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Title: Intraoperative Dexmedetomidine to Prevent Postoperative Delirium: In Search of the Magic Bullet

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Agitation and delirium are important targets for quality improvement across inpatient healthcare settings due to the time- and resource-intensive nature of the screening, diagnosis, and management process. In the general patient population, no prophylactic pharmacologic treatment has demonstrated widespread effectiveness in preventing delirium. Several studies have failed to find a magic pharmacologic bullet for the prevention of delirium – ketamine and haloperidol have recently failed to impress.\(^1\)\(^2\) Dexmedetomidine is an attractive pharmacologic option due to its biologic plausibility in modifying several known contributors to delirium, including attenuating inflammatory mediators and catecholamines, providing analgesia, reducing delirium-inducing medications, and promoting natural sleep-wake cycles, among other plausible neuroprotective mechanisms. Data on postoperative delirium after intraoperative dexmedetomidine administration are conflicting, and the diverse mechanisms by which it may act have prompted trials in a variety of populations, with a variety of doses and administration schema. If providing dexmedetomidine intraoperatively to a diverse group of patients otherwise receiving usual care has not been effective,\(^3\) could its use in a highly-protocolised, homogenous setting reveal an effect?

In this month’s edition of the *Journal*, Kim et al.\(^4\) report the results of a double-blinded randomized efficacy trial of 143 patients undergoing thoracoscopic lung resection surgery. Patients were randomized to receive general anesthesia with either sevoflurane + dexmedetomidine at 0.5 mcg/kg/hr (started immediately prior to anesthesia induction and continued until the end of surgery) or sevoflurane + placebo. Anesthetic depth was titrated to maintain a bispectral index of 45 +/- 5 and blood pressure within 20% of baseline. Emergence
agitation was measured with the Riker sedation agitation scale at one minute after extubation, then every 15 minutes until discharge from the post-anaesthesia recovery unit (PACU). Patients were then assessed for postoperative delirium with either the Confusion Assessment Method (CAM) or CAM-ICU starting after PACU discharge and every 4 hours for intensive care unit (ICU) patients or three times daily for ward patients until postoperative day 3. The authors demonstrated a decrease in emergence agitation in the dexmedetomidine group (13% vs. 35%; relative risk [95% CI] 0.38 [0.18 to 0.79]; p = 0.011) without a corresponding increase in oversedation but, disappointingly, no difference in postoperative delirium (25% vs. 25%).

There were reasons for optimism. Studies comparing the incidence of delirium and other adverse neurocognitive outcomes based on particular sedation strategies in the ICU setting have found significant benefit with use of dexmedetomidine compared with benzodiazepines and propofol. Not surprisingly, focus has turned to investigation of whether intraoperative use of dexmedetomidine may also prove effective as a delirium prevention measure. Results were encouraging in focused surgical groups – for example, in cardiac and orthopedic surgery, where significant tissue trauma is expected. In a recent meta-analysis, Wu and colleagues found a significant reduction in postoperative delirium with perioperative use of dexmedetomidine in patients undergoing cardiac surgery. In a subgroup analysis of the 3 studies (480 patients) with intraoperative dexmedetomidine use, the relative risk (RR) for development of postoperative delirium was 0.38 (95% CI 0.20 to 0.72). Two studies recently demonstrated a decreased incidence of postoperative delirium or postoperative agitation with intraoperative dexmedetomidine sedation compared with propofol sedation in elderly patients undergoing hip
surgery under regional anaesthesia. Despite these promising results, the delirium prevention
effects of dexmedetomidine have not been replicated in a non-selective surgical patient
population. A randomized controlled trial by Deiner and colleagues\textsuperscript{3} studying the effect of
dexmedetomidine 0.5 mcg/kg/hr vs. placebo infused intraoperatively and for 2 hours in the
recovery room in elderly patients undergoing major noncardiac surgery similarly demonstrated
no reduction in postoperative delirium to postoperative day 5 in the dexmedetomidine group.
The authors concluded that, because of its short duration of action, the beneficial effects end
when the infusion is discontinued. We add to this the results of Kim and colleagues, who –
despite a highly protocolised intervention in a well-specified population, undergoing a
procedure causing limited tissue trauma – were also unable to demonstrate efficacy.

Conflicting results in existing studies bring up several questions around the optimal
\textit{intraoperative} use of dexmedetomidine that have yet to be answered. First, is there an optimal
target \textit{patient population}? Second, is there an optimal \textit{dosing strategy}? And third, is there an
optimal \textit{time frame}? A recent study by Su and colleagues\textsuperscript{11} sheds light on the third question. The
authors demonstrated a reduction in delirium incidence with a subanaesthetic dose of
dexmedetomidine (0.1 mcg/kg/hr) administered prophylactically to elderly patients admitted to
the ICU after non-cardiac surgery.\textsuperscript{11} The positive effect of this study conducted in the
\textit{postoperative} period raises the question of whether infusion of dexmedetomidine during the
\textit{intraoperative} period alone is enough. The pathophysiology of postoperative delirium is
incompletely understood, however among the many putative contributors are
neuroinflammation, exposure to delirium-inducing medications, pain, and interruption in sleep
hygiene. These insults are ubiquitous in surgical patients, but none are limited to the intraoperative period. Inflammatory cytokine and catecholamine levels in surgical patients remain elevated at least through postoperative day one.\(^{12}\) Perhaps, then, it is not plausible that a complex disease process with multifactorial mechanisms and multiple contributors could be prevented in certain patient populations with a single intraoperative intervention such as a short-term, low-dose dexmedetomidine infusion. Like other areas of anesthesia and surgical care, there is a collective need to think beyond the operating room: postoperative delirium as a \textit{perioperative} phenomenon.

Furthermore, the literature on this subject is confused by inconsistency in defining emergence agitation, emergence sedation, and postoperative delirium. \textit{Delirium} is defined according to the gold standard criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as an acute, fluctuating alteration in thought content (i.e., inattention) and consciousness (i.e., level of arousal). Emergence delirium is defined as “very early onset of postoperative delirium before or on arrival to the recovery room.”\(^{13}\) Agitation scales such as the Riker sedation agitation scale or the Richmond Agitation Sedation Scale (RASS) are commonly used to quantify emergence delirium in the literature,\(^{13}\) prompting a change in terminology to “emergence agitation” in this article. A need to harmonize terminology and criteria for diagnosis of perioperative neurocognitive dysfunction with those used by the broader clinical community exists, and recently a multi-specialty international working group convened to create consensus surrounding nomenclature and diagnosis of perioperative cognitive change.\(^{14}\) The term “perioperative neurocognitive disorder” was agreed upon as an umbrella term containing pre-
existing cognitive impairment, acute events such as delirium, and cognitive decline occurring in
the postoperative period. The group recommended that postoperative delirium, defined as
delirium occurring in the hospital up to one week after surgery and otherwise meeting DSM-5
criteria for diagnosis of delirium, be formally recognized as a specific sub-category of delirium. A
lucid interval between emergence agitation (also termed emergence delirium or excitation) and
postoperative delirium is preferable, but not necessary, to make this diagnosis.

In this study, *emergence agitation* was measured throughout the PACU stay, and *postoperative
delirium* was measured only after PACU discharge. However, there is no clear line that
demarcates where agitation ends and delirium begins. Emergence agitation is clinically
important to the extent that it makes patients difficult to manage in the immediate
postoperative period, and it may increase patients’ exposure to delirium-inducing sedative
medications. Furthermore, there is a relationship between level of sedation and diagnosis of
delirium; level of arousal has the potential to affect delirium diagnosis even when using a valid
screening tool. We must be particularly careful to ensure that the delirium outcome is not
misrepresented as a result of sedation level, particularly when sedatives are being trialled as a
preventative measure.

So where does that leave us with investigation of dexmedetomidine as a preventative measure
for postoperative delirium? As discussed above, the effects of intraoperative dexmedetomidine
infusion on postoperative delirium have been inconsistent. A search of ClinicalTrials.gov using
the terms “postoperative delirium” and “dexmedetomidine” reveals 3 studies of intraoperative
dexmedetomidine to prevent delirium which are actively recruiting, with an additional 2 not yet recruiting, so optimism persists. However, the current level of evidence does not allow professional organizations to recommend the intraoperative use of dexmedetomidine in unselected patients as a delirium prophylaxis measure. In fact, few preventative interventions can be recommended with a strong evidence base. The study by Kim and colleagues would not change recommendations, but do support consideration of intraoperative use of dexmedetomidine for patients at high risk of emergence agitation.

Should we keep looking at dexmedetomidine as the missing magic bullet? Should we abandon it altogether? Should we be altering our approach to compare dosing strategies, timing of administration, or specific patient populations? Perhaps, but the more likely answer is this – postoperative delirium is complex and multifactorial. Prevention altogether is unlikely with a single, short-lived intervention. Rather, prevention requires, first of all, accurate identification of patients who are at high risk of developing postoperative delirium, followed by coordinated prevention and treatment efforts carried out by a team of committed perioperative professionals – nurses, surgeons, anesthesiologists, rehabilitation specialists, dieticians, social workers, case managers, patients, and families. A proactive, coordinated approach may not be the magic bullet, but it is more likely to hit the target than a single intervention.
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