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Arginine–vasopressin and corticosteroids in septic shock: engaged but not yet married!

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Considerable efforts have been made to spare excessive catecholamine exposure and avoid side effects when treating patients with refractory septic shock. Until recently, physiological replacement of arginine–vasopressin (AVP) and corticosteroid (CS) deficits was considered promising but equivocal to improve end-organ function [1], reduce new-onset tachyarrhythmias [2], shorten duration of shock [3], and improve survival [4]. However, two large multicenter randomized controlled trials failed to demonstrate mortality reduction when using physiological doses of AVP [5] and CS [6] and hampered the initial enthusiasm for their widespread use.

In this issue of *Intensive Care Medicine*, Torgersen et al. [7] evaluate the effect on mortality of adding CS to

AVP in 159 patients with severe septic shock. Patients included in this single-center retrospective study were relatively ill, as outlined by high baseline sepsis-related organ failure assessment (SOFA) score (median score 15), frequent requirement of continuous renal replacement therapy (99/159, 62.3%), and overall intensive care unit (ICU) mortality (97/159, 61.0%). This sample is not fully representative of the severe sepsis population currently encountered in ICUs [8]. Because treatment assignment was not randomized, the authors used three different statistical analyses to account for baseline characteristics imbalance: multivariate logistic regression, Cox proportional hazard model, and Cox model stratified to matched pairs based on propensity score. Both adjusted analyses and propensity score determination were based on co-variables such as age, year of admission, baseline SOFA score, and initial AVP dose, and ignored potentially significant confounders or cointerventions like fluid resuscitation or early effective antimicrobial therapy. Improved survival at 28 days was demonstrated with the Cox proportional hazard model, but not with other statistical analyses, maybe due to lack of power. These results should be cautiously interpreted and must not lead to hasty conclusions regarding the benefits of combining AVP and CS.

Two previous studies using retrospective design and prone to similar biases reported consistent results [9, 10]. Bauer et al. [9] compared 21 patients receiving AVP and CS with 21 patients infused with AVP without CS. Patients were matched for age, sex, acute physiology score component of the acute physiology and chronic health evaluation (APACHE), number of vasopressors, and primary ICU service [9]. Patients receiving CS were more likely to be alive and weaned off vasopressors at day 7 (80.9 vs. 47.6%, $p = 0.02$), although the 28-day and hospital mortality were not statistically different. In another retrospective analysis of 778 patients with septic shock enrolled in a multicenter randomized controlled

Fig. 1 Effect on 28-day mortality of adding CS or not to AVP in patients with septic shock

trial [5], Russell et al. [10] reported that patients receiving CS ($n = 588$) had decreased 28-day mortality when treated with AVP and norepinephrine when compared to norepinephrine alone (35.9 vs. 44.7%, $p = 0.03$). Paradoxically, among patients not receiving CS ($n = 190$), AVP was associated with a trend toward increased mortality compared to norepinephrine (33.7 vs. 21.3%, $p = 0.06$). However, among all patients who received AVP, adding CS had no effect on 28-day mortality (Fig. 1).

The findings of Torgersen, Russell, and Bauer et al. are hypothesis-generating and make physiological sense. Cross talk between CS and AVP may occur at several levels. On the one hand, AVP increases ACTH secretion by corticotrophic cells through V1b receptors independently of CS negative feedback [11]. This mechanism plays a minimal role under basal conditions, but may become essential during acute stress [12]. On the other hand, CS usually inhibit AVP release centrally [13], whereas enhanced blood content or delayed clearance of AVP has been observed with CS administration in septic shock [10, 14], although this finding was recently challenged [15]. In addition, both CS and AVP can modulate or block ATP-sensitive potassium channels, and restore calcium content and constrictive ability of smooth muscle cells [16, 17]. CS may also retrieve AVP sensitivity of vascular V1a receptors, which are suspected to be downregulated in sepsis [18]. These effects may be

mediated by rapid onset of nongenomic mechanisms without protein synthesis involvement, including direct interaction/competition between peptidergic ligands and their respective membrane receptors [19]. In this respect, starting CS before or during AVP infusion did not alter the potential benefit of this combination in the current study [7]. Another putative mechanism is a V1 receptor-independent effect through the resolution of inflammatory processes, including the pleiotropic anti-inflammatory activities of CS and the immunomodulatory properties of AVP on microbial-induced inflammation [20, 21].

In summary, underlying mechanisms of potential interaction between AVP and CS are complex and speculative, although several cross-talk pathways exist. To date, there is insufficient evidence to strongly support a liberal use of either AVP or CS alone or a combination of both in the treatment of septic shock. Therefore, to evaluate the effect on mortality of AVP and CS alone or in combination, an adequately powered 2×2 factorial double-blind randomized controlled trial with appropriate interaction testing [22] is now warranted.

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Conflict of interest None of the authors have any relevant conflict of interest to disclose.

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