

Moving away from benzodiazepine as a primary sedative in the intensive care unit; is clonidine a viable alternative?

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Current pain, agitation, and delirium (PAD) guidelines endorse a benzodiazepine-sparing approach to aid in achieving optimal patient outcomes.^[1] Several benzo-sparing strategies, including protocolized and frequent pain, sedation and delirium assessments, achieving the goal of awake and alert, utilization of bolus and symptom-triggered, patient-specific pharmacotherapy, interruption of sedatives, a pain-first approach or analgosedation, early mobilization, rotation of medications, and adjustment of ventilator settings are nonmedication specific principles shown to improve clinical outcomes in mechanically ventilated (MV), intensive care unit (ICU) patients. These techniques and strategies have been associated with some of the most relevant clinical outcomes including a decrease in discomfort, ventilator-associated pneumonia, length of MV, and ICU and hospital length of stay.^[2,3] Interestingly, extremely few well-conducted sedative versus sedative trials show improvements in these hard clinical outcomes.

Dexmedetomidine is an effective agent for PAD management and a viable alternative to benzodiazepine therapy. Dexmedetomidine maintains a light level of sedation, while minimizing the deep sedation commonly seen with benzodiazepines. In randomized, controlled trials, dexmedetomidine has been associated with shorter duration of delirium and MV compared to benzodiazepine infusion, specifically midazolam.^[4] It should be noted, however, that these trials showing a

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reduction in MV duration are not without criticism. For example, the mean dose of midazolam in the SEDCOM trial was approximately 5 mg/h (based on the average patient weight of 88 kg); an extremely high dose by clinical standards when the goal is to keep a patient awake and alert.^[5] Dexmedetomidine is relatively safe with fairly predictable cardiovascular (CV) effects (most frequently hypotension and bradycardia). These CV risks can often be mitigated by avoiding the use of bolus therapy and extending titration intervals to no more frequently than every 30 min.^[6]

The cost of dexmedetomidine is often a concern in many parts of the world. There are several strategies to address the cost of dexmedetomidine including use of alternative medication or by following restrictive institution specific guidelines. A recent publication on dexmedetomidine stewardship showed an institution's approach to managing the benefits of the drug versus the cost. The guideline followed in this analysis supports judicious use of dexmedetomidine in patients who fail traditional therapy.^[7] Another important note in terms of cost is in certain parts of the world dexmedetomidine will lose its patent in the near future and is likely going to be price reduced.

We commend the investigators for their fine analysis

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entitled “comparison of clonidine and dexmedetomidine for short term sedation of ICU patients” published in this month’s journal.^[8] This trial examined the efficacy and safety of clonidine as an alternative to dexmedetomidine in MV patients. The authors conclude both agents are effective, although clonidine is associated with a higher risk of hypotension. This paper adds to the literature suggesting clonidine may be a useful medication for PAD management although further investigation is needed to confirm these findings.

We support the author’s conclusion although we think there are some key critiques of this analysis. (1) The authors assessed and titrated to Ramsay Sedation Score (RSS) but pain and delirium assessment scores were not reported. Therefore, it is hard to tell if the pain-first approach was employed prior to the use of either sedative. (2) The goal RSS in this trial was 3-4 yet an RSS of 5, corresponding to awake and alert, may have been a more appropriate goal and these patients may have been more deeply sedated than would be desired in clinical practice. (3) Dexmedetomidine performed better statistically than clonidine, therefore lumping them both as effective may be slightly misleading.

It is also important to note that the relatively high incidence of hypotension in the clonidine arm is concerning. A recent trial published on clonidine in noncardiac surgery patients highlights safety concerns with a troubling increase in clinically important hypotension and nonfatal cardiac arrest.^[9] Although a different patient population than this study, when combined with the results of this analysis it raises concerns about the safety of this medication.

The current analysis should be considered hypothesis generating and clonidine should be further investigated before it is systematically used for management of PAD.

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