Intensive Care Med (2019) 45:902–903
https://doi.org/10.1007/s00134-019-05642-w

EDITORIAL

Vasopressin in septic shock: what we know and where to next?

Paul J. Young[1,2*], Anthony Delaney[3,4] and Balasubramanian Venkatesh[4,5]

Noradrenaline is the vasopressor administered most commonly to patients with distributive shock [1]. However, in one study, 17.2% of patients with septic shock in United States hospitals received vasopressin, usually in combination with catecholamines [2]. In the Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial [3], which included patients from Australia, the United Kingdom, New Zealand, Saudi Arabia, and Denmark, usage was similar with 16.8% of patients receiving vasopressin at baseline. On the other hand, in the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial, an European trial, only 0.08% of patients were receiving vasopressin at baseline [4]. Such variability in usage reflects uncertainty. Accordingly, the individual patient data (IPD) meta-analysis in this issue by Nagendran and colleagues including randomized clinical trials (RCTs) comparing vasopressin with noradrenaline in patients with septic shock is both timely and informative [5].

An IPD meta-analysis, like an aggregate data meta-analysis, provides an overall estimate of the treatment effect from included RCTs, but in addition allows hypothesis testing in relation to specific subgroups defined on patient level baseline characteristics. This increased ability to assess patient level subgroups effects, comes at a significant cost with respect to the resources required to acquire, standardise and reanalyse patient level data from disparate trials [6]. The authors of this well-conducted IPD meta-analysis are to be commended for their efforts. This IPD meta-analysis included all major RCTs evaluating vasopressin therapy in septic shock and provides important insights for clinical practice. The observed 95% CIs were consistent with an effect of vasopressin therapy on 28-day mortality in septic shock that ranged between 14 percentage points relative decrease in mortality and 12 percentage points relative increase in mortality. Vasopressin therapy was associated with a reduced risk of cardiac arrhythmias, a trend towards a reduced requirement for renal replacement therapy and a greater risk of digital ischaemia. As the effect on mortality estimate is wide and encompasses clinically important effects, it is inappropriate to conclude that vasopressin therapy does not affect mortality in patients with septic shock; clinically important uncertainty with regard to the effect on mortality persists. The often dramatic blood pressure response to vasopressin and the observation that the duration of hypotension is strongly associated with an increased risk of death in patients with septic shock [7] will likely provide a rationale for continued use of vasopressin in septic shock until more definitive information about its effect on mortality overall, and in particular subgroups, is available.

Unfortunately, despite the promise for an IPD meta-analysis to provide information on subgroup effects, the data from this analysis provide little guidance as to which specific patients are most likely to benefit from (or be harmed by) vasopressin therapy. There was no demonstrated heterogeneity of treatment response in any subgroup pair. While the lack of demonstrated heterogeneity in relation to higher vs. lower doses of catecholamines at baseline might lead clinicians to infer that evidence does not support the use of vasopressin therapy in catecholamine refractory shock, power to detect such heterogeneity for this, and other, subgroup comparisons was likely limited. Moreover, it is notable that no RCT has evaluated the use of vasopressin in patients who remain hypotensive on high dose catecholamines. In patients with catecholamine refractory shock, those who fail to achieve

*Correspondence: paul.young@ccdhb.org.nz
[1] Intensive Care Unit, Wellington Regional Hospital, Private Bag 7902, Wellington South, New Zealand
Full author information is available at the end of the article

Springer

prescribed blood pressure targets despite high dose catecholamines, the common choice of vasopressin as an adjunctive therapy [1] remains reasonable.

There are other uncertainties. A small number of clinicians use vasopressin as a first line therapy in septic shock [1]. As most patients included in this IPD meta-analysis were receiving catecholamines at baseline, the safety and efficacy of this practice remains uncertain. Similarly, as noradrenaline was the comparator agent in all trials, it is unclear whether vasopressin is a useful adjunct in patients who are receiving adrenaline or other drugs.

Overall, based on observed 95% CI, the worst-case scenario is that vasopressin therapy kills one in every 22 patients with septic shock who receive it; the best case is that it saves the life of one in every 19 patients who receive it. The bottom line is that, despite a high-quality synthesis of available evidence, we have inadequate information. Nagendran and colleagues suggest that future trials should focus on long-term outcomes in select patient groups and should incorporate cost-effectiveness analyses. We agree and also consider that a better understanding of the effect of vasopressin therapy on quality of life is essential, particularly given the observed increase in ischaemic events with this treatment, which might be expected to have a substantial impact on quality of life of survivors of sepsis. Moreover, having established the range of possible treatment effects and the side effect profile, in an ideal world, we would now focus on narrowing treatment effect estimates by conducting much larger trials powered to detect a minimum clinically important difference (for example an absolute mortality difference of 1.5%).

Assuming a baseline mortality rate of 38.6% [5], a sample size of ≈44,000 patients is required to detect a mortality effect of 1.5% with 90% power. Such a sample size would provide substantial power to detect differential effects in subgroups and would likely be regarded as providing definitive evidence. The problem is that this sample size is formidable and, given that the largest trial of septic shock ever conducted included 3800 patients and took more than 4 years to complete [3], enrollment would likely be impossible with a conventional RCT. On the other hand, septic shock is clearly a global health problem and, on a global scale, there are plenty of patients to randomize. A registry-embedded RCT that uses existing data sources is one possible way of increasing the feasibility of conducting such a mega trial.

The plausible effect of most ICU interventions on mortality in heterogenous populations is small [8], but small differences matter on a global scale. The logistic impediments to conducting true mega trials in patients with septic shock are substantial and for now, are likely insurmountable. However, for vasopressin in septic shock, as for many other ICU interventions, ultimately we will need to think much bigger than we have before, if we are to understand truly how these treatments affect survival.

Author details
[1] Intensive Care Unit, Wellington Regional Hospital, Private Bag 7902, Wellington South, New Zealand. [2] Medical Research Institute of New Zealand, Wellington, New Zealand. [3] Department of Intensive Care, Royal North Shore Hospital, Sydney, NSW, Australia. [4] George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia. [5] Intensive Care Unit, Wesley and Princess Alexandra Hospitals, Brisbane, QLD, Australia.

Compliance with ethical standards

Conflicts of interest
The author declares that they have no competing interests.

Publisher's Note

Received: 2 May 2019 Accepted: 6 May 2019
Published online: 13 May 2019

References

1. Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, Cecconi M, Dubin A, Dunser MW, Duranteau J, Gordon AC, Hamzaoui O, Hernandez G, Leone M, Levy B, Martin C, Mebazaa A, Monnet X, Morelli A, Payen D, Pearse R, Pinsky MR, Radermacher P, Reuter D, Saugel B, Sakr Y, Singer M, Squara P, Vieillard-Baron A, Vignon P, Vistisen ST, van der Horst ICC, Vincent JL, Teboul JL (2019) Current use of vasopressors in septic shock. Ann Intensive Care 9:20
2. Vail EA, Gershengorn HB, Hua M, Walkey AJ, Wunsch H (2016) Epidemiology of vasopressin use for adults with septic shock. Ann Am Thorac Soc 13:1760–1767
3. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J, Investigators AT, The Australian-New Zealand Intensive Care Society Clinical Trials G (2018) Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 378:797–808
4. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, Francois B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohe J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E, Network C-T (2018) Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 378:809–818
5. Nagendran M, Russel JA, Walley KR, Brett SJ, Perkins GD, Haijar L, Mason AJ, Ashby D, Gordon AC (2019) Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med. https://doi.org/10.1007/s00134-019-05620-2
6. Ioannidis JP, Rosenberg PS, Goedert JJ, O'Brien TR, International Meta-analysis of HIVHG (2002) Commentary: meta-analysis of individual participants' data in genetic epidemiology. Am J Epidemiol 156:204–210
7. Maheshwari K, Nathanson BH, Munson SH, Khangulov V, Stevens M, Badani H, Khanna AK, Sessler DI (2018) The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med 44:857–867
8. Ridgeon EE, Bellomo R, Aberegg SK, Sweeney RM, Varughese RS, Landoni G, Young PJ (2017) Effect sizes in ongoing randomized controlled critical care trials. Crit Care 21:132