Neurocrit Care (2024) 41:711–712
https://doi.org/10.1007/s12028-024-02065-4

NEUROCRITICAL CARE SOCIETY

RESPONSE TO LETTER TO THE EDITOR

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

Keeley Bernhardt[1], William McClune[1], Matthew J. Rowland[2,3] and Akshay Shah[4*]

We thank Dr. Rodrigues et al. for their interest in our systematic review and meta-analysis [1]. We agree that the current evidence on the efficacy and safety of hypertonic saline (HTS) for improving outcomes in traumatic brain injury in inconclusive.

However, the trial sequential analysis (TSA) provided by Dr. Rodrigues on the primary outcome of Glasgow Outcome Score at 6 months lacks key information on the baseline assumptions used to generate the TSA, similar to those used when designing a clinical trial. There are no data on event rates in the control group or the anticipated effect size of HTS. TSA requires these same assumptions to generate a required information size, futility boundaries, and trial sequential boundaries for statistical significance. All of this can provide useful information for clinical trialists on the required number of participants in future trials. A detailed primer on the conduct and interpretation of TSA can be found elsewhere [2].

We would also like to draw the readership's attention on the limitations of TSA. Variations in the assumptions can generate vastly different, and sometimes unrealistically large, required information sizes. This becomes a problem in meta-analyses that contain sparse data or low events rates, which was in part why we opted not to perform a TSA in our original review. In 2019, the Cochrane Scientific Committee Expert Panel recommended against the routine use of sequential methods for updated meta-analyses [3]. Their reasons included the inability of TSA to accommodate multiple different thresholds for different outcomes, a focus on a particular outcome that may not be important to all stakeholders, and the inability of TSA to control for trials that have already been performed because meta-analyses are, by definition, retrospective and observational in nature.

*Correspondence: akshay.shah@linacre.ox.ac.uk
[4] Nuffield Department of Clinical Neurosciences, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK
Full list of author information is available at the end of the article

This letter is a response to the Letter to the Editor available at https://doi.org/10.1007/s12028-024-02066-3.

These comments refers to the article available online at https://doi.org/10.1007/s12028-023-01771-9.

Author details
[1] University of Oxford Medical School, Oxford, UK. [2] Wellcome Wolfson Institute for Experimental Medicine, Queen's University, Belfast, UK. [3] Cardiovascular, Renal and Metabolism Group, Novartis, UK. [4] Nuffield Department of Clinical Neurosciences, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK.

Author Contributions
K.B., W.M., and A.S. made substantial contributions to the content of this article, including conception and review. All authors approved the final version to submit for publication.

Source of Support
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest
M.J.R. is a co-investigator on the UK Sugar or Salt trial (ISRCTN 16075091) which is comparing hypertonic saline versus mannitol in patients with traumatic brain injury. The other authors declare no relevant conflicts of interest.

Ethical Approval/Informed Consent
No ethical approval was required for this study because the source data have all been published.

Publisher's Note

Received: 1 July 2024 Accepted: 3 July 2024
Published: 17 August 2024

Springer

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