After the Rebranding and Cost Increase, the Use of Vasopressin Continues to Increase Yearly Especially in Case of Acute Kidney Injury With Septic Shock: Is There Recent Data Justifying It?

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To the Editor:

Sacha et al (1) showed that vasopressin was utilized in 42.6% of acute kidney injury (AKI) before and increased to 54.6 % after rebranding, which seems to be high despite the cost increase. We reviewed potential justifications for the vasopressin increased use in AKI during septic shock (SS) after rebranding (2). Just after rebranding in 2016, Gordon et al (2) reported the results of the multicenter trial Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH), which compared the effect of these two vasopressors on AKI in adult patients with SS. Rationale for this study was the landmark Vasopressin and Septic Shock Trial (VASST), done in 2014 before rebranding. This study found an association between low-dose vasopressin (0.01–0.03 U/min) and decreased mortality in less severe SS but no difference between vasopressin and norepinephrine on global mortality or organ dysfunction rates (3). Post hoc analysis of the VASST study suggested that vasopressin treatment is associated with reduced progression to AKI, decreased need for renal replacement therapy (RRT), and reduced mortality in SS patients at risk of AKI (4). This concurred with earlier small clinical studies, demonstrating improvement in creatinine clearance (CCL) in vasopressin-treated patients (4). In the VANISH study, there were fewer RRTs in the vasopressin group (2).Unfortunately, the VANISH study did not find a difference in the number of kidney failure-free days in surviving patients receiving vasopressin or norepinephrine (2). The reduction in the number of RRTs in the vasopressin group but without any difference in the number of kidney failure-free days in survivors between groups had procured only some meager scientific solace (4). Many meta-analyses, however, did not reveal any significant improvements with vasopressin regarding AKI (4). Since rebranding, only one study has shown a favorable effect of vasopressin on AKI risk in sepsis. This was a study performed in an ovine model of sepsis by Okazaki et al (5). This study showed that vasopressin infusion did not significantly affect renal medullary perfusion or Po_2 and induced a sustained (6 hr) ~2.5-fold increase in CCL (5). Vasopressin reduced sepsis-induced mesenteric hyperemia (+61 ± 13 to +9% ± 6%) (5). Norepinephrine transiently (2 hr) improved CCL (by ~3.5-fold) but worsened renal medullary ischemia (to –64% ± 7%) and hypoxia (to –71% ± 6%) (5). Therefore, clearly, low-dose vasopressin (0.03 international units [IU]/min [0.03–0.05 IU/min]) as first vasopressor

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and ideally alone significantly improves CCL and renal function in this animal model (5). Although there are significant improvements in CCL function favoring vasopressin instead of norepinephrine, there is not sufficient evidence to dramatically increase the use of vasopressin in AKI long after rebranding. Human randomized controlled trials using the new approach by Okazaki et al (5) (using a special load dose vasopressin titration [0.03–0.05 IU/min] as first vasopressor and ideally alone) are needed to see if we can confirm these new findings. Although waiting for these trials, there is or has been no justification for the increased use of vasopressin for AKI now, or in the recent years.

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REFERENCES

1. Sacha GL, Kiser TH, Wright GC, et al: Association between vasopressin rebranding and utilization in patients with septic shock. *Crit Care Med* 2022; 50:644–654
2. Gordon AC, Mason AJ, Thirunavukkarasu N, et al: Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA* 2016; 316:509–518
3. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
4. Honore PM, Jacobs R, De Waele E, et al: Vasopressin versus noradrenaline as initial therapy in septic shock. Is vasopressin-related renal protection doomed to "vanish" in the haze? *Ann Transl Med* 2016; 4(Suppl 1):S47
5. Okazaki N, Iguchi N, Evans RG, et al: Beneficial effects of vasopressin compared with norepinephrine on renal perfusion, oxygenation, and function in experimental septic acute kidney injury. *Crit Care Med* 2020; 48:e951–e958

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We appreciate the interest of Honore et al (1) in our article recently published in *Critical Care Medicine*, evaluating the association between vasopressin rebranding and its utilization in patients with septic shock (2). We are similarly interested in the discussion of vasopressin utilization in patients with acute kidney injury (AKI, termed "acute kidney failure" in our study) but want to emphasize that our results reported in Table 1 reflect characteristics in patients with septic shock prior to and after vasopressin rebranding. Specifically, the results in Table 1 reflect the frequency of AKI in patients identified in the before (42.6%) and after (54.6%) vasopressin rebranding cohorts. In the Premier Healthcare Database, during our study time frame of January 2010 and March 2017, there were 138,313 patients who were identified as having AKI present on admission. Of these patients with AKI, 40,254 (29.1%) received vasopressin: 20,841 of 79,907 (26.1%) patients with AKI before vasopressin rebranding and 19,413 of 58,406 (33.2%) patients with AKI after vasopressin rebranding. However, we cannot differentiate if the increase in vasopressin utilization was targeting patients with AKI to improve renal function or if the presence of AKI was associated with a phenotype or severity of septic shock that drove the vasopressin prescribing pattern. We agree with the authors that, to date, studies have failed to conclusively demonstrate that vasopressin improves overall renal function, which should be an area of continued study.

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