Patient Safety Tip of the Week

January 24, 2017

Dexmedetomidine to Prevent Postoperative Delirium

Post-operative delirium is a significant problem in the elderly associated with excessive morbidity and mortality, prolonged hospital lengths of stay, poor long-term functional and cognitive outcomes, discharge to places other than home, and excessive costs. Estimates of its occurrence range up to 65%, even higher when patients require ICU care. So the search for interventions to prevent postoperative delirium has been important. Many of our prior columns on delirium (see the list below) have focused on multi-component non-pharmacological approaches to prevention (and treatment) of delirium. However, the improvements have been modest.

Pharmacologic interventions to prevent or treat delirium have been elusive. A recent literature review (Tremblay 2016) found fourteen articles that reported a reduced incidence of post-operative delirium using pharmacological agents: eight with antipsychotics, two with statins, one with melatonin, one with dexamethasone, one with gabapentin, and one with diazepam. However, Tremblay concludes that study designs, methodological issues, or authors' interpretations raise questions on these conclusions and that further double-blinded randomized clinical trials should be conducted before administering pharmacological agents to reduce postoperative delirium in a non-research setting.

One drug that has generated significant interest over the past several years is dexmedetomidine, an α2-adrenoreceptor agonist, often used as a sedation agent in the ICU because it might be associated with less delirium. In our February 10, 2009 Patient Safety Tip of the Week "Sedation in the ICU: The Dexmedetomidine Study" we discussed the SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study, which concluded that dexmedetomidine was as effective as midazolam at keeping patients in the desired sedation range and was associated with a reduced prevalence of delirium and reduced time to extubation (Riker 2009). However, we urged caution in interpreting the conclusions of that study because of several methodological and other concerns outlined in our column. We again discussed dexmedetomidine in our June 16, 2015 Patient Safety Tip of the Week "Updates on Delirium". And in our April 2016 What's New in the Patient Safety World column "Dexmedetomidine and Delirium" we discussed the Dexmedetomidine to Lessen ICU Agitation (DahLIA) study was a double-blind, placebo-controlled, parallel-group randomized clinical trial in 15 ICU's in Australia and New Zealand (Reade 2016).. Subjects were ICU patients who were deemed to be ready for extubation except that they

had delirium. Dexmedetomidine increased ventilator-free hours at 7 days compared with placebo and reduced time to extubation and accelerated resolution of delirium.

See those previous columns for our cautions and concerns about dexmedetomidine despite several promising studies.

More recently, Su and colleagues did a randomized, double-blind, placebo-controlled trial in two tertiary-care hospitals in Beijing, China on patients aged 65 years or older who were admitted to intensive care units after non-cardiac surgery (Su 2016). They randomly assign patients to receive either low-dose (sub-sedative) intravenous dexmedetomidine or placebo from intensive care unit admission on the day of surgery until 0800 h on the first day after surgery. The CAM-ICU was the tool used to assess for delirium. Their reported results are remarkable. The incidence of delirium in the dexmedetomidine group was just 9%, compared to 23% in controls. That translates to a number needed to treat (NNT) of 7.4! The results applied equally whether patients were intubated or not and applied to all 3 subtypes of delirium. And there were significant benefits in the dexmedetomidine group compared to the control group for ICU length of stay, time to extubation (in those who were intubated), sleep quality, and early hospital discharge. There was no difference in the incidence of overall adverse events or 30-day mortality. Moreover, the safety profile of dexmedetomidine was excellent. Patients receiving dexmedetomidine did not have higher rates of bradycardia or hypotension (as is often seen with higher doses) and actually had lower rates of hypertension, tachycardia, and hypoxemia than the placebo group. There was also a suggestion that the delirium-reducing effect was dose-dependent in that the dexmedetomidine dose (the rate of the infusion x the duration of the infusion) was negatively correlated with the occurrence of delirium.

These results sound too good to be true! Such pronouncements always raise our "hype radar" or "spin radar" (see our February 16, 2010 Patient Safety Tip of the Week "Spin/Hype…Knowing It When You See It").

In the editorial accompanying the Su study, Kronzer and Avidan (Kronzer 2016) provide a very thoughtful assessment of the methodology in the Su study that should temper our enthusiasm about the reported results. They note that the consent for participation took place after surgery and that patients' families provided consent in 58% of the cases. That raises the possibility (or should we say likelihood) that some of the patients may have already had delirium before they were even entered into the study. They also note that the CAM-ICU was the tool used to ascertain the presence of delirium. The CAM-ICU is an excellent tool for assessing intubated ICU patients who are unable to speak but it is a non-verbal assessment tool that is not as good as those in which verbal communication can help better identify the presence of delirium. And there was no baseline assessment for delirium or cognitive function. Lastly, they challenge the biological plausibility (i.e. that a sub-sedative very low dose of a sedative agent could be given to awake, non-delirious patients to prevent delirium). They felt such was counterintuitive. Kronzer and Avidan point out the numerous instances in which initially promising interventions turn out not to work when large well-conducted studies are done. They therefore consider the

work by Su et al to be hypothesis-generating and look for replication of the findings in other studies.

While Kronzer and Avidan may have a good point about the biological plausibility, we actually think Su and colleagues had some good rationale for doing this study. They had noted several previous studies touting dexmedetomidine for prevention of delirium but all had used higher doses and the control groups were receiving active sedative drugs like benzodiazepines. Because dexmedetomidine provides anxiolysis, sedation, and modest analgesia and is touted not to be associated with significant respiratory depression, many have felt it has the potential to be an ideal candidate for prophylaxis against development of delirium. And they chose the low (sub-sedative) dose of dexmedetomidine because they felt it would likely not have the bradycardia or hypotension seen with higher doses. And a previous study had shown nighttime infusions of dexmedetomidine were associated with sleep improvements.

Nevertheless, we think the criticisms raised by Kronzer and Avidan are legitimate and we agree that prophylactic use of dexmedetomidine to prevent delirium should not be adopted as a usual practice until further validation studies are done.

Perhaps the biggest factor pushing everyone to look at dexmedetomidine is its purported minimal respiratory depression. Now, even that has been called into question by a new study that compared ventilatory responses to hypoxia and hypercapnia during sedation with dexmedetomidine and propofol in healthy male volunteers (Lodenius 2016). Those researchers found that dexmedetomidine-induced sedation reduces ventilatory responses to hypoxia and hypercapnia to a similar extent as sedation with propofol. This finding implies that sedation with dexmedetomidine interacts with both peripheral and central control of breathing.

So, given that there is currently no clearcut pharmacological agent to prevent post-op delirium, what are we to do? A very interesting pragmatic clinical trial recently addressed delirium prevention in patients age 65 and older who underwent surgery for hip fracture (Freter 2016). Rather than intervene with all the elements of multifactorial interventions that have been used for delirium prevention, the researchers used only those that lent themselves to easy incorporation into postoperative preprinted orders. Those that fit included interventions for nausea, nighttime sedation, pain control, and bowel and bladder care. The postoperative preprinted orders had the same elements as the standardized postoperative orders for hip surgery patients with several differences:

- Acetaminophen was ordered on a scheduled, rather than prn, basis and the doses and frequency of as-needed opioid analgesics were lower.
- Trazadone was used for required nighttime sedation (control patients often received chloral hydrate or zopiclone).
- For nausea, domperidone was used instead of dimenhydrinate.
- Urinary catheters were removed on POD#2, followed by determination of post-void residuals.
- Laxatives were given on a scheduled, rather than prn, basis.
- For severe agitation low doses of haloperidol were specified.

Delirium occurred significantly less frequently (27% vs. 42% in controls on POD#1 and 7% vs. 30% in controls on POD#5) despite the fact that more patients in the intervention group had pre-existing dementia, a known risk factor for delirium. More patients in the intervention group had early postoperative bowel movements and more urinary catheter removals on POD#2. Significantly, intervention patients received less opioid analgesia (24 mg morphine equivalents vs. 44 mg morphine equivalents in controls). But, although the intervention group had less postoperative delirium, there were no differences in length of stay, mortality, or nursing home placement rates.

While we anxiously await studies that might validate use of pharmacological agents, such as dexmedetomidine, to prevent postoperative delirium we need to stick with multi-component non-pharmacological interventions such as HELP, the Hospital Elder Life Program (see our October 21, 2008 Patient Safety Tip of the Week "Preventing Delirium" and our September 2011 What's New in the Patient Safety World column "Modified HELP Helps Outcomes in Elderly Undergoing Abdominal Surgery") or tools like the ABCDEF Bundle (see our September 20, 2016 Patient Safety Tip of the Week "Downloadable ABCDEF Bundle Toolkits for Delirium").

Some of our prior columns on delirium assessment and management:

- October 21, 2008 "Preventing Delirium"
- October 14, 2008 "Managing Delirium"
- February 10, 2009 "Sedation in the ICU: The Dexmedetomidine Study"
- March 31, 2009 "Screening Patients for Risk of Delirium"
- June 23, 2009 "More on Delirium in the ICU"
- January 26, 2010 "Preventing Postoperative Delirium"
- August 31, 2010 "Postoperative Delirium"
- September 2011 "Modified HELP Helps Outcomes in Elderly Undergoing Abdominal Surgery"
- December 2010 "The ABCDE Bundle"
- February 28, 2012 "AACN Practice Alert on Delirium in Critical Care"
- April 3, 2012 "New Risk for Postoperative Delirium: Obstructive Sleep Apnea"
- August 7, 2012 "Cognition, Post-Op Delirium, and Post-Op Outcomes"
- February 2013 "The ABCDE Bundle in Action"
- September 2013 "Disappointing Results in Delirium"
- October 29, 2013 "PAD: The Pain, Agitation, and Delirium Care Bundle"
- February 2014 "New Studies on Delirium"
- March 25, 2014 "Melatonin and Delirium"
- May 2014 "New Delirium Severity Score"
- August 2014 "A New Rapid Screen for Delirium in the Elderly"
- August 2014 "Delirium in Pediatrics"
- November 2014 "The 3D-CAM for Delirium"

- December 2014 "American Geriatrics Society Guideline on Postoperative Delirium in Older Adults"
- June 16, 2015 "Updates on Delirium"
- October 2015 "Predicting Delirium"
- April 2016 "Dexmedetomidine and Delirium"
- April 2016 "Can Antibiotics Lead to Delirium?"
- July 2016 "New Simple Test for Delirium"
- September 20, 2016 "Downloadable ABCDEF Bundle Toolkits for Delirium"

References:

Tremblay P, Gold S. Prevention of Post-Operative Delirium in the Elderly Using Pharmacological Agents. Can Geriatr J 2016; 19(3): 113-126 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5038927/

Riker RR, Shehabi Y, Bokesch PM, et al for the SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients. A Randomized Trial. JAMA. 2009; 301(5):489-499. Published online February 2, 2009 http://jama.jamanetwork.com/article.aspx?articleid=183300

Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. JAMA 2016; Published online March 15, 2016 http://jama.jamanetwork.com/article.aspx?articleid=2503421

Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. The Lancet 2016; 388(10054): 1893-1902 Published: 15 October 2016 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30580-3/fulltext

Kronzer VL, Avidan MS. Preventing postoperative delirium: all that glisters is not gold Vanessa L Kronzer. The Lancet 2016; 388(10054): 1854-1856 Published: 15 October 2016 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)31353-8/fulltext

Lodenius A, Ebberyd A, Hårdemark A, et al. Sedation with Dexmedetomidine or Propofol Impairs Hypoxic Control of Breathing in Healthy Male Volunteers: A Nonblinded, Randomized Crossover Study. Anesthesiology 2016; 125(4): 700-715
http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2540550&resultClick=3

Freter S, Koller K, Dunbar M, MacKnight C, Rockwood K. Translating Delirium Prevention Strategies for Elderly Adults with Hip Fracture into Routine Clinical Care: A Pragmatic Clinical Trial. J Am Geriatr Soc 2016; Early View 22 NOV 2016
http://onlinelibrary.wiley.com/doi/10.1111/jgs.14568/epdf

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