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NEUROCRITICAL CARE SOCIETY

LETTERS TO THE EDITOR

Could Hypertonic Saline Improve Clinical Outcomes in Traumatic Brain Injury? A Trial Sequential Analysis

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Dear Editor,

I read with interest the article of Bernhardt et al. [1], focusing on the clinical efficacy and safety of hypertonic saline (HTS) compared with other agents in reducing intracranial pressure and improving outcomes in patients with acute traumatic brain injury (TBI). Given the significant clinical implications of the findings presented, I conducted a trial sequential analysis (TSA) to further evaluate the statistical robustness of the outcomes including Glasgow Outcome Scale (GOS) score at 6 months and the risk of adverse hypernatremia. The TSA provides a systematic approach to account for the cumulative impact of evidence, helping to reduce the risk of random errors that can occur due to repeated tests of significance in meta-analyses, as well as the possibility of prematurely ending studies based on insufficient data [2, 3]. A TSA (TSA version 0.9.5.10 Beta) was performed using raw data from the original meta-analysis with an 80% statistical power and a type I error of 5%. The cumulative z-score for the effect of HTS on the GOS score at 6 months did not cross the trial sequential monitoring boundary or the conventional significance boundary (Fig. 1a). This indicates that the current evidence is insufficient to conclude definitively whether HTS improves GOS scores at 6 months in patients with TBI, and it is unclear whether additional data are needed to reach the required information size. Given that the z-curve remains well within the boundaries and considering the critical clinical importance of functional outcomes in TBI management, our analysis suggests that additional high-quality randomized controlled trials are needed to establish or refute the efficacy of HTS in improving long-term neurological outcomes. The TSA for the risk of adverse hypernatremia associated with other agents demonstrated that the cumulative z-score crossed the trial sequential monitoring boundary, indicating a statistically significant increase in the risk of hypernatremia when using other agents (Fig. 1b). However, because of the number of included patients, further trials are needed to cross the required information size of 659 patients to detect a meaningful effect. In conclusion, this TSA reveals that additional high-quality randomized controlled trials are necessary because the current evidence remains uncertain to conclusively determine whether HTS significantly improves GOS scores in patients with TBI, as the z-curve did not approach the significance boundaries. There exists a potential risk of a type II error, indicating that the true effect of HTS might go undetected because of inadequate data. For the risk of adverse hypernatremia, although the z-curve crossed the significance boundary, suggesting an increased risk with other agents use, reaching the required information size is crucial to confirm these findings.

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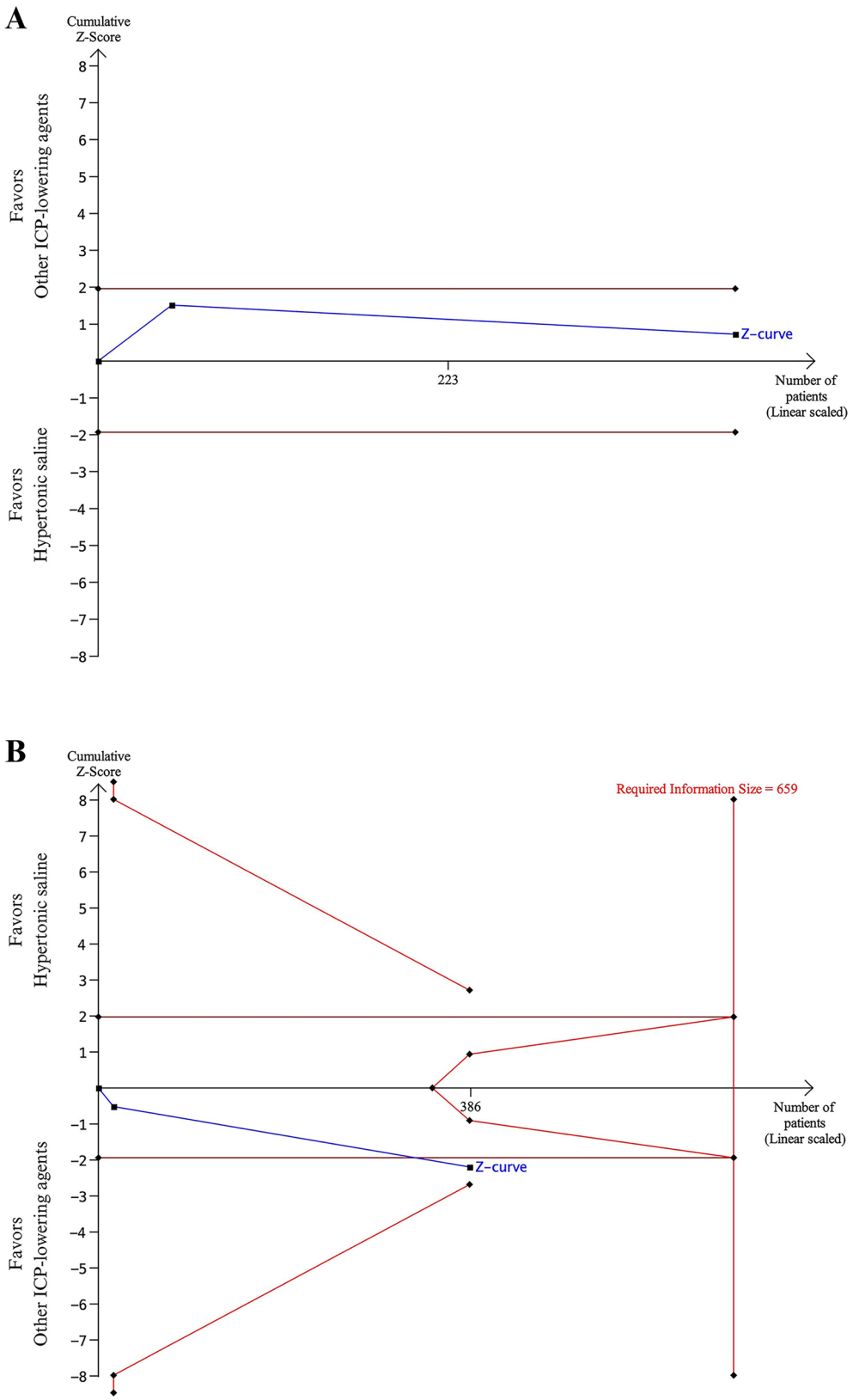

Fig. 1 The graph displays the trial sequential analysis of (a) Glasgow Outcome Scale score at 6 months and (b) adverse hypernatremia

Author contributions
Amanda Cyntia Lima Fonseca Rodrigues was responsible for all aspects of the research, including study design, data collection and analysis, interpretation of results, and manuscript preparation. The final manuscript was approved by the author.

Sources of support
None.

Conflicts of interest
Dr. Rodrigues declares no conflict of interest.

Ethical approval/informed consent
I confirm that this article adhered to ethical guidelines and there was no need for ethical approvals (institutional review board) or informed consent.

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References

1. Bernhardt K, McClune W, Rowland MJ, Shah A. Hypertonic saline versus other intracranial-pressure-lowering agents for patients with acute traumatic brain injury: a systematic review and meta-analysis. Neurocrit Care. 2024;40(2):769–84.
2. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol. 2017;17(1):39.
3. Kulinskaya E, Wood J. Trial sequential methods for meta-analysis. Res Synth Methods. 2014;5(3):212–20.