Dexmedetomidine vs propofol in intensive care unit patients

Valeria Fadda, Dario Maratea, Sabrina Trippoli, Andrea Messori

Valeria Fadda, Dario Maratea, Sabrina Trippoli, Andrea Messori, HTA Unit, ISTAV Toscana Centro, Regional Health Service, 50100 Firenze, Italy

Author contributions; Fadda V and Maratea D conducted the analyses; Trippoli S and Messori A designed the study and wrote the letter.

Correspondence to: Dr. Andrea Messori, HTA Unit, Area Vasta Centro Toscana, Regional Health System, Via San Salvi 12, 50100 Firenze, Italy; andrea.messori.it@gmail.com

Telephone: +39-338-9513583 Fax: +39-571-701319

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Abstract

Dexmedetomidine is indicated as a sedative agent in intensive care units (ICUs). While several clinical trials and two meta-analyses have compared this agent with propofol or midazolam, the results were variable depending on the specific end-point (e.g., duration of mechanical ventilation, ICU mortality, maintaining a target depth of sedation, incidence of delirium episodes, length of hospital stay). Hence, the effectiveness of this new agent vs the comparators seems to be controversial. Trial sequential analysis (TSA) is a statistical technique that can estimate the optimal, cumulative number of patients that would be needed to generate a conclusive result. We therefore applied a TSA model to the most recent meta-analysis evaluating dexmedetomidine. A total of 10 randomized controlled trials were included in our analysis. According to our results, the comparison of dexmedetomidine vs propofol showed no proof of incremental effectiveness for the end-points of length of ICUs stay and incidence of delirium episodes. In contrast, futility (i.e., proof of no incremental effectiveness) was demonstrated for the end-point of mechanical ventilation. Hence, the results for the comparison of dexmedetomidine vs propofol were inconclusive for the first two end-points; on the other hand, conclusiveness was reached for the third end-point advantage. We conclude that the place of dexmedetomidine in therapy in critically ill patients is still very uncertain and further controlled trials are still needed.

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Key words: Dexmedetomidine; Propofol; Midazolam; Sedation; Intensive care unit; Mechanical ventilation; Hospital stay; Meta-analysis; Trial sequential analysis

Core tip: Dexmedetomidine, a sedative agent for critically ill patients, has been studied in several randomized trials and in two meta-analyses. The clinical results were conflicting because of the diversity of the end-points and the small size of most studies. Since trial sequential analysis can improve the interpretation of controversial meta-analyses, we applied this technique to dexmedetomidine. According to our results, the comparison of dexmedetomidine vs propofol showed no proof of incremental effectiveness (for length of intensive care units (ICUs) stay and incidence of delirium) or of no incremental effectiveness (for duration of mechanical ventilation). Hence, the therapeutic role of dexmedetomidine in ICU is still uncertain.


TO THE EDITOR

Dexmedetomidine is increasingly being used as a sedative agent in intensive care units (ICUs)[1,2]. Several clinical trials have compared this relatively new agent with propofol or midazolam[3], based on the end-point of maintaining a target depth of sedation (i.e., score of 0 to -3 according to the Richmond Agitation Sedation Scale). Most of these trials have shown non-inferiority[3] or no difference[3,4] for dexmedetomidine vs the comparator. Sedative
Two meta-analyses[1,4] have evaluated the effectiveness of dexmedetomidine as a sedative agent in ICUs. The most recent one was conducted by Xia et al[5] and included 10 randomized controlled trials that compared dexmedetomidine with propofol according to a variety of end-points (namely: length of ICU stay, ICU mortality, duration of mechanical ventilation and incidence of delirium episodes). The pooled results showed no difference between the two treatment strategies in duration of mechanical ventilation (5 trials, 895 patients) and ICU mortality (5 trials, 267 patients). On the other hand, dexmedetomidine showed a significantly lower incidence of delirium (3 trials, 658 patients) and shorter length of ICU stay (5 trials, 655 patients) than propofol.

Trial sequential analysis (TSA)[7] is a relatively new technique that can be applied to the clinical material included in a meta-analysis. The main advantage of TSA lies in its ability to re-interpret a non-significant meta-analysis and, in particular, to differentiate its results between inconclusiveness (i.e., no proof of difference) and demonstrated non-inferiority/futility (i.e., proof of no difference). Another advantage is that TSA estimates the “optimal information size” for the comparison under examination and is therefore able to indicate how many patients would be required to generate a conclusive result[8-10]. As regards its limitations, on the one hand TSA shares virtually all limitations already known for meta-analysis; on the other hand, one specific limitation of TSA is represented by the need to declare a pre-specified margin for the incremental clinical benefit (i.e., the threshold separating a clinically irrelevant benefit from clinically relevant one); this margin is essentially the same as that commonly employed for sample size estimation or non-inferiority statistics.

To test to which degree the results of the above mentioned meta-analysis were conclusive and to determine the optimal information size for this therapeutic problem, we carried out a TSA to re-analyze the data of Xia et al[5]. Our analysis examined the following three end-points: length of ICU stay, duration of mechanical ventilation and incidence of delirium episodes. Our assumptions included two-sided testing, type 1 error = 5%, power = 80%. The assumption of no difference (or margin) was defined as a difference of ≤ 1 d for the end-point of length of ICU stay, a difference of ≤ 6 h for the end-point of duration of mechanical ventilation, and a relative risk reduction of ≤ 40% for the incidence of delirium episodes. As usual, the output of the analysis was represented by the Z-curve graph; in this graph, the boundaries for superiority, inferiority and futility were determined according to the O’Brien-Fleming alpha-spending function. All calculations were carried out using specific statistical software (TSA, User Manual for TSA, Copenhagen Trial Unit 2011, software downloadable at www.ctu.dk/tsa).

Figure 1 summarizes the results of our TSA. Overall, our findings indicate that the comparison of dexmedetomidine vs propofol is inconclusive (i.e., no proof of incremental effectiveness) for the two end-points of length

Figure 1 Trial sequential analysis of 10 randomized controlled trials evaluating dexmedetomidine vs propofol according to the end-points of length of Intensive Care Unit stay (in days, Panel A), length of mechanical ventilation (in days, Panel B) and delirium episodes (Panel C). In the Z-curve (represented in blue), individual trials correspond to individual segments; trials are plotted in chronological order (from left to right). The X-axis indicates the cumulative number of patients; the starting point of the Z-curve is always at X = 0, i.e., inclusion of no trials. Abbreviations and symbols: Red lines are the boundaries for superiority or inferiority, and green lines for futility (i.e., proof of no incremental effectiveness). T: Treatment arm (dexmedetomidine); C: Control arm (propofol).
of ICU stay (Panel A) and incidence of delirium episodes (Panel C). On the other hand, our results demonstrate futility (i.e., proof of no incremental effectiveness) for the end-point of mechanical ventilation (Panel B). As shown in Figure 1, the last point of the Z-curve remained within the area of inconclusiveness (since the curve did not cross any boundaries) in Panels A and C; in contrast, in Panel B, the Z-curve crossed the boundary of futility and therefore reached a conclusive but negative result. More importantly, in the two panels showing inconclusiveness (i.e., Panels A and C), the number of patients enrolled in the available trials was much lower than the optimal information size as determined by the TSA model.

We conclude that further data are still needed to assess the place of dexmedetomidine in therapy in critically ill patients.

REFERENCES


