Patient Safety Tip of the Week

November 13, 2018

Antipsychotics Fail in ICU Delirium

In our many columns on the diagnosis and management of delirium we've noted that pharmacologic management of delirium has been largely unsuccessful. There have been multiple studies looking at use of haloperidol or the newer atypical antipsychotic medications for treating delirium, but all were either small trials or had problems with study design or other methodological issues. Yet we've continued to see frequent use of these medications to treat patients experiencing delirium. We've long awaited a well-done randomized, controlled trial to finally put the issue to rest. It appears we finally have that study.

The MIND-USA trial, a study conducted at 16 medical centers in the US (Girard 2018), randomized 566 ICU patients with acute respiratory failure or shock and hypoactive or hyperactive delirium to receive intravenous boluses of haloperidol, ziprasidone, or placebo. Patients were assessed twice daily while they were receiving the intervention by trained research personnel using the CAM-ICU tool and the Richmond Agitation–Sedation Scale (RASS), both validated tools we've discussed in many of our prior columns.

The median number of days alive without delirium or coma was 8.5 in the placebo group, 7.9 in the haloperidol group, and 8.7 in the ziprasidone group (differences not statistically significant). There were also no significant between-group differences with respect to the secondary end points (30-day and 90-day survival, time to freedom from mechanical ventilation, and time to ICU and hospital discharge) or the frequency of extrapyramidal symptoms. There was also no reduction in the use of sedatives or opioids in those receiving the active drugs compared to those on placebo.

Perhaps one remaining issue is what to do in hyperactive delirium. In the current study, 89% of patients had hypoactive delirium, and only 11% had hyperactive delirium. In the editorial accompanying the MIND-USA trial, Bleck (Bleck 2018) points out that hypoactive delirium, seemingly less of a management problem, nevertheless hampers cooperation with nursing, physical therapy, and other activities.

And, it's probably good that this study suggests we not use these antipsychotics in delirium in the ICU. Another recent study (Park 2018) had looked at mortality rates in patients with MI who were treated with haloperidol or atypical antipsychotics. Their results suggest a small increased risk of death within seven days of initiating haloperidol compared with initiating an atypical antipsychotic in patients with acute myocardial infarction. 7.8% of haloperidol recipients died within 7 days of treatment initiation,

versus 5.5% of atypical antipsychotic recipients. After multivariable adjustment, mortality risk was about 50% higher with haloperidol, and the increased risk appeared only during the first 4 days of treatment.

Use of haloperidol prophylactically to prevent delirium has also been the topic of multiple small or anecdotal studies, with mixed results. Recently, 2 randomized controlled trials failed to demonstrate any benefit from use of haloperidol to prevent delirium. Schrijver et al. (Schrijver 2018) conducted a multicenter, double-blind, stratified, block randomized, placebo-controlled trial at six Dutch hospitals. Patients age ≥70 years, acutely admitted through the emergency department for general medicine or surgical specialties and at risk for delirium were randomized (n = 245) to either low-dose oral haloperidol or placebo. Delirium incidence was 19.5% in the haloperidol group versus 14.5% in the placebo group. There were no statistically significant differences between the groups with respect to delirium duration, hospital length of stay, or 3-month mortality. The authors conclude that prophylactic use of haloperidol in this population is not recommended.

In another study from the Netherlands (van den Boogaard 2018), researchers in the REDUCE trial assessed the impact of prophylactic use of haloperidol on survival among critically ill adults at high risk of delirium. They randomized 1789 critically ill adults treated at 21 ICU's in a double-blind, placebo-controlled trial. Nonpharmacological interventions for delirium prevention are also routinely used in the study hospitals. There was no difference in the primary study outcome, median days patients survived in 28 days. There was also no difference in 15 secondary outcomes, including delirium incidence, 28-day delirium-free and coma-free days, duration of mechanical ventilation, and ICU and hospital length of stay. The authors conclude their findings do not support the use of prophylactic haloperidol for reducing mortality in critically ill adults.

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. We've discussed dexmedetomidine in our Patient Safety Tips of the Week for February 10, 2009 "Sedation in the ICU: The Dexmedetomidine Study" and June 16, 2015 "Updates on Delirium" and our April 2016 What's New in the Patient Safety World column "Dexmedetomidine and Delirium". See those previous columns for our cautions and concerns about dexmedetomidine despite several promising studies.

And, in our January 24, 2017 Patient Safety Tip of the Week "Dexmedetomidine to Prevent Postoperative Delirium" we discussed a study from China that had results that sounded too good to be true. Su and colleagues (Su 2016) did a randomized, double-blind, placebo-controlled trial in two tertiary-care hospitals on patients aged 65 years or older who were admitted to intensive care units after non-cardiac surgery. 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 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. The editorial accompanying the Su study (Kronzer 2016) provided a very thoughtful assessment of the methodology in the Su study that tempered our enthusiasm about the reported results.

But another recent study (Skrobik 2018) sought to see if nocturnal dexmedetomidine prevents delirium and improves sleep in critically ill adults. This two-center, double-blind, placebo-controlled trial randomized 100 delirium-free critically ill adults receiving sedatives to either low-dose IV dexmedetomidine or placebo until ICU discharge. Nocturnal dexmedetomidine was associated with a greater proportion of patients who remained delirium-free during the ICU stay compared to placebo (80% vs. 54%, p=0.006).

These studies are in contrast to another study that randomly assigned elderly (>68 years) patients undergoing major elective noncardiac surgery to dexmedetomidine or saline placebo infused during surgery and for 2 hours in the recovery room (Deiner 2017). The researchers found no difference in postoperative delirium between the dexmedetomidine and placebo groups (12.2% vs 11.4%). After adjustment for age and educational level, there was also no difference in the postoperative cognitive performance between treatment groups at 3 months and 6 months.

So low-dose dexmedetomidine shows some promise as a prophylactic therapy to prevent delirium. But the studies to date have been single- or double-center studies with relatively small numbers. Before we jump on the dexmedetomidine bandwagon, we'd like to see a larger multi-center trial similar to the REDUCE trial.

How about preventing postoperative delirium? Two recent studies looked at the relationship between anesthesia practices and delirium. The STRIDE (A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients) study (Sieber 2018) was a double-blind randomized clinical trial comparing depth of anesthesia to occurrence of delirium in 200 patients ≥65 years who were undergoing nonelective hip fracture repair with spinal anesthesia and propofol sedation. Surprisingly, the researchers found that lighter sedation failed reduce the rate of delirium in severely ill people. Overall incident delirium risk was 36.5% (39% vs 34% in heavier and lighter sedation groups, respectively, not statistically significantly different).

But, in a prespecified subgroup analysis, when stratified by the Charlson comorbidity index (CCI), sedation levels did affect the delirium risk. In low comorbid states (CCI = 0), heavier vs lighter sedation levels more than doubled the risk of delirium (hazard ratio, 2.3).

Another study (Bang 2018), presented so far only in abstract form, looked at more than 96,000 patients in Korea aged 65 years and older receiving hip fracture surgery. Those researchers found patients who received regional anesthesia had better 30-day mortality and delirium outcomes compared to those who received general anesthesia.
The delirium prevalence was 22.7% in those receiving general anesthesia vs. 18.1% in those receiving regional anesthesia ($p<0.0001$). The difference remained statistically significant even after matching by use of propensity scores. The regional anesthesia patients also had lower rates of ICU admission, ventilator care, hospital costs, and complications including pulmonary embolism, cerebral hemorrhage and cerebral infarction.

Quite frankly, we were surprised at the relatively low rates of delirium for a patient population that we know in the US has much higher rates for delirium. But the answer lies in the manner in which they defined delirium. They were using an administrative database and defined delirium as the record of intravenous administration of haloperidol, risperidone and quetiapine at least once during the indexed period, That obviously vastly underidentifies delirium compared to use of tools like the CAM. So the jury is still out on this issue, though it certainly makes sense from a biological plausibility standpoint that patients undergoing regional anesthesia might have lower rates of delirium than those undergoing general anesthesia.

So, now that we know we shouldn't be using antipsychotic drugs in patients with delirium, and aren't yet sure if there is pharmacological prophylaxis to prevent delirium, what are we to do?

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").

Treating clinicians in the MIND-USA trial mentioned above were educated about the "ABCDE" treatment bundle (assess, prevent, and manage pain; both spontaneous awakening and breathing trials; choice of analgesia and sedation; assess, prevent, and manage delirium; and early mobility and exercise) and were encouraged to perform the treatment bundle to mitigate delirium among the patients in the ICU.

In an editorial accompanying the REDUCE study, Delaney et al. (Delaney 2018) comment on the attractiveness of the non-pharmacological interventions used in the study. They categorize these as "doing less" (avoiding excessive sedation, benzodiazepines, nocturnal noise, stimulation) and continued provision of relatively "simple therapies" (mobilization, maintaining a day-night schedule, noise reduction). They note some may require planning and cooperation of a multidisciplinary team, but they are readily undertaken "irrespective of the complexity and challenge of the

environment". They also say future studies on the efficacy of non-pharmacologic strategies should include evaluation of sleep hygiene bundles (earplugs, eye patches, music therapy, reduced noise levels). See also our November 6, 2018 Patient Safety Tip of the Week "More on Promoting Sleep in Inpatients".

In our January 24, 2017 Patient Safety Tip of the Week "Dexmedetomidine to Prevent Postoperative Delirium" we also described a pragmatic clinical trial that used the EMR to implement several elements of multifactorial interventions that have been used for delirium prevention in patients age 65 and older who underwent surgery for hip fracture (Freter 2016). That program resulted in a substantial reduction in delirium rates in the intervention group compared to a control group.

One of the components of many of the multidimensional programs for delirium is putting familiar objects from home in the patient rooms and encouraging family and friends visit with patients. One meta-analysis (Nassar 2018) found that flexible visiting policies in ICU's were associated with a 61% reduced frequency of delirium (odds ratio 0.39). Family members' satisfaction was also improved. But there may be a downside: they may be associated with an increased risk of burnout among ICU professionals.

An innovative study looked at **storytelling** as a way to reduce delirium (Danila 2018). A pilot study of 50 patients age 65 or older was conducted at UAB (University of Alabama at Birmingham) Highlands Hospital. Two artists-in-residence, part of UAB's Institute for Arts in Medicine, visited the patients once for 15 minutes of bedside storytelling or poetry during their hospital stay. Patients were asked if they would like to hear a story or poem, and could choose the type, whether it be religious, humorous, a folk or fairy tale, or a legend or myth. The session was designed to be interactive, with the patient's having the opportunity to reflect on the story or poem and share stories from his or her own life. Participants exposed to the storytelling/poetry intervention had a lower delirium screening score at hospital discharge compared with those in the control group. The result remained significant after adjusting for age, baseline cognitive impairment, and general well-being.

And don't forget that delirium is a risk factor for other patient safety issues, especially **falls**. A recent study (Ferguson 2018) showed that a nursing-driven hospital-wide delirium program targeting improvements in risk identification, prevention, detection, and treatment resulted in reduced rates of delirium-related falls. A delirium risk identification form to be completed for every hospitalized patient at the time of admission facilitated appropriate, timely initiation of the bundle. The bundle consisted of evidence-based nonpharmacological interventions that included efforts to minimize, treat, or prevent sensory deprivation or overload; impaired sleep-wake cycle; immobility; poor nutrition or dehydration; urinary retention; constipation; suboptimal pain management; deliriogenic medications; unnecessary lines or tethers; hypoxia; and alcohol withdrawal. Over the course of the program, delirium falls decreased from 0.91 to 0.50 per patient day (P = .0002). A decrease in overall falls was also noted (P = .0007).

Lastly, we'd be remiss if we didn't refer you to Sharon Inouye's description of her journey in geriatric medicine and delirium research (Inouye 2018). Her work in developing HELP, the Hospital Elder Life Program, led to many of our multi-component non-pharmacological interventions 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"
- January 24, 2017 "Dexmedetomidine to Prevent Postoperative Delirium"
- March 21, 2017 "Success at Preventing Delirium"
- July 2017 "HELP Program Reduces Delirium Rate and LOS"
- January 2018 "What Happens After Delirium?"
- February 20, 2018 "Delirium and Falls"

- October 2018 "Rapid Screening for Delirium"

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