Does the Addition of Vasopressin to Catecholamine Vasopressors Affect Outcomes in Patients With Distributive Shock?

TAKE-HOME MESSAGE

In patients with distributive (eg, septic) shock, the addition of vasopressin or vasopressin analogues to catecholamine therapy may decrease the rate of atrial fibrillation and need for renal replacement therapy but may also increase the risk of digital ischemia.

METHODS

DATA SOURCES

The authors searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception through February 25, 2018. Trial registries were searched through http://www.isrctn.com for unpublished or ongoing trials. References of eligible articles were reviewed and experts were consulted to identify additional trials. Additionally, the authors hand searched the last 2 years' worth of conference proceedings for the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the American Thoracic Society.

STUDY SELECTION

Studies included randomized trials comparing vasopressin (or analogues), with or without catecholamine vasopressors, with catecholamine vasopressors alone in adults with distributive shock. Distributive shock was defined as septic shock, post–cardiovascular surgery vasoplegia, neurogenic shock, or anaphylaxis. Any dose, duration, and other cointerventions

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshots (SRS) series. The source for this systematic review snapshot is: **McIntyre WF, Um KF, Alhazzani W, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. *JAMA*. 2018;319:1889-1900.**

Results

Comparison of catecholamines with and without vasopressin on outcomes in distributive shock.

Outcome	No. of Studies (No. of Participants)	Relative Risk With Vasopressin (95% CI)	I^2, %
AF	13 (1,462)	0.77 (0.67–0.88)	1
1-mo mortality, all studies	17 (2,904)	0.89 (0.82–0.97)	0
1-mo mortality, low risk of bias	2 (1,049)	0.96 (0.84–1.11)	0
RRT	6 (805)	0.74 (0.51–1.08)	70
Digital ischemia	9 (1,963)	2.38 (1.37–4.12)	0

CI, Confidence interval; *AF*, atrial fibrillation; *RRT*, renal replacement therapy.

The search identified 1,210 unique citations, with 23 randomized trials, totaling 3,088 patients, included in the review. Twenty-one studies enrolled patients with septic shock, one study enrolled post–cardiac surgery patients, and one study included both patient types. There were no studies of patients with anaphylaxis or neurogenic shock. Vasopressin was studied in 13 trials, and terlipressin (8 trials) was the most commonly studied analogue. Most trial protocols did not require that vasopressin be used with other

were allowed. Two reviewers independently screened studies for eligibility and exclusion, with disagreements resolved through discussion.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently abstracted data on the intervention and outcomes. The primary outcome was the incidence of atrial fibrillation. Planned secondary outcomes included mortality, need for renal replacement therapy, myocardial injury, stroke, ventricular arrhythmias, and length-of-stay metrics. Digital ischemia and acute kidney injury were post hoc secondary outcomes. Primary study authors were contacted for clarifications and outcome data not listed in primary reports. Quality was assessed for individual studies with the Cochrane Risk of Bias Tool, and Grading of Recommendations Assessment, Development and Evaluation was used to define the overall quality of evidence. Meta-analyses were conducted with random effects in instances of low clinical heterogeneity. The primary analyses are reported as relative risk with 95% confidence intervals. Sensitivity analyses were performed including only studies at low risk of bias.

vasopressors but allowed the addition of catecholamines if needed. The comparator agent was norepinephrine in 19 of 23 studies.

Results from 13 studies suggested that atrial fibrillation was less common in patients randomized to vasopressin, with the results unchanged when only trials with low risk of bias were included. Vasopressin administration was also associated with reduced 1-month mortality in the 17 studies in which mortality data were available. However, in the sensitivity analysis limited to trials with low risk of bias, there was no effect on mortality (Table). Overall, rates of renal replacement therapy were similar between groups. However, the sensitivity analysis including only trials with low risk of bias found lower rates of renal replacement therapy with vasopressin use (relative risk 0.70; 95% confidence interval 0.53 to 0.92). Digital ischemia was more common with vasopressin. There were no differences in other secondary outcomes, including myocardial injury, stroke, ventricular arrhythmias, and length-of-stay metrics.

Commentary

Despite many comparative studies, the ideal vasopressor for patients with shock, including septic shock, is unknown.[1] Vasopressin is an endogenous peptide that is depleted in patients with septic shock and that can be infused to increase vascular tone and increase blood pressure.[2] It has been hypothesized that vasopressin may decrease myocardial demand and arrhythmogenesis in patients with shock by allowing lower doses of cardiac-stimulating catecholamines.[3] This systematic review seeks to define whether the addition of vasopressin to catecholamines is superior to catecholamines alone in distributive shock.

Distributive shock may be caused by anaphylaxis, vasoplegia after cardiac surgery, or neurogenic causes but in the emergency department (ED) setting is usually caused by septicemia. Many of the patients driving the atrial fibrillation results, however, were not septic. Hajjar et al[4] studied patients with vasoplegia after cardiac surgery and found that 82% of controls developed atrial fibrillation and carried 75% of the weight of the atrial fibrillation analysis. Limiting the analysis to only septic patients resulted in a similar point estimate in effect size, but the result was no longer statistically significant (relative risk 0.76; 95% confidence interval 0.55 to 1.05).

More important, the apparent effect on mortality found in this meta-analysis was driven by small studies at high risk of bias, including some that were published in abstract form only. When the mortality analysis was restricted to studies at low risk of bias, there was no evidence of benefit.

Outside of one study with high risk of bias and markedly outlier results,[5] vasopressin consistently appeared to decrease the need for renal replacement therapy. This likely benefit was countered by a consistent finding of increased digital ischemia. Because the primary studies did not provide information on the severity of the ischemia, which could range from transient discoloration to necrosis and amputation, the effect of this finding on patients is unclear.

Interpretation of the results of this review is complicated by the clinical heterogeneity of the included studies. Some trials studied vasopressin; others, terlipressin or other analogues. The control groups mostly received norepinephrine, but in a few trials vasopressin was compared with placebo or other catecholamines. Titration of

vasopressin and comparator agents was highly variable, as was the addition of other catecholamines to the vasopressin-treated patients. Additionally, inclusion and exclusion criteria were variable. For example, cirrhosis or cancer was an inclusion criterion in some trials but an exclusion criterion in others. It is thus unclear whether the results should be considered widely generalizable or should be applied differently to different populations. No studies in patients with anaphylaxis or neurogenic shock were identified, and results may not be generalizable to these populations.

This review suggests that the addition of vasopressin or analogues to catecholamines may decrease atrial fibrillation and renal replacement therapy while increasing digital ischemia in patients with septic shock.[6] The effect on mortality is unclear. Further work is needed to examine these medications in ED patients with distributive shock to determine the ideal treatment regimens.

1. Gamper G, Havel C, Arrich J, et al. Vasopressors for hypotensive shock. *Cochrane Database Syst Rev*. 2016;2:CD003709.
2. Bujik SE, Bruining HA. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*. 1998;98:187.
3. Dunser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med*. 2009;24:293-316.
4. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: the VANCS randomized controlled trial. *Anesthesiology*. 2017;126:85-93.
5. Dunser MW, Mayr AH, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation*. 2003;107:2313-2319.
6. McIntyre WF, Um KF, Alhazzani W, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. *JAMA*. 2018;319:1889-1900.