Commentary

# Dexmedetomidine for agitated delirium in intensive care unit intubated patients

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Since 1999, when the Food and Drug Administration gave its approval for use in mechanically ventilated patients in intensive care unit (ICU), dexmedetomidine has gained a growing interest among intensivists worldwide. Over the last years, a series of studies on the use of dexmedetomidine in different settings showed that it may provide significant advantages also in the perioperative period and for procedures requiring sedation outside the operating room (1). Nevertheless, sedation of critically ill patients remains the cornerstone use of dexmedetomidine. In fact, in 2011 the European Medicines Agency approved the use of dexmedetomidine only for light sedation in ICU patients (Richmond Agitation-Sedation Scale (RASS) score of between 0 and −3). To this goal, the administration of dexmedetomidine seems to provide significant advantages in comparison with traditional sedatives by reducing the duration of mechanical ventilation, the ICU stay (2) and the occurrence of delirium (3). Although the literature data are still inconclusive, dexmedetomidine has been also proposed for the management of adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal (3). A clinical experience published early this year showed that dexmedetomidine may be useful as a rescue drug for treating agitation due to delirium refractory to haloperidol in 132 ICU non-intubated patients (4). To evaluate the potential benefits provided by the use of dexmedetomidine for treating agitated delirium, Reade and coworkers conducted a multinational, randomized, double-blind study including 71 mechanically ventilated patients in whom extubation was considered inappropriate because of the severity of agitation and delirium (DahLIA trial) (5). The authors demonstrated that dexmedetomidine compared to placebo group provide a significant decrease of mechanical ventilation time by about 17 hours (at 7 days) and an accelerate resolution of delirium. These results were associated to a shortening of ICU and hospital length of stay in the dexmedetomidine group. As expected, patients treated with dexmedetomidine received less propofol, antipsychotics and opioids, but a higher percentage of these patients were treated with antipsychotics 24 hours prior to randomization. The authors concluded that in mechanically ventilated patients with agitated delirium the addition of dexmedetomidine to standard therapies may be beneficial.

This pragmatic trial provides important information for the daily management of patients intubated with agitated delirium, particularly because the protocol was based almost entirely on an easy to apply nursing protocol. The trial also confirmed the safety of the drug by reporting a very low incidence (only 5.3%) of bradycardia in the dexmedetomidine group, which is considerably lower than incidence reported in previous trials: MENDS (6) (17%), SEDCOM (7) (42.2%) and MIDEX/PRODEX (8) (14.2–13%).

Although the study resulted positive, there are some points that need to discussed to get more insight the true meaning of DahLIA trial. First of all, it should be remembered that the study was early stopped. The original statistical plan considered that 96 patients had to be enrolled in order to demonstrate a decrease of 20 hours of ventilation between the two groups but only 74 patients were randomized and of these only 71 patients were subjected to analysis. Although the authors provided a post-hoc simulation that indicated only a 7% probability of null effect if the trial would have included the planned 96 patients, the early trial stop associated to the low number of patients studied may hamper the strength of the results observed. In addition, it is noteworthy that for enrolling

74 more than 20,000 patients have been screened (<0.5%). The characteristics of the investigated population are very uncommon and, thus, the true impact of the study results in clinical practice may result marginal.

A further point to be discussed concerns the enrolled patients who received tracheostomy. In fact, a much greater proportion of patients in the dexmedetomidine group (17.9%) were tracheostomized compared to the placebo group (6.9%). Although the role of tracheostomy in critically ill patients is still debated, it has been demonstrated that tracheostomy may have an indirect effect on mechanical ventilation time by the reduction of ventilator-associated pneumonia and sepsis risk (9). To evaluate the possible bias related to the difference in tracheostomy proportions between the two groups, the investigators performed a sensitivity analysis by excluding patients with tracheostomy and concluded that there were no significant differences compared to the overall results of the primary endpoint. However, it is important to point out that 13% of the enrolled patients underwent tracheostomy during the study period which appears to be a large percentage considering study admission criterion was represented by a need of mechanical ventilation attributable only to a high degree of agitation.

Recently, Turunen *et al.* (10) have highlighted a median sparing ICU total cost of 2,656 euros per patient in the MIDEX/PRODEX trials receiving dexmedetomidine. Carrasco *et al.* (4) demonstrated a favorable cost-effectiveness profile of dexmedetomidine compared to haloperidol in the management of refractory delirium with a direct benefit due to the decrease of ICU stay and also an intangible or difficult-to-quantify benefit resulting by the potential decrease of orotracheal intubation risk. Consequently, the direct cost of dexmedetomidine, that is 17 times higher than haloperidol, was fully covered by direct and indirect benefits. In DahLIA study, 77% of the patients in the dexmedetomidine group were extubated within 48 hours after randomization (20.5% within 24 hours) against 59.4% in the placebo group. In addition, despite no significant, the dexmedetomidine group showed a shorter ICU (1.5 days) and hospital length of stay. By applying the same approach proposed by Carrasco *et al.* (4), also the DahLIA study confirms the financial cost-benefit provided by the use of dexmedetomidine in ICU patients with refractory agitated delirium.

Intensivists and nurses face daily difficulties related to delirium in intubated patients and, unfortunately, the available tools are limited. In this context, dexmedetomidine may represent a valuable option but to our knowledge only few studies have shown its superiority compared to other strategies (4,5,11). Therefore, further appropriate studies and clinical experiences are needed to support the widespread use of dexmedetomidine in delirious patients. Indeed, at least 29 trials dealing with this issue are underway (www.clinicaltrial.gov) and, thus, in the coming years we could find out whether the positive results observed in the DahLIA trial represent only the first chapter of the successfully use of dexmedetomidine to lessen ICU agitated-delirium.

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## Footnote

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