Intensive Care Med (2018) 44:1964–1966
https://doi.org/10.1007/s00134-018-5290-x

EDITORIAL

Terlipressin or norepinephrine, or both in septic shock?

Johan Mårtensson[1,2*] and Anthony C. Gordon[3,4]

Vasopressor therapy is one of the cornerstones in the management of septic shock when intravenous fluid resuscitation is insufficient to maintain a mean arterial pressure (MAP) above 65 mmHg [1]. Norepinephrine is the recommended first-choice vasopressor, but hyporesponsiveness represents a significant clinical problem and high doses are sometimes required to achieve the target MAP. Such high-dose catecholamine therapy may increase the risk of life-threatening arrhythmias, immunosuppression, and mortality [2–4].

In response to concerns about high-dose norepinephrine therapy in septic shock, adjunctive treatment with vasopressin has been suggested [1]. In the Vasopressin and Septic Shock Trial (VASST), adding low-dose vasopressin (0.01–0.03 U/min) to existing norepinephrine treatment did not decrease mortality in patients with septic shock compared with norepinephrine mono-therapy [5]. However, among patients with less severe shock and among those enrolled within 12 h there appeared to be a possible survival benefit with vasopressin, suggesting that early initiation may be beneficial.

Yet, the Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial found no difference in kidney failure-free days or mortality with early (within 6 h) initiation of vasopressin therapy (up to 0.06 U/min) compared with norepinephrine alone among 409 septic shock patients [6].

In addition to vasoconstriction via vasopressin V1-receptor activation, vasopressin may cause unwanted side effects via activation of V2-receptors in the renal collecting ducts (antidiuretic effect) and on endothelial cells (prothrombotic effect via Von Willebrand factor release), V3-receptors in the pituitary gland (increased ACTH secretion) and oxytocin-receptors on vascular endothelial cells (increased nitric oxide synthase activity causing vasodilation). Terlipressin, a synthetic vasopressin analogue with greater selectivity for the V1-receptor, may therefore be an attractive alternative to vasopressin.

Experimental animal data suggest that terlipressin attenuates fluid accumulation and prolongs survival time compared with vasopressin [7]. In addition, data from small randomised controlled trials suggest that terlipressin improves short term renal function in patients with type 1 hepatorenal syndrome [8] and that it may even improve survival in patients with liver cirrhosis and septic shock compared with norepinephrine [9]. However, data on the safety and efficacy of terlipressin therapy in septic shock patients without liver failure are scant.

In a recent article in *Intensive Care Medicine*, Liu et al. report the results of a randomised, multicenter, double blind, controlled trial comparing norepinephrine alone

*Correspondence: johan.martensson@sll.se
[2] Function Perioperative Medicine and Intensive Care, Karolinska University Hospital, 171 76 Stockholm, Sweden
Full author information is available at the end of the article

Springer

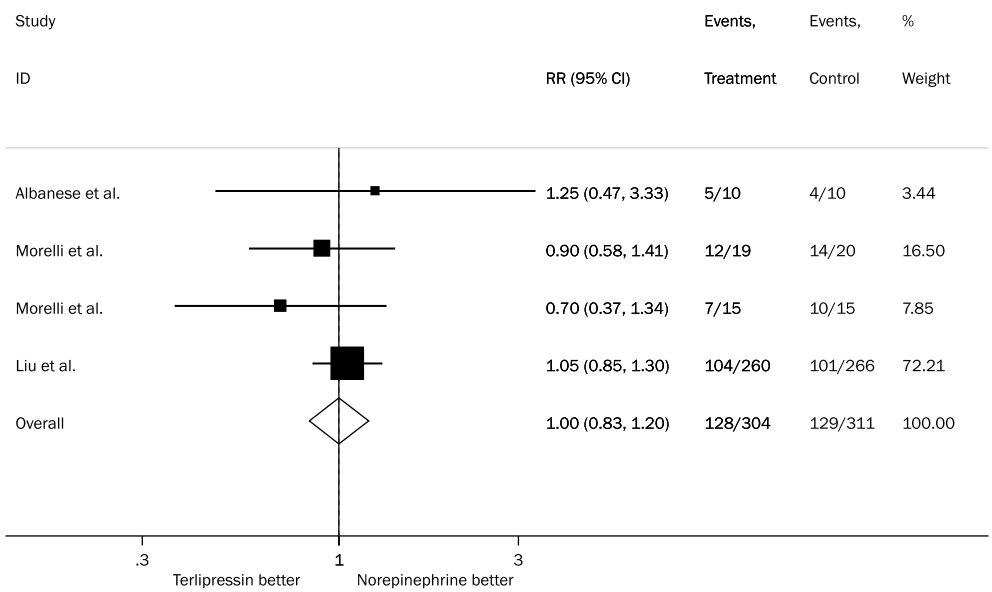

Fig. 1 Meta-analysis of mortality in randomised trials comparing terlipressin (Treatment) with norepinephrine (Control) in adult patients with septic shock

with early terlipressin infusion (20–160 μg/h) plus norepinephrine in patients with septic shock [10]. The study was stopped due to futility after enrolment of 50% of scheduled patients. In the 526 randomised and analysed patients, they found no difference in 28-day mortality (primary outcome; 38 vs. 40%, $P=0.63$), vasopressor-free days or change in SOFA score during the first week after randomisation. This informative study hence confirms the findings of previous pilot investigations showing no mortality benefit when terlipressin is used alone or is added to norepinephrine (Fig. 1) [11–13].

The striking difference in serious adverse events, particularly digital ischemia, reported by Liu et al., requires attention. Overall, 1.5% of patients treated with norepinephrine alone suffered from digital ischemia; an identical incidence to VANISH trial patients receiving norepinephrine only. However, in the study by Liu et al., digital ischemia occurred in 13% of patients receiving terlipressin (c.f. 5.4% with vasopressin in the VANISH trial). In addition, the authors found a greater prevalence of diarrhea (2.7% vs 0.3%), but importantly not acute mesenteric ischemia, in the terlipressin group.

The high incidence of digital ischemia may have several possible explanations. Firstly, the risk of terlipressin-induced ischemic events increases with hypovolemia. In the study by Liu et al., most cases of digital ischemia occurred in the first 24 h. Unfortunately, the amount of pre-randomisation fluid administration was not reported. It is therefore unclear whether patients were "adequately" fluid resuscitated before entering the trial.

Secondly, some studies demonstrate that cardiac index is significantly decreased with terlipressin but not with norepinephrine [11, 12]. An increase in systemic vascular resistance at the expense of cardiac index may indeed compromise organ blood flow and contribute to adverse ischemic events. But since cardiac index was not measured by Liu et al., we can only speculate about whether such hemodynamic alterations contributed to the high rate of adverse events.

Finally, terlipressin is known to have a longer effective half-life than both norepinephrine and (arginine) vasopressin, but the pharmacokinetics of lysin-vasopressin, the active metabolite of terlipressin, during continuous infusion in septic shock has not been established. Preliminary safety with low-dose infusion (approximately 110 μg/h) was reported in one small trial but adverse events other than atrial fibrillation were not assessed [13]. However, in patients with liver cirrhosis and septic shock who received up to 312 μg/h, the overall rate of adverse events was 41% with 29% experiencing "peripheral cyanosis" [9]. In view of the high rate of serious adverse events, the maximum terlipressin infusion rate should likely be significantly less than 160 μg/h in patients with septic shock.

In all, it appears that the terlipressin doses used to treat patients with hepatorenal syndrome may be too high in patients with septic shock. If there is a place for terlipressin infusion in such patients, a safe dose range needs to be established first. In the meantime, how should clinicians manage vasopressors in septic shock?

It makes sense to continue to use norepinephrine as first line therapy. As doses rise, then early use of vasopressin appears to be the logical second line vasopressor. It has been tested in multiple randomised controlled trials and a recent meta-analysis found its use led to lower rates of atrial fibrillation and possibly lower rates of mortality and requirement for renal replacement therapy [14]. However, digital ischemic events were higher in that analysis too, reminding us that adequate fluid resuscitation, repeated assessment of cardiac output and targeting the lowest acceptable MAP for each individual patient to avoid high-dose vasopressors where possible, remain important components in the management of septic shock.

Author details
[1] Department of Physiology and Pharmacology, Section of Anaesthesia and Intensive Care, Karolinska Institutet, Stockholm, Sweden. [2] Function Perioperative Medicine and Intensive Care, Karolinska University Hospital, 171 76 Stockholm, Sweden. [3] Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London, London, UK. [4] Intensive Care Unit, Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK.

Acknowledgements
ACG is funded by a National Institute of Health Research (NIHR) Research Professorship award (RP-2015-06-018) and supported the NIHR Comprehensive Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. ACG reports that he has received speaker fees from Orion Corporation Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare, Bristol-Myers Squibb and GSK, and received Grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution.

Received: 27 June 2018 Accepted: 29 June 2018
Published online: 13 July 2018

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377
2. Russell JA (2007) Vasopressin in vasodilatory and septic shock. Curr Opin Crit Care 13:383–391
3. Stolk RF, van der Poll T, Angus DC, van der Hoeven JG, Pickkers P, Kox M (2016) Potentially inadvertent immunomodulation: norepinephrine use in sepsis. Am J Respir Crit Care Med 194:550–558
4. Martin C, Medam S, Antonini F, Alingrin J, Haddam M, Hammad E, Meyssignac B, Vigne C, Zieleskiewicz L, Leone M (2015) Norepinephrine: not too much, too long. Shock 44:305–309
5. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358:877–887
6. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, Santhakumaran S, Ashby D, Brett SJ, Investigators V (2016) Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA 316:509–518
7. Rehberg S, Ertmer C, Kohler G, Spiegel HU, Morelli A, Lange M, Moll K, Schlack K, Van Aken H, Su F, Vincent JL, Westphal M (2009) Role of arginine vasopressin and terlipressin as first-line vasopressor agents in fulminant ovine septic shock. Intensive Care Med 35:1286–1296
8. Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, Gulberg V, Sigal S, Teuber P (2008) A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 134:1360–1368
9. Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, Sharma MK, Bhadoria AS, Kumar G, Joshi YK, Sarin SK (2017) A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int 37:552–561
10. Liu Z, Chen J, Kou Q, Lin Q, Huang X, Tang Z, Kang Y, Zhou L, Song Q, Sun T, Zhao L, Wang X, He X, Wang C, Wu B, Lin J, Yuan S, Gu Q, Qian K, Shi X, Feng Y, Lin A, He X, Guan X (2018) Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Med. https://doi.org/10.1007/s00134-018-5267-9
11. Albanese J, Leone M, Delmas A, Martin C (2005) Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. Crit Care Med 33:1897–1902
12. Morelli A, Ertmer C, Lange M, Dunser M, Rehberg S, Van Aken H, Pietropaoli P, Westphal M (2008) Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. Br J Anaesth 100:494–503
13. Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, Bachetoni A, D'Alessandro M, Van Aken H, Pietropaoli P, Westphal M (2009) Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care 13:R130
14. McIntyre WF, Um KJ, Alhazzani W, Lengyel AP, Hajjar L, Gordon AC, Lamontagne F, Healey JS, Whitlock RP, Belley-Cote EP (2018) Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. JAMA 319:1889–1900