Editorial Commentary

Terlipressin or norepinephrine in septic shock: do we have the answer?

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Provenance: This is an invited article commissioned by the Section Editor Xue-Zhong Xing [National Cancer Center (NCC)/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China].

Comment on: Liu ZM, Chen J, Kou Q, *et al.* Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Med 2018;44:1816-25.

Submitted Feb 02, 2019. Accepted for publication Feb 18, 2019.
doi: 10.21037/jtd.2019.05.07
View this article at: http://dx.doi.org/10.21037/jtd.2019.05.07

Despite increased attention on prevention and early aggressive treatment with antibiotics and smart fluid resuscitation, there remains high morbidity and mortality from septic shock globally (1). Frequently septic patients develop persistent distributive shock that often requires vasopressor infusion to restore adequate mean arterial pressure (MAP) in order to provide adequate perfusion to critical organs and tissues. Although there are a variety of catecholamines available to increase blood pressure in these critically ill patients, the unmet need for additional therapies remains because of the persistently high morbidity and mortality of septic shock.

Norepinephrine is the first line vasopressor in patients who do not respond to adequate fluid resuscitation (1). Recently there have been multiple randomized controlled trials (RCTs) of alternative non-catecholamine vasopressors including vasopressin (2,3), selepressin (4) and angiotensin II (5). Vasopressin is now considered the Surviving Sepsis Guidelines-recommended second vasopressor to be added to norepinephrine in refractory septic shock. This recommendation was based on multiple studies especially the pivotal Vasopressin and Septic Shock Trial (VASST) which added low dose vasopressin (0.01–0.04 units/hour) to ongoing norepinephrine compared to norepinephrine mono-therapy in septic shock. Although the 28-day mortality rates were similar, the vasopressin arm had lower mortality in those patients with less severe shock. However, recent studies have reported that the efficacy of vasopressin in clinical practice may be disappointing (6). Sacha and colleagues (6) reported a 45% response rate to vasopressin (defined by decreased catecholamine dose and stable blood pressure by six hours after initiation of vasopressin) and that patients treated after 12 hours and those with a high lactate had a lower response to vasopressin. There is also concern about potential vasopressin toxicity because vasopressin activates V2 receptors on endothelial cells (that can be prothrombotic) and in the renal collecting ducts (that can potentially decrease urine output. Those concerns are the rationale for assessing vasopressin-like agents that have more V1a agonism such as terlipressin or that are pure V1a agonists such as selepressin.

Terlipressin is a synthetic analogue of vasopressin which has greater affinity for the V1 receptor that is the mechanism of vascular smooth muscle vasoconstriction in response to vasopressin and thus could be associated with less side effects than vasopressin (7). Animal model studies have shown similar vasoconstrictive efficacy with terlipressin *vs.* vasopressin and less fluid retention with terlipressin which is critical for septic shock patients.

Terlipressin has been primarily studied in critically ill patients with hepatorenal syndrome and small studies have demonstrated improved renal function in these challenging patients. However, there is equipoise around use of terlipressin or norepinephrine in septic shock (8-14).

Liu and colleagues addressed this question by conducting a multicenter, RCT of terlipressin *vs.* norepinephrine in septic shock in China (15). They are to be commended for their efforts in implementing a large pivotal RCT in a country which historically has not performed such large RCTs in critical care.

They randomized 617 patients to terlipressin (n=312) or norepinephrine infusion (n=305) plus standard care which included open label vasopressors. They used an a priori modified intent-to-treat primary analysis of the primary endpoint, 28-day mortality in a subgroup (terlipressin n=260; norepinephrine n=266). There was no difference in 28-day mortality (terlipressin =40%, norepinephrine =38%, p NS). Selected secondary endpoints such as days alive and free of vasopressors and change in Sepsis Organ Failure Assessment (SOFA) score did not differ between groups. However, there were more serious adverse events in the terlipressin than the norepinephrine group (30% *vs.* 12%, P<0.01).

The authors conclude that there is no difference in mortality between terlipressin and norepinephrine but that terlipressin has more serious adverse events.

This RCT was powered for mortality and the main result was negative suggesting that the result in a true negative. However, the assumed mortality rates and absolute risk reduction [identical to what was used on the VASST (3)] are quite high for the period of the RCT conduct. The mortality rates in the norepinephrine were higher than reported in recent RCTs in septic shock such as early goal-directed therapy (16-19); that is somewhat surprising. The trial was also stopped at the second interim analysis because of the a priori futility analysis.

Terlipressin and norepinephrine were administered as continuous infusions of 20–160 mg/h. terlipressin or 4–30 mg/min. norepinephrine (a low to moderate dose of norepinephrine) to achieve a target MAP of 65–75 mmHg. Terlipressin is often initiated with a bolus followed by an infusion but this was not done in the current RCT and that may have limited the beneficial effects of terlipressin reported in prior studies (20). In both groups, the bedside nurse could also administer open label norepinephrine, dopamine or epinephrine to achieve target MAP. Study drug was weaned when the patient had been hemodynamically stable for 12 hours, a reasonable aspect of the protocol. The study drug could be withheld if a pre-defined serious adverse event occurred. If a patient was weaned off study drug and later redeveloped septic shock, then the assigned blinded study drug was restarted during the same ICU admission.

The inclusion criteria were septic shock defined as hypotension despite "adequate" fluid resuscitation (not defined as to volume or type of fluid). The MAP during the treatment period was remarkably high, about 80 mmHg, i.e., higher than the target MAP of 65–75 mmHg (Liu *et al.*, Figure 2).

The use of short term (28-day) mortality for septic shock interventions has existed for decades but recent authors have questioned the validity of such a hard endpoint and have argued for more creative endpoints similar to the field of cardiology. Recently the United States Food and Drug Administration approved angiotensin II for the treatment of septic shock (5). There has been discussion of the FDA rationale for approving angiotensin II using and approving a novel primary endpoint of MAP elevation at three hours (21).

These investigators should be congratulated for conducting a high-quality trial, with an interesting design, incorporating a blinded placebo infusion in what is a challenging research area. The strengths of the study include well-matched patients modified intent-to-treat primary analyses, and the method for organ dysfunction analyses (22).

What are the wider implications of the Liu's RCT? Prior RCTs establish that norepinephrine is the vasopressor of first choice and that vasopressin may be added but that dopamine should be avoided because of early vasopressin (2) *vs.* norepinephrine, norepinephrine *vs.* epinephrine (23), norepinephrine *vs.* dopamine (24) and vasopressin *vs.* norepinephrine in septic shock (3). A recent propensity matched cohort study (25) from the VASST coordinating center showed that lower doses of vasopressin were associated with similar outcomes compared to NE. Patients who received early vasopressin and norepinephrine increased MAP to the target of 65 mmHg faster than those receiving norepinephrine monotherapy (26).

For the clinician we agree with Liu and colleagues that there is no difference in mortality between terlipressin and norepinephrine but that terlipressin has more serious adverse events. Thus, norepinephrine remains the vasopressor of first choice but that vasopressin or terlipressin could be added to patients with refractory septic shock who do not respond to norepinephrine.

Acknowledgements

Dr. Russell reports having received an investigator-

initiated grant from Grifols (entitled "Is HBP a mechanism of albumin's efficacy in human septic shock?") that was provided to and administered by UBC.

Footnote

Conflicts of Interest: Dr. Williams reports consulting fees in the last 3 years from Ferring (selepressin), AKPA (recombinant soluble thrombomodulin) and Lajolla Pharmaceuticals (angiotensin II). Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to the use of PCSK9 inhibitor(s) in sepsis and related to the use of vasopressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell was a founder, Director and shareholder in Cyon Therapeutics Inc. Dr. Russell is a shareholder in Molecular You Corp (in the last 36 months). Dr. Russell reports receiving consulting fees in the last 3 years from: (I) Asahi Kesai Pharmaceuticals of America (AKPA) (developing recombinant thrombomodulin in sepsis). (II) SIB Therapeutics LLC (developing a sepsis drug). (III) Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin).

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Cite this article as: Williams MD, Russell JA. Terlipressin or norepinephrine in septic shock: do we have the answer? J Thorac Dis 2019;11(Suppl 9):S1270-S1273. doi: 10.21037/jtd.2019.05.07

