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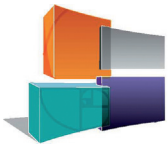

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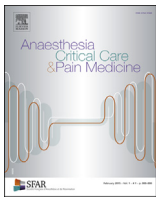

Editorial

Selepressin in septic shock: A wake-up call for new drugs

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Despite more than three decades of intensely investigating patients with septic shock, their mortality rate remains unacceptably high, particularly when the use of high-dose norepinephrine is required. An observational study reported mortality rates exceeding 80% for patients receiving intravenous norepinephrine doses above 1 μg/kg/min [1], and endogenous elevation of norepinephrine serum concentrations has also been associated with increased mortality in patients with chronic congestive heart failure [2]. While one may assume that norepinephrine levels rise in response to increasing severity in patient condition, there is no proof of directionality. This association therefore suggests that treating patients with septic shock with exogenous norepinephrine may in fact be counterproductive.

Indeed, norepinephrine may not be the ideal medication for the treatment of septic shock. High-dose norepinephrine generates immunosuppression, thereby potentially contributing to the infectious process [3–5]. Norepinephrine increases blood pressure by triggering contraction of vascular smooth muscle. This effect is mediated through α-receptors that activate the inositol triphosphate cascade, resulting in a massive release of intracellular calcium into the systemic circulation. However, α-receptors undergo downregulation in patients with severe inflammation.

These are all good reasons for attempting to identify alternatives to norepinephrine. Vasopressin, one such alternative, is a neuroendocrine mediator released by the posterior hypophysis. Vasopressin modulates an intracellular chain of action similar to that of norepinephrine; i.e. a release of intracellular calcium through the phospholipase C signaling cascade [6]. However, it does so by activating V1a, V1b and V2 receptors. Contrary to norepinephrine, vasopressin can maintain activity in acidotic conditions [7]. Experimentally, in low doses, it can also act synergistically with norepinephrine [8].

To date, no randomised controlled trial (RCT) comparing treatment of patients with septic shock with norepinephrine *versus* vasopressin has revealed a survival difference [9,10]. Similarly, no study has found more deleterious effects when using either one of these vasopressors. Accordingly, vasopressin was endorsed as a second line vasopressor in the 2016 Surviving Sepsis Guidelines [11]. However, the clinical equivalence found in studies thus far has discouraged several European agencies from licensing vasopressin and/or approving reimbursement to healthcare facilities providing this medication, thereby effectively eliminating clinician discretion concerning medication choice.

Vasopressin induces intracellular activation via V1a receptors, which triggers vasoconstriction. However, vasopressin also activates V1b and V2 receptors, both of which set in motion eventual extravascular fluid loss [6]. This effect is undesirable in septic shock where less fluid administration has been associated with increased survival. Selepressin, a newly available, short-acting vasopressin analogue, acts selectively on V1a receptors, thereby avoiding fluid retention. Animal models of ovine septic shock consistently show that administration of selepressin is accompanied by less net fluid gain than administration of arginine-vasopressin [12–14]. A pioneer randomised controlled study recently conducted in adult patients with early septic shock ($n = 53$) also confirmed lower net fluid gain among patients treated with selepressin *versus* those treated with placebo [15]. Observational studies show a clear and consistent association between net positive fluid balance and poorer outcomes in septic shock [16,17]. Therefore, it is logical to infer that the reduced fluid gain in septic patients treated with selepressin will also improve outcomes.

In a well-designed multicentre trial conducted in 63 intensive care units across five countries (Belgium, Denmark, France, the Netherlands and the United States), Laterre et al. randomised 868 patients with septic shock to norepinephrine plus placebo ($n = 283$) or norepinephrine plus selepressin ($n = 585$) [18]. The primary endpoint sought was a composite 1.5-day reduction in ventilator- and vasopressor-free days. Assuming the baseline of ventilator-free days was 10 days and that of vasopressor-free days was 20 days, such a difference would represent a 7.5 to 15% improvement (power 91%, 1-tailed α-error 0.2). Treatment allocation and outcomes analyses were blinded. An adaptive platform was used for this study, enabling the analysis of several dosing regimens of selepressin, as well as patient recruitment until the sample sizes required for the study endpoints were met.

No significant differences were found between the two groups in the primary outcome of ventilator- and vasopressor-free days

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(mean 15.0 *vs* 14.5 days; difference 0.6 days [95% CI − 1.3 to 2.4]; $P = 0.30$). Here again, no significant differences were found between the two groups in the secondary endpoints of 90-day mortality, kidney replacement therapy–free days or ICU free-days. The negative results of this study can be added to those of a long list of RCTs conducted in patients with sepsis. Like vasopressin before it [9,10], treatment with selepressin seems to provide no advantage over treatment with norepinephrine.

In recent years, a slew of criticism has been directed towards the design of large, international sepsis trials. These aimed at recruiting a large number of patients within a short time frame and therefore traditionally use broad inclusion and narrow exclusion criteria. Such "simplification bias" could easily have diluted meaningful findings. The mortality rates observed in such studies are often lower than those of unselected ICU populations [1] and in many of the participating centres the number of recruited patients was far lower than the average number of septic patients overall, suggesting significant selection bias. Although the 30-day mortality rate in the study of Laterre et al. reasonably reflects unselective cohorts (∼35%) and the average APACHE scores were not low (∼26), the patient cohort is probably somewhat selective. Approximately 14 patients were recruited per study centre (868/63) over a period of 25 months (i.e. around 0.6 patient/centre/month). Most ICUs see a much larger number of patients with sepsis.

Laterre et al. noted a lower net fluid balance in the first 24 h with selepressin than with placebo (81 mL/h *vs.* 107 mL/h, difference −26 mL/h [95% CI, −38 to −14]; $P < 0.001$) but this difference disappeared in later follow-up. Clearly, the differences found in net fluid balance failed to translate into positive outcomes. Most studies tying a positive fluid balance to mortality in sepsis were observational [16,17], which precludes causal inference. The most severely ill patients require more fluids. This association could easily have biased most observational studies on the topic, as many were unadjusted for the disease severity of patients, both chronic and acute ones. Furthermore, death occurs in septic shock when all physiologic reserves have been exhausted. In this clinical situation, most interventions are likely to be purely cosmetic.

Laterre et al. did not require complex monitoring, probably in order to simplify study participation. Selepressin, like all vasopressin analogues, is a potent vasopressor. Contrary to norepinephrine which also affects β receptors, Selepressin has no direct inotropic cardiac effects. A physiological study that randomised 20 patients with septic shock to terlipressin (a pro-drug of vasopressin) and norepinephrine showed a more significant drop in cardiac index among patients treated with terlipressin than among those treated with norepinephrine ($P < 0.05$) [19]. Vasopressin analogues may induce a low flow state if the cardiac index decreases in response to vasoconstriction. Measurement of cardiac function is also conspicuously missing in the two other major RCTs that assessed vasopressin and its analogues in patients with sepsis [9,10].

Laterre et al. chose to seek study drug superiority rather than non-inferiority [18]. Most RCTs conducted in patients with septic shock have targeted superiority. However, antibiotics are nowadays almost routinely studied, approved and licensed based on proof of non-inferiority [20,21]. Now, infectious disease medications, for example, are rarely expected to demonstrate proof of superiority and drug agencies are generally willing to approve competing drugs provided there is proof of safety. Many new drugs are licensed in a similar process in oncology as well [22]. These flexibility and abundance have likely led to important incidental discoveries.

An increased risk of ischemic events is often cited as a cause of concern with regards to vasopressin and its analogues. Laterre et al. found a similar rate of adverse events in the study and control groups; cardiac ischemia 6.6% *vs.* 5.6% and mesenteric ischemia 3.2% *vs.* 2.6% respectively [18]. The coagulation sequential organ failure assessment (SOFA) score was higher with selepressin than with placebo, a finding attributed to the effect of V1a on platelet aggregation [23]. Other studies have supported the safety of vasopressin and its analogues. One single centre study of patients in vasoplegic shock after cardiac surgery showed that patients randomised to treatment with vasopressin ($n = 149$) had less severe complications and lower 30-day mortality than those treated with norepinephrine ($n = 151$) [24]. Another single centre study of severe trauma patients showed that patients randomised to receive vasopressin ($n = 49$) required significantly less blood products (median 1.4 *vs.* 2.9; $P = 0.01$) than those receiving placebo ($n = 51$). The amount of crystalloids and vasopressors administered and mortality were similar in the two groups [25].

The way a drug is used can affect its efficacy. In the study conducted by Laterre et al. the selepressin group received less steroids than the placebo group (13.7% *vs.* 22.9%; OR, 0.53 [95% CI, 0.37 to 0.78]; $P = 0.001$) [18]. A preliminary study comparing a historical cohort receiving only norepinephrine ($n = 86$) to patients treated with norepinephrine combined with low-dose terlipressin and intravenous hydrocortisone ($n = 26$) showed a reduction in the 72-hour severity score [26]. Such findings require confirmation that will be much more difficult to acquire with RCTs than from routine data collection if the drug remains unlicensed.

Laterre et al. should be congratulated for providing excellent data on the equipotency and safety of selepressin in septic shock [18]. The effect of a single excellent drug can be entirely obscured by poor practice and it is nearly impossible to control for all the factors affecting patient outcome in critical illness. The findings of Laterre et al. encourage further use of selepressin in routine practice. It is unlikely to expect that a single drug (i.e. norepinephrine) should be appropriate for all patients with all the disease conditions leading to septic shock. It is therefore unclear why in septic shock, a syndrome associated with > 40% mortality, despite the obvious need to expand the number of drugs available to practicing clinicians, some drug agencies are still refusing to provide access to new anti-hypotensive drugs. Experts in critical illness should be allowed using their considerable experience and clinical judgment when selecting the drug most appropriate for their individual patient with septic shock.

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