparing vasopressin to norepinephrine in patients with septic shock (14). The early use of vasopressin compared with norepinephrine did not improve the number of kidney failure-free days, but decreased the need of renal replacement therapy and spared the total dose of norepinephrine required to maintain the blood pressure. Again, the incidence of adverse events was similar among the groups. Finally, a small single center randomized clinical trial compared terlipressin to norepinephrine in cirrhotic patients with septic shock (15). The authors reported a superiority of the terlipressin group in the primary outcome of maintaining a mean arterial pressure higher than

65 mmHg in the first 48 hours. However, the terlipressin group had a significant higher need of combination therapy (association of a second vasopressor).

In summary, it seems that vasopressin and its analogue terlipressin might have an important role in reducing norepinephrine requirements in patients with septic shock, and this effect could lead to potential improvements in kidney function. However, data from the most recent and largest randomized clinical trials did not demonstrate a beneficial effect of these drugs in patient–centered outcomes and the most recent one found a significant increase in adverse events, without any significant improvement in survival to corroborate its use as a first line agent.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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