The best sedation drug—a quest for the holy grail?

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Over the last 15 years, knowledge on sedation has increased substantially and as a result, the paradigm of sedation practices has moved entirely from a deep sedated, unconscious patient to an awake, collaborative and moving ventilated patient. Over-sedation is increasingly recognized as a cause morbidity resulting in an extended length of stay and longer duration of mechanical ventilation. Early deep sedation has also been associated with higher in-hospital mortality in an observational study performed in 45 Brazilian ICUs (1). Reflecting the current evidence, the most recent guidelines of the Society of Critical Care Medicine recommend titration of sedatives to achieve light sedation unless clinically contraindicated (2).

Besides the depth of sedation, agents commonly used have also been a source of criticism in the last decade. In contrast with previous guidelines where the use of lorazepam was the primary sedation option (3), current guidelines recommend benzodiazepine-sparing drugs to reduce acute brain dysfunction and time on the ventilator (2). This recommendation was based on the studies that concluded that benzodiazepine use was associated with a higher risk of developing delirium/coma (4,5). Recent meta-analysis suggests that benzodiazepine-sparing sedation regimens may reduce ICU length of stay and duration of mechanical ventilation (6). However, studies until now were unable to answer whether there are significant differences between propofol and dexmedetomidine in comparison to benzodiazepines or as compared to one another (7,8). One large randomized trial of a mixed population of critically ill patients (PRODEX) showed no major benefit of dexmedetomidine use as compared to propofol regarding the duration of mechanical ventilation, the length of stay in the ICU and mortality (8).

To try to fill this gap of knowledge, Klompas *et al*. (9) evaluated 9,603 patients for over a 7-year period, comparing hazard ratios for ventilator-associated events (VAEs), extubation rates, hospital discharge, and hospital death amongst benzodiazepines, propofol, and dexmedetomidine. This is a well-designed, retrospective study, in which the authors adjust for severity and type of illness, comorbidities, time of initiation of mechanical ventilation, among other factors that could have influenced sedative choice. The authors concluded that non-benzodiazepine sedation was associated with less time to extubation compared to benzodiazepines, while, in direct comparison, dexmedetomidine was associated with less time to extubation compared to propofol and may, therefore, be a preferred agent in selected patients. No clear mortality benefit has been reported with the use of either dexmedetomidine or propofol in this cohort.

The greatest strength of this article is the large number of patients enrolled. It is also a real-world study of non-selected patients, which evaluates actual sedation practices. However, some issues should be mentioned to put the conclusions in context.

Firstly, the authors did not include data about processes of care like daily sedative interruption and goals of sedation, as well as the depth of sedation attained. As mentioned before, early deep sedation is associated with higher mortality, and it is not unreasonable to think that midazolam and propofol use may be a marker of profound sedation, instead of a cause of higher mortality *per se* (1). Also, sedation practices have changed substantially during the study period, favoring a benzodiazepine-sparing and analgesia-centered approach.

This changing practice during the long period of the study may have led to bias in the analysis.

Secondly, reflecting the 2002 SCCM guidelines recommendations, the majority of patients have used benzodiazepines, making it difficult to compare with current prospective studies. It is not clear if this difference between propofol and dexmedetomidine would still happen in a benzodiazepine-sparing environment. On the other hand, dexmedetomidine was used mainly in surgical patients, and propofol, in medical patients. Although the authors have made comparisons between cardiac surgery and non-cardiac surgery patients, even when cardiac surgery was excluded from the analysis, dexmedetomidine was mainly used in surgical patients, who are expected to have a shorter time to extubation and length of stay. Once more, dexmedetomidine use may be a marker of light sedation in a subset of patients who are expected to be extubated shortly after arrival in the ICU.

No sedative-analgesic agent is sufficiently superior to other agents to warrant its use in all clinical situations. As a result, selection of an agent must be individualized according to patient characteristics and the clinical situation. The etiology of the distress, the expected duration of therapy, potential interactions with other drugs, the desired depth of sedation, and pharmacokinetic modifying factors are important considerations whenever selecting an agent. The article of Klompas *et al*. (9) brings new pieces of evidence to improve the selection of the best sedative agent to achieve light sedation in critically ill patients. More prospective large controlled studies are necessary to improve the understanding of the individual risk and benefits profiles of different sedatives.

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Footnote

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