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Stress ulcer prophylaxis in adult neurocritical care patients—no firm evidence for benefit or harm

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See related research by Liu et al., http://www.ccforum.com/content/19/1/409

In volume 19 (2015) of *Critical Care*, Liu et al. [1] present a systematic review of risks and benefits of stress ulcer prophylaxis (SUP) in adult neurocritical care patients. A total of eight randomised controlled trials (RCTs) on SUP with proton pump inhibitors or histamine-2 receptor antagonists versus placebo or no prophylaxis in neurocritical care patients was assessed. The authors conclude that SUP is superior to placebo/no prophylaxis in reducing gastrointestinal (GI) bleeding and all-cause mortality, while not increasing the risk of nosocomial pneumonia [1].

We would like to thank the authors for highlighting an important topic with significant clinical equipoise; however, we are worried that biased results and conclusions are presented. First, the review holds methodological limitations, including the fact that no predefined sensitivity analysis with continuity correction in the zero-event trials was planned or performed, and importantly the risk of random errors using trial sequential analysis (TSA) was not assessed. Applying TSA to the three trials with lowest risk of bias [1] suggests that an estimated required information size of 2005 patients and 1790 patients are needed to confirm or reject a 20 % relative risk reduction or increase in GI bleeding and all-cause mortality, respectively. Consequently, the cumulative meta-analysis presented, including 829 patients, is severely underpowered, with a high risk of presenting spurious findings [2]. Second, all included trials had a high risk of bias, which increases the risk of overestimating the benefit and underestimating harm [3]. Third, the authors have not assessed the potential harms of SUP adequately, as no data were included on the important patient-centred outcome measures of *Clostridium difficile* infection and cardiovascular events [4]. Finally, applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) [5] to the results highlights that the quantity and quality of evidence are low (downgraded for risk of bias and imprecision), and that there is no firm evidence for benefit or harm of SUP versus placebo/no prophylaxis in adult neurocritical care patients.

In summary, adequately powered, high-quality RCTs are needed to inform us on whether adult critically ill patients, including those receiving neurocritical care, benefit from routine treatment with SUP.

Authors' response

Bolin Liu, Shujuan Liu, Anan Yin and Javed Siddiqi

We appreciate the attention and correspondence from Krag et al. First, as they pointed out, TSA might be a new promising attempt to reduce the random error risk and to increase the information size of a cumulative meta-analysis. We believed that the application of this analysis may add more statistical confidences to the conclusion. However, the present meta-analysis was performed in compliance with the recommendations of the Cochrane Collaboration for intervention reviews [6]. At present, it is not compulsory to conduct TSA in a

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meta-analysis. Second, zero-cell corrections are necessary for the Mantel–Haenszel methods if the same cell is zero in all included studies [7], which was not the case in the present study. Finally, and most importantly, in line with our conclusion, Krag et al. are conservative with the superiority of SUP versus placebo/no prophylaxis in adult neurocritical care patients. As indicated in our meta-analysis, the robustness of our conclusions is limited by the lack of trials with low risk of bias, sparse data, heterogeneity among trials, and concern regarding small trial bias [1]. While the present meta-analysis favoured the use of SUP in adult neurocritical care patients based on the preliminary evidence to date, more definitive conclusions can only be drawn from larger, well-designed, RCTs.

Abbreviations

GI: gastrointestinal; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RCT: randomised controlled trial; SUP: stress ulcer prophylaxis; TSA: trial sequential analysis.

Competing interests

MK, AP, JW and MHM are chairing a research programme on SUP (www.sup-icu.com) but have no other financial or non-financial conflicts of interests. The remaining authors declare that they have no competing interests.

Authors' contributions

MK, AP, JW and MHM contributed to the conception and design, drafted/revised the manuscript, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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