Vasopressor weaning in sepsis: Debate is being continued!

Noradrenaline and vasopressin are the two most commonly used vasopressors in the management of septic shock, and current Surviving Sepsis Guidelines recommend noradrenaline as a primary vasopressor and vasopressin as an additional therapy to reduce the dose of noradrenaline.[1] Discontinuation of vasopressor therapy in septic shock patients after improvement of hemodynamics is controversial. From a pharmacological point of view, it may be prudent to taper vasopressin first as it has a longer half-life than noradrenaline.[2] Moreover, vasopressin has clinically significant effects on splanchnic circulation and cardiac output.[3] However, available clinical data in this area diverge, and limitations of the research studies prevent evidence-based decision making. Several retrospective cohort studies and a single randomized controlled trial (RCT) have evaluated this question.

A small single-center RCT compared 'noradrenaline first' versus 'vasopressin first' tapering strategies.[4] This study was prematurely stopped after recruiting 85 patients as the incidence of hypotension after 1 hour of stopping the vasopressor was nearly 3 times higher with the 'noradrenaline first' strategy when compared to the 'vasopressin first' strategy. Apart from being a small single-center study, it has several limitations; for example, patients of the 'vasopressin first' group had a lower oxygenation status and a higher need for mechanical ventilation.

Sacha *et al.*[5] evaluated the effect of order of vasopressor discontinuation in a cohort of more than 500 patients of septic shock. They reported no difference in the incidence of hypotension within 24 h of vasopressor discontinuation between 'noradrenaline first' and 'vasopressin first' strategies. However, adjusted Cox regression analysis reported that when the 'vasopressin first' strategy was applied, the time to develop hypotension was shorter.

Table 1: Summary of recent evidence in vasopressor weaning in sepsis

Author and Year	Design	Sample Size	Major Findings	Biases
Jeon 2018	Randomized controlled trial	*n*=78	The incidence of hypotension is 68.4% in the NA group versus 22.5% in the VP group within 1 hour. The time to hypotension was shorter in the NA group. ICU mortality and 28-day mortality were similar. Hospital mortality was higher in the VP group.	Small sample size Single-center study Patients in the VP group had a lower P/F ratio and a higher need for MV.
Hammond 2019	Retrospective cohort	*n*=154	Clinically significant hypotension requiring intervention occurred more frequently in the VP group (67.8% vs 10.8%; *P*<0.001). The duration of ICU stay and the duration of hospital stay were similar. VP was significantly associated with hypotension in adjusted analysis [OR (95% CI) 13.8 (3.4-56.3)].	Lack of protocolized vasopressor weaning Lack of standardized additional therapies such as corticosteroids Wide confidence interval in the adjusted analysis Small sample size
Bauer 2010	Retrospective cohort	*n*=50	The incidence of hypotension is 55.6% in the VP group versus 15.6% in the NA group (*P*=0.008). The time to hypotension was lower in the VP group (*P*<0.001). Discontinuation of VP was associated with hypotension (adjusted Cox regression analysis, *P*=0.006) The length of ICU stay and the length of ICU mortality were similar.	Small sample size Patients receiving the corticosteroid were higher in the NA group. The NA group consisted of a higher number of patients from surgical ICU. The vasopressor weaning protocol was not mentioned.
Sacha 2018	Retrospective cohort	*n*=545	The overall incidence of hypotension was similar in 24 h (*P*=0.28). The increase in vasopressor dose was higher in the VP group (*P*<0.001). Hospital mortality and ICU mortality were similar VP group patients developed hypotension early (*P*<0.0001).	NA group patients had higher MAP at vasopressor discontinuation. Vasopressor weaning was not protocolized.
Song 2021	Retrospective cohort	*n*=2035 *n*=961 (septic shock)	VP group patients had a higher incidence of hypotension (*P*<0.001), a longer time to shock reversal (*P*=0.009), and higher hospital (*P*=0.006) and 28-day mortality (*P*<0.001). The risk of hypotension was higher in the VP group after adjustment of possible confounders [OR (95% CI) 4.1 (3.3, 5.1)]. 28-day mortality was higher in the VP group in adjusted analysis (*P*<0.001). The need for RRT was higher in the VP group in adjusted analysis (*P*<0.001). In the septic shock cohort, the incidence of hypotension was higher in the VP group (*P*<0.001).	The incidence of cancer was higher in the VP group, and it was not adjusted in logistic regression. The noradrenaline maximum dose was higher in the VP group (in the sepsis cohort). VP was not titrated.

NA=noradrenaline, VP=vasopressin, ICU=intensive care unit, P/F ratio=PaO_2/FiO_2 ratio, MV=mechanical ventilation, MAP=mean arterial pressure, OR=odds ratio, CI=confidence interval

On the other hand, two previous retrospective cohort studies also reported a higher incidence of hypotension when vasopressin is discontinued before noradrenaline.[6,7] Various factors such as fluid boluses before discontinuation of vasopressors, dose and duration of the corticosteroid, and use of additional therapies, such as midodrine, etc., might have confounded the result. Unmasking of relative vasopressin deficiency might also be contributing to hypotension as its serum level decreases significantly at 24 h.[8]

Recently, a large retrospective study evaluated the 'noradrenaline first' strategy and the 'vasopressin first' strategy in patients with shock.[2] That study included more than 2000 patients' data, and nearly half of them had septic shock. The 'vasopressin first' strategy was associated with a higher incidence of hypotension, a longer time to shock resolution, and interestingly higher hospital and 28-day mortality. These were significant imbalances at several baseline variables, such as Charlson's comorbidity index, prevalence of cancer, sepsis, diabetes mellitus, requirement of renal replacement therapy, use of corticosteroids, and maximum noradrenaline dosing. The authors reported both adjusted analysis and unadjusted analysis and that the 'vasopressin first' strategy was associated with worse outcomes. However, it is worth mentioning that prevalence of cancer was not adjusted in the analysis, and it might have contributed not only to the increased incidence of hypotension but also to increased 28-day and hospital mortality.

It is evident from the current available data that reported evidence diverges and it is difficult to draw a meaningful conclusion [Table 1]. Although a single RCT reported possible benefits of the 'vasopressin first' strategy, it had several serious limitations. Most of the other retrospective studies reported a higher incidence of hypotension when the 'vasopressin first' strategy is applied. Apart from being retrospective in design, all individual studies have several limitations. Along with this, vasopressin was abruptly stopped in many instances, rather than a true 'tapering'. In the absence of a well-designed RCT, it is evident that hypotension after vasopressor weaning is multi-factorial and a large multi-center trial is necessary to account for those confounding factors. However, patients' clinical conditions, such as cardiac output, systemic vascular resistance, heart rate, etc., could be used to decide the vasopressor weaning strategy until we have further evidence.

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