Editorial

Targeting light versus deep sedation for patients receiving mechanical ventilation

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Each year, millions of patients within intensive care units (ICUs) across the world are exposed to invasive monitors, procedures, devices, and mechanical ventilation as part of their treatment that necessitates analgesia and sedation for associated pain and anxiety (1,2). As clinicians, we aim to support healing while minimizing the discomfort these diagnostic procedures or therapies frequently evoke. To this end, sedation is commonplace within the ICU. Historically, patients were kept deeply sedated while on mechanical ventilation with the thought being that recall of critical illness would be both psychologically and physically harmful (3,4). This practice was carried out despite the lack of evidence that prevention of recall with drug-induced comas could reduce psychological stress. Findings describing the risk of amnesia or recall of delirious memories themselves provoking psychological stress among survivors have since altered this perception, with amnesia of the ICU stay being associated with *worse* neuropsychological sequelae (5-7). Studies involving patients on mechanical ventilation have reproducibly shown a decrease in duration of mechanical ventilation and both ICU and hospital length of stay with daily pauses of sedative infusions without increased cognitive or psychological risk (8-11). The effects of these daily pauses in sedation do not take into consideration the level of sedation that is maintained for the patient throughout the rest of the day and whether this depth of sedation has equally important effects on short and long-term patient outcomes. The systematic review and meta-analysis by Stephens *et al.* aims to address this knowledge gap by investigating the correlation between early sedation depth and patient-centered outcomes (12).

The current recommendations by the Society of Critical Care Medicine are to maintain light sedation in all patients receiving mechanical ventilation, recognizing that this is a conditional recommendation given the low quality of available evidence (13). Much of this lack of evidence stems from inconsistency in how light sedation is defined. The two most validated and reliable sedation scales recommended for use on mechanically ventilated patients in the ICU are the Sedation agitation scale (SAS) and the Richmond agitation sedation scale (RASS), both of which are scored numerically based on the patient's depth of sedation (14,15). Despite the reproducibility and clarity of the sedation scales themselves, there is no defined cutoff for light sedation, inhibiting comparison across scales and even between studies using the same scale, which was recognized in the nine studies included within this meta-analysis. Seven of the nine studies defined deep sedation as a RASS score of −3 to −5. In contrast, one study used a RASS score of −4 or −5 to define deep sedation, and yet another study defined deep sedation as a Glasgow coma scale (GCS) of less than 9. Importantly on the RASS scale, a score of −3 is still responsive to voice whereas as a score of −4 or −5 is unarousable to voice and typically deemed in coma, making this cutoff point a

clinically important distinction. Furthermore, those studies that utilized the definition of a RASS score –3 to –5 for deep sedation had inconsistent criteria over the time period in which that score was obtained (e.g., RASS scores only obtained on ICU arrival, utilization of median RASS scores, including 85% of RASS measurements). This lack of a clear definition for sedation depth is a noticeable limitation that the authors point out in their discussion, which contributes greatly to the high statistical heterogeneity of the review. An additional important limitation of this systematic review and meta-analysis is the small number of randomized controlled trials obtained and the inclusion of non-randomized, observational studies.

Despite these limitations, the authors find important results regarding the relationship between early sedation depth and patient mortality, duration of mechanical ventilation, and ICU length of stay. Early sedation depth is a modifiable treatment target that has the potential to improve both short and long-term patient outcomes and deserves further discussion and investigation. The limited amount of high-quality studies produced by the authors' extensive database searches further illustrates the need for more research on this topic. Admittedly, the authors' searches may have been expanded by not limiting studies to only those that examined early sedation practices. This review was not designed to analyze causality, and patient disease severity could not be accounted for within the observational studies. Consequently, the effects of sedation practices alone on the outcomes of mechanically ventilated patients are difficult to deduce from this manuscript. A large prospective study examining early sedation intensity published after the systematic review, however, adds additional support to the review's findings (16). That study found that increasing sedation intensity (i.e., higher proportion of deeper sedation) predicted increased risk of death, delirium, and delayed time to extubation.

Given the high statistical heterogeneity discussed prior, subgroup meta-analysis was performed, with subgroups including studies originally designed to examine early sedation, studies using RASS to measure sedation depth, prospective studies, and retrospective studies. The primary outcome of mortality was significantly lower in the light sedation versus deep sedation groups across all the subgroup analyses. Duration of mechanical ventilation remained significantly decreased in the lightly sedated patients throughout all subgroups. Additional secondary outcomes including hospital and ICU length of stay, delirium, and tracheostomy frequency had more variability. Interestingly, the only subgroup analysis that revealed a significant decrease in delirium frequency for patients lightly sedated was that of prospective studies, although all other subgroups revealed a trend that did not reach statistical significance.

In six studies that included data regarding sedative medication choice, the majority utilized fentanyl, morphine, propofol and midazolam, with a small minority of patients (3.2%) receiving dexmedetomidine. Although used sparingly within this meta-analysis, dexmedetomidine is associated with increased patient alertness, and its use within the ICU setting has been associated with a reduction in time to extubation, decreased mortality, and shortened lengths of stay within the ICU and hospital (17-21). It is possible that the predominance of midazolam and propofol, along with a lack of dexmedetomidine usage within this meta-analysis, underestimated the potential benefits of light sedation in current practice, specifically regarding the outcome of delirium. Dexmedetomidine has been shown to reduce the frequency of delirium across several study populations when used for ICU sedation compared to propofol and benzodiazepines (20-23). There is also increasing concern around the use of benzodiazepines and long-term psychological effects among ICU survivors including anxiety, depression, and PTSD (24).

It is important to remember that the indication for initiating sedative medications in mechanically ventilated patients is for patient safety and comfort. Medication choice and depth of sedation targeted should be decided deliberately and made clear, weighing both the risks and benefits. This study is important in helping to describe those potential risks and benefits, as well as illustrating the dearth of evidence behind much of the sedation choices that are made regularly while caring for critically ill patients. This study continues to align with current guidelines regarding sedation depth, with light sedation recommended whenever clinically appropriate for mechanically ventilated patients. As sedation practices evolve and sedating medications continue to transition away from benzodiazepines towards analgesia-based sedation and utilization of dexmedetomidine, the effects of lighter sedation targets will likely continue to show improved patient outcomes without posing additional risk to our patients.

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Footnote

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