

Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: A Discussion of the Level of Evidence

To the Editor:

We read with great interest Hajjar *et al.*'s article¹ that was published in the January 2017 issue of *ANESTHESIOLOGY*. Norepinephrine, the most commonly recommended vasopressor agent for vasoplegic shock states, can cause unfortunate side effects; therefore, researchers strive to find a therapeutic alternative. Several small trials have already evaluated the efficacy of vasopressin in postoperative vasoplegic shock with promising results. Hajjar *et al.*'s choice to design a randomized, controlled trial *versus* a reference treatment double-blind trial is likely to produce a high level of evidence. However, there are some methodologic biases in this study that we would like to discuss.

In line with current recommendations, this trial was recorded in Clinicaltrial.gov before the date of its first inclusion.² However, the modification of the main endpoint 1 yr after inclusion began is a bias that should be explained, regarding both substance and form. The authors cite "the lack of outcome data in cardiac surgery," but this does not meet the criteria defined as "acceptable" by the Consolidated Standards of Reporting Trials in modifying the endpoint during the study. This type of modification is only acceptable according to the Consolidated Standards of Reporting Trials if "external information becomes available from other studies."³ To our knowledge, this is not the case here. Therefore, it is important, from our point of view, to clarify this point as it is liable to bias the results and lead to erroneous conclusions.

Furthermore, the proportion of factors likely to explain postoperative renal failure may be statistically different between groups. In the norepinephrine group, the incidence of chronic renal dysfunction may be higher (29.1% *vs.* 24.8%) than in the vasopressin group. In addition, the proportion of patients treated with antihypertensive agents affecting the renin angiotensin aldosterone system may increase as well (46.4% *vs.* 35.6%). In this article, it is impossible for the reader to understand if the authors statistically tested these variables, because no statistical information is provided either in the table legend or in the main text. This is an important point because it is well known that preoperative chronic renal dysfunction increases the risk of postoperative acute renal failure after on-pump cardiac surgery.⁴ In addition, when taking into account the acute renal dysfunction (57% of events in this study), the modified composite endpoint may be directly impacted. Therefore, it seems crucial to discuss this point.

Finally, intention to treat analysis is a technique that prevents the emergence of an attrition bias by retaining

the benefit of randomization as much as possible. However, this benefit is likely to be compromised if randomized patients are excluded from the analysis. In that case, there is no guarantee that the groups analyzed will be comparable. This may then lead to an increase in the first species risk.⁵ We note that in the article by Hajjar *et al.*, 25 patients were excluded after randomization on the grounds that they were already receiving one of the two treatments in question. The exclusion of a patient who meets exclusion criteria that were not originally defined is not necessarily biased and may even be justified.⁵ Nevertheless, the authors gave evidence here of the absence of bias by arguing that the number of excluded patients is distributed equally between the two randomization groups. In our view, this justification is not viable: it is the characteristics of excluded patients, and not the quantity, that underlie the validity of randomization.

Again, while we appreciate the topic of this study, some major biases severely limit both the internal and external validity of this publication and should, in our opinion, be widely discussed. While the use of vasopressin in postoperative cardiac surgery may be an interesting alternative to norepinephrine, the proof of its effectiveness remains to be established by additional studies.

Competing Interests

The authors declare no competing interests.

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