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Reply to Tejani and Schwenger

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Dear Editor,

We are grateful to Tejani and Schwenger for their interest in our recent publication about the use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients [1] and the opportunity to discuss our study further in this letter.

First, we agree with Tejani and Schwenger [2] that heterogeneity is an important issue in meta-analyses. The heterogeneity between pooled studies in our study was primarily on the continuous outcomes. This was, perhaps, not surprising because continuous outcomes are in general associated with a higher degree of variance than categorical outcomes. Our planned stratified analyses based on elective versus non-elective or high doses versus standard doses did not identify these factors as significant reasons for their heterogeneity. However, we found that the effect of dexmedetomidine on length of intensive care unit (ICU) stay was no longer significant after excluding studies that did not have both double-blinding and allocation concealment. The other plausible clinical reasons for the unexplained heterogeneity,

including different ICU discharge criteria, case-mix, and rescue sedative agents, were discussed in our manuscript. Further sensitivity analyses of these plausible reasons without concrete data from the original studies were, however, not possible. We disagree with Tejani and Schwenger that post hoc analysis should be used to change how the pre-planned analyses should be conducted and presented in a meta-analysis.

Second, delirium is a difficult clinical condition to define and diagnose, especially for patients with hypomania, and this issue was further confounded by many different tools to diagnose delirium as discussed in our manuscript. This is a limitation of many clinical randomised controlled trials or observational studies on delirium. In order to facilitate readers to appreciate the diversity of tools used, we have described the different sedation scales and targets used in pooled studies in Table 1 of our manuscript and we believe this limitation has been adequately and explicitly discussed in our manuscript.

Third, analysing studies with more than one comparison is challenging in a meta-analysis. The possible ways may include Bonferroni adjustment, pooling all subgroups comparisons into a single comparison, or adjustment of the sample size of the subgroup with repeated comparisons. Adjustment of the variance associated with each comparison is, however, difficult for the last two methods. We have used Bonferroni adjustment in our previous meta-analysis and believe this is a slightly better way to handle the issue of multiple computations and comparisons [3]. Using this method of adjustment and multiplying the *p* values associated with the two main outcomes of this meta-

analysis by 2 did not change our conclusion on effects of dexmedetomidine on length of ICU stay ($P = 0.004$) and duration of mechanical ventilation ($P = 0.84$).

In summary, we thank Tejani and Schwenger for their interest and comments on our meta-analysis. We believe heterogeneity of the pooled studies has been adequately discussed and explicitly emphasised in the abstract as well as text of our manuscript. The conclusion of our meta-analysis remains the same; the limited evidence suggested that dexmedetomidine might reduce length of ICU stay in some critically ill patients, but the risk of bradycardia was significantly higher when both a loading dose and high maintenance doses were used. More studies are needed to define which subgroups of critically ill patients are most likely to benefit from using dexmedetomidine as a primary sedative agent.

References

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