

Dexmedetomidine: Toward a paradigm shift in ICU sedation

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Dexmedetomidine, a highly selective α_2 -agonist, has sedative, analgesic, and sympatholytic properties. It is 8 times more specific for α_2 -adrenoceptors than clonidine. The mechanism of action is unique and differs from those of currently used sedatives. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing sedation, analgesia, hypotension, and bradycardia. In addition to reduced respiratory depression, dexmedetomidine scores over the currently used Intensive Care Unit (ICU) sedatives like midazolam and propofol in having analgesic properties that help reduce the opioid requirement and the associated side effects.

In this issue of IJCCM, PN Shah and colleagues present the results of an open-label, randomized control trial, comparing short-term (<24 h) postoperative ICU sedation between dexmedetomidine and propofol in the Indian population.^[1] The objective of the study was to evaluate the safety and efficacy of dexmedetomidine in comparison to propofol for short-term sedation in the ICU. Results of only 30 cases (15 in each arm), which is a subset of the total number of cases done (100), have been analyzed; hence, this study is not adequately powered to answer these questions. Another important limitation is that it is an open-labeled study sponsored by the manufacturer of the drug dexmedetomidine. This may leave a potential for bias, especially when subjective criteria like the quality of sedation of the two drugs is being compared by the investigators. Further, observers can easily distinguish propofol, being milky white in color, from dexmedetomidine, which is colorless. Blinding could have overcome this potential for bias, but was not done.

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Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.132465

Quick Response Code:



Most studies assessing safety of this drug have been conducted in the western population. This is a randomized study conducted in Indian patients. Though inadequately powered, it is worth noting that none of the 15 cases randomized to the dexmedetomidine arm had any adverse events. Studies have shown that the most notable adverse effect of dexmedetomidine is bradycardia.^[2] In this study, cardiovascular stability and respiratory function were both well maintained. The overall assessment of efficacy both by the patient and investigator was significantly better with dexmedetomidine. Visual Analogue Scale (VAS) alone was used for pain assessment and fentanyl boluses were administered thereafter. Though this scale has limitations for use in sedated patients, the same was followed in both arms. There was an additional use of fentanyl in the propofol arm, suggesting that dexmedetomidine has some analgesic properties.

A similar study comparing propofol and dexmedetomidine for short-term ICU sedation, which was done in the UK,^[3] showed dexmedetomidine to be both safe and acceptable sedative when both the clinicians' and patients' perspectives were considered. The cardiovascular response of the patients in the two arms was also similar, except that dexmedetomidine did not increase the heart rate of those in whom it was administered. These properties along with the analgesic qualities and lack of respiratory depression make

dexmedetomidine advantageous for patients at risk for myocardial ischemia.

At the time this study was conducted, dexmedetomidine was only licensed for use for up to 24 h sedation in the ICU. A randomized control trial comparing the efficacy and safety of prolonged sedation with dexmedetomidine or midazolam in ventilated patients showed similar time spent at targeted sedation level. Patients who received dexmedetomidine spent less time on the ventilator, experienced less delirium, and developed less tachycardia and hypertension.^[2] Today dexmedetomidine is being widely used for long-term sedation in the ICU patients.

Delirium, an acute brain dysfunction, can occur in as high as 80% of seriously ill patients in the ICU and is a serious concern in intensive care today. Patients with delirium have longer hospital stay and lower 6-month survival than that of patients without delirium, and may be associated with long-term cognitive impairment after ICU discharge. There are numerous risk factors for delirium in critically ill patients; these include the use of sedatives and analgesics like benzodiazepines and opiates. Although studies have consistently identified benzodiazepines (both lorazepam and midazolam) as risk factors for delirium, the data regarding opioids are less consistent.^[4] A meta-analysis of four randomized control trials comparing dexmedetomidine with other sedatives like midazolam, lorazepam, and propofol has shown significant reduction in delirium with the use of dexmedetomidine.^[5] Dexmedetomidine will be a useful drug to reduce the incidence of ICU delirium.

A recent multicentric prospective longitudinal cohort study conducted in Australia and New Zealand by the SPICE study investigators^[6] found early deep sedation to be an independent predictor of delayed time to extubation and long-term mortality (180 days). Use of dexmedetomidine may have an advantage over the other sedative agents in maintaining lighter levels of sedation during early sedation.

The most recent clinical practice guidelines for management of pain, agitation, and delirium in adult patients in the ICU^[7] recommend maintaining light levels of sedation, which is associated with improved clinical outcomes. They recommend sedation strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) to be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients. This is the first time that dexmedetomidine has been recommended over benzodiazepines, which we have been using for decades.

Dexmedetomidine, a novel α_2 -receptor agonist, has sedative, analgesic, and sympatholytic properties. It provides superior quality of sedation with reduced respiratory depression and delirium. Sedation strategies have undergone a paradigm shift. Current strategies now aim to improve ICU outcome by reducing delirium and targeting light sedation. Dexmedetomidine is likely to play a central role in this strategy.

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How to cite this article: Myatra SN. Dexmedetomidine: Toward a paradigm shift in ICU sedation. *Indian J Crit Care Med* 2014;18:271-2