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Daily sedation interruption in children warrants further study

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Dear Editor,

We read with considerable interest the article by Vet and colleagues describing results of a randomized, controlled trial of daily sedation interruption (DSI) in the context of a sedation protocol.¹ We applaud the investigators' innovative study design in adding to the evidence for analgesia/anxiolysis practice in pediatric intensive care. However, we are concerned that the authors/editors chose to include in the conclusion and the "Take-home message" the secondary mortality finding that does not deserve such emphasis, particularly when the authors also note that the study data safety monitoring board could find no reasonable connection with DSI and causes of death. Moreover, there is no obvious biological plausibility between DSI and increased risk for death. As the authors suggest, it is very likely that the mortality difference, 6 deaths in the DSI group and none in the control group, is an outlier occurrence in both directions. The authors provided enough details to conclude that there was no temporal relationship with the intervention and death and that it is extremely unlikely that any plausible occurrence other than random chance accounted for the imbalance.

There are, however, several aspects of the investigation that deserve further comment: (1) Details of the sedation protocol remain obscure. In particular, were bedside nurses empowered to wean analgesics/anxiolytics based on target COMFORT scores? How did "active tapering" of sedation actually occur? (2) Was there a defined approach for differentiating agitation that might be due to unresolved pain, anxiety, delirium, withdrawal or normal oppositional behavior, as each deserves a separate intervention? (3) With increasing evidence of the risks of benzodiazepines, it is surprising that the sedation protocol began with and escalated midazolam to 300 ug/kg/h, before addition of morphine analgesia. A more common approach, including that advocated by the ICU Liberation Campaign

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(www.iculiberation.org), is to “treat pain first”, and derive the sedation effect of the analgesic, as unresolved, prolonged pain and benzodiazepine administration both represent common antecedents for delirium. (4) Although the authors nicely demonstrate balanced illness severity scores between the two study groups, another key variable is immune competency status. Were those also balanced? (5) Given that the protocol was really not blinded and that the control group demonstrated 5 times the need for reintubation, might the control group have been pushed harder in terms of weaning and extubation? Was a common approach to mechanical ventilation weaning, including daily extubation readiness testing, utilized?

This investigation reminds us that such studies are exceedingly important but exceedingly complicated.ⁱⁱ In the final analysis, this article should send investigators back to the drawing board, instead of falsely concluding that the lack of answers has closed the door and answered this line of inquiry. In contrast, things are actually just getting started. In all aspects of (critical care) medicine, clinicians are rediscovering that “less is more.” In moving forward, probably the most important thing is to redesign a study that achieves greater separation of medication exposure between groups. A multidisciplinary team of investigators should collaborate to make such an investigation a reality.

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