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Brief Communication

Dexmedetomidine: A "New" Weapon for an Old War. Some Reflections, Some Review of Recent Literature

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Abstract

Patients admitted in ICUs do frequently need from sedation to mitigate uncomfortable or painful maneuvres. Tracheal intubation, mobilization of the patient for grooming or wound dressing review are some examples of unpleasant experiences.

Besides, some patients are quiet and collaborator even during intubation and mechanical ventilation, but it is not infrequent to find psychomotor agitation during ICU admission, so that the physician and the nurses find severe difficulties to manage the normal evolution of respiratory weaning and rehabilitation processes are impaired.

We need the patients to be calm and quiet, but at the same time, alert and cooperative, and its difficult to reach this balance.

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INTRODUCTION

Let us think for a moment in our patients at the ICU: do they look comfortable?

If our answer is "yes, they do", then let us pose another question: are our patients overly large sedated?.

Several years ago [1], in 1946, it was published an article complaining about changes in management of mental illness, from mechanical to chemical restraint due to the excessive sedation of patients with barbiturates and similar compounds. The main motivation, as the autor exhibits, was to keep the patients quiet and the nights of the attendants undisturbed.

In the present, many ICU protocols include also some kind of mechanical restraint even though patients are under sedation, so maybe the progress is still insufficient in this regard.

ISSUES IN SEDATION AT ICU

Several drugs are used to sedate patients at the ICU or, out of the intensive care area, to perform some uncomfortable or painful procedures like gastrointestinal endoscopy, long radiologic explorations like magnetic resonance, dental extractions or implants.

Our pharmacological arsenal includes several and well compounds like propofol, benzodiacepines, opioids, etomidate and dexmedetomidine.

Propofol is an intravenous anesthetic used for induction of general anesthesia or procedural sedation, and can be used only by parenteral route in bolus, in infusión or in some combination of the two [2]. The mechanism of action for propofol is thought to be related to the effects on GABA receptors in the brain.

Propofol is probably the most used sedative drug worldwide, with a very fast onset and a quite fast end of effect when used in moderate doses (short explorations or procedures). However, long time-high doses of propofol infusions can be responsible for a so called "propofol infusion syndrome" [3] that is poorly understood, but seems to be multifactorial and includes cardiac and muscular cell injury. **Benzodiazepines** is another group of frequently used sedatives in the ICU. Midazolam is probably the most used parenteral benzodiazepine in preanesthesia medication and also in sedative procedures in and out ICU. Its onset is fast, and the disposable antidote flumazenil makes of midazolam a secure resource when sedation is administered outside the operating room (i.e. endoscopy room). Nevertheless, in Intensive Care Units, benzodiazepines seem have lost their place as a first-line sedatives [4] and should probably be restricted to some specific situations like seizures, alcohol withdrawal or intractable agitation.

Opioids are still a central tool in analgesia management and should not be forgotten in a daily practice, as long as patients need to feel free from pain as much as being sedated to feel free from anxiety. But two points should be taken into account:

1) is not desirable pretending opioids should be the only sedative drug for a patient, nor the only analgesic drug. Multimodal strategies (combining opioids with, i.e. non steroidal antinflammatory drugs or with ketamine) and 2) total opioid exposure should be reduced as much as posible to avoid side effects like constipation, respiratory depression, hyperalgesia or tolerance.

Etomidate is no longer administered as a continuous infusión for anesthetic maintenance or sedation due to its effects on adrenocortical axis [5]. Even the bolus administration (i.e. for tracheal intubation) has been questioned [6].

Dexmedetomidine(Dex) belongs to alpha-2 agonists group of sedative drugs. The pattern of sedation induced by this family of chemical compounds is quite different from other sedatives, so that patients keep active performance of arousal and responsiveness with less frequent respiratory depression [7]. This pharmacologic effect is different from classic sedative drugs that influenced on GABA system. Dexmedetomidine (Dex), dextrorotatory enantiomer ofmedetomidine, is a highly selective alpha 2-adrenergic, and important sedative andanalgesic effects. Its sedative effect occurs through inter-action with postsynaptic alpha2-receptors in the locus coeruleus, reduces noradrenalin release, and facilitates the action of inhibitory neurons, particularly gamma-aminobutyric acid system. The analgesic effect is promoted by the action of alpha2-receptors on dorsal horn and supraspinal cord and decreased release of substance P [8].

Dexmedetomidine also presents analgesic, ansiolytic and sympatholytic effects that could be helpful in preventing or treating delirium situations.

The action of dexmedetomidine on sympathetic nervous system is accompanied by side effects of hypotension and bradicardia in a variate range. Episodes of bradycardia, hypotension and sinus arrest have been associated with rapid iv administration (e.g. bolus) or in patients with high vagal tone (e.g. pediatric population).

In ICU sedation, use of loading bolus is not completely needed and it could avoid some of these unconvenient effects, mainly when patient is converted from another sedative or hemodynamic compromise is a concern.

Dose for maintenance infusion ranges betweeen 0.2 to 1.5 mcg/kg/hour as several randomized controlled trials have reported [9,10]. Although infusion rates as high as 2.5 mcg/kg/hour have been used, it is thought that doses >1.5 mcg/kg/hour do not add to clinical efficacy [11]. Titration of continuous dose administration is recommended to be performed every 30 minutes until adequate sedative level is achieved. Manufacturer recommends duration of infusion should not exceed 24 hours; however, randomized clinical trials have demonstrated efficacy and safety comparable to lorazepam and midazolam with longer-term infusions of up to ~5 days [12,13]. One concern is how to perform withdrawal of dexmedetomidine infusion in patients who received long- erm infusions of dexmedetomidine. Clonidine is recognised to be a good alternative but initiation of enteral administration of this drug is not protocolized or widely employed, and thus, the decision is left to the individual care teams [14].

In a recent metanalyse [15], dexmedetomidine seemed to reduce the incidence of neurocognitive dysfunction, even though a more detailed research could not achieve enough statistical evidence.

Another metanalysis performred in 2015 by Lebot [16], addresses the issue of the impact of intraoperative administration of dexmedetomidine on the opioid consumption and on postoperative nausea and vomiting (PONV) incidence. Conclusions of this metanalysis indicate that intraoperative dexmedetomidine (*versus* placebo) demonstrates intra and postoperative analgesic and opioid-sparing effect, no impact time of recovery from anesthesia and reduction in PONV in adult surgical patients.

CONCLUSIONS

Dexmedetomidine has enlarged our resources for sedation, and, although lack of strong evidence, this drug could be a very useful tool in the management of delirium, agitation and stress in the ICU patient.

Nevertheless, a careful use of the drug is esential to avoid not desirable side effects like hypotension and bradicardia.

Despite our pharmacologic selection, we never can loose the perspective: the main influence on the patient's psychological status is, for long, staff proficiency and competence. No one medication can substitute human contact and empathy, but, indeed, lack of education and training to deal with confused patients is reported [17].

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