Introduction

Delirium is a state of acute impaired brain function associated with disorientation, unstable state of alertness, and disrupted attention, experienced especially by older adults admitted to the hospital, with the potential for adverse patient outcomes. Of hospitalized patients, the highest rate of delirium occurs in the older patients. Development of delirium is associated with longer hospital lengths of stay, significantly higher risk of functional decline, loss of independent living, and increased mortality both during hospitalization stay and following discharge. Delirium develops through a complex interaction between the patient’s baseline vulnerability (patient predisposing risk factors before hospitalization) and precipitating factors or insults (events that occur during hospitalization) (1). Some of the vulnerability factors identified include advanced age, cognitive impairment or dementia, and pre-existing co-morbidities. Over the last two decades, a large body of literature has focused on the clinical manifestations, risk factors and outcomes of delirium. In the perioperative period, the possible risk factors for the development of postoperative delirium in older patients include an unfamiliar environment, sleep disturbances (2-4), and exposure to medications that have the potential for profound effects on the central nervous system.

In this lecture, we will focus on two of the potentially reversible risk factors associated with postoperative delirium – sleep disruption, and postoperative pain and pain management.
Sleep disruption

Delirium and sleep disruption are both common in hospitalized older adults. Sleep disturbance, including changes in sleep patterns and architecture (especially sleep fragmentation), and decreased quality of sleep are commonly observed in older subjects. In the hospital, environmental factors and health care practices further contribute to sleep disruption in the older patients. Among environmental factors are the noise levels, ambient light, and measurement of vital signs, medications administration, and performance of medical procedures and tests. Additionally, many sedative and analgesic agents potently suppress slow wave sleep which has the strongest association with homeostatic recovery function of sleep.

A number of studies using actigraphy which measures motor activity patterns demonstrate that patients who have undergone surgery experienced postoperative sleep disturbance (5, 6). Recently, we performed a pilot study of 24 patients to determine the tolerability of the SEDline brain monitor in critically ill older patients. In all enrolled subjects, we were able to continuously monitor their EEG and retrieve the raw EEG for review and analysis. The recordings have been scored for sleep stages and arousals according to the 2007 American Academy of Sleep Medicine guidelines. Our data show trends consistent with previously published reports on sleep among ICU patients. Specifically, 1) sleep was distributed throughout the day and night rather than being consolidated at night, and 2) there was a noticeable absence of REM sleep, and 3) patients did not have a normal sleep cycle, where individuals transition from lighter to deeper sleep and alternate between NREM and REM sleep in approximately 90 minute cycles. We further compared the sleep data between patients with delirium vs. those without. Overall, the duration of wakes after sleep onset tended to be longer (725 ± 715 vs. 702 ± 499 min) in those with delirium vs. those with no delirium. Also, the number of transitions between sleep stages appears to be higher in patients with
delirium vs. those without (25 ± 540 vs. 180 ± 138/hr of sleep), suggesting that patients who develop delirium may have impaired sleep continuity and abnormal sleep stage dynamics prior to the development of symptoms. These results are corroborated by a study by Osse et al. (7) who studied 79 patients undergoing cardiac surgery and found that the activity amplitude and the daytime activity/minute and restlessness index were significantly higher, and the daytime number of immobility minutes significantly lower for patients without delirium or those with short delirium episodes. In another cohort of postoperative geriatric patients, Jacobson et al. also reported a significant disruption of the diurnal rest-activity cycle in delirious patients (8).

Postoperative pain and pain management

To date, few studies have examined events in the postoperative period that may contribute to the occurrence of postoperative delirium. Two related and possibly modifiable factors in the postoperative period are postoperative pain and analgesic medications. Although prior studies suggest that postoperative pain and analgesia are associated with postoperative delirium (9, 10), the relative importance of these two factors on postoperative delirium remains unclear. For example, Lynch et al. studied patients ≥ 50 years of age undergoing elective noncardiac surgery and reported that pain which occurred at rest in the postoperative period was associated with postoperative delirium (10). In contrast, Marcantonio et al. reported that pain did not increase the risk of postoperative delirium (9). Since postoperative pain management techniques have changed substantially in recent years, an examination of the association of current pain management strategy on the incidence of delirium is indicated. Accordingly, we investigated whether the method of postoperative pain management, medication types, and the severity of postoperative pain may impact the occurrence of postoperative delirium, when controlling for other co-variates. In one
study, we examined whether the mode of postoperative analgesia delivery, medication type, and pain severity were associated with the occurrence of postoperative delirium (11). In this study, 46% of patients developed postoperative delirium on the first or second day (11). By multivariate logistic regression, we found that the age-adjusted odds of postoperative delirium increased with both preoperative pain at rest and postoperative increase in rest pain.

We next conducted a nested cohort study of 335 patients who used on-demand Patient Controlled Analgesia (PCA) alone for postoperative pain control (12). We found that postoperative delirium did not limit PCA use. Further, pain scores were higher in patients with delirium, despite more opioid use. This study provides direct evidence that studies of postoperative delirium need to consider the role of pain and pain management as potential etiologic factors.

To build on this work, we sought to determine whether preoperative risk for delirium moderates the association between postoperative pain and opioids and incident delirium (13). First, we developed a prediction model to determine which patients were at greatest risk for the development of delirium based on only preoperative patient data. We hypothesized that pain and opioid increased the incidence of postoperative delirium for patients at high-risk of developing delirium. We found that significantly higher incidence of postoperative delirium was found among patients with one or more of the following preoperative risk factors: 1) preoperative cognitive impairment, 2) a history of central nervous system disorder, 3) a higher surgical risk level, 4) major spine or joint arthroplasty surgery, and 5) female (table 1). The effects of high levels of postoperative pain and/or using high postoperative opioid doses on the development of postoperative delirium differed for those at high versus low preoperative risks. Therefore, optimizing methods of postoperative pain control is an important clinical goal in older patients at risk for postoperative delirium, particularly in those identified to be at high preoperative risk.
Table 1

Low risk is defined when patients have 3 risk points or fewer and high risk with 4 or more risk points.
The risk points are defined by giving 1 point to each of the independent risk factors identified in the model where:
Female gender = 1 point
A history of central nerve system disorder = 1 point
Preoperative TICS score (≤30 = 2 points, 30-35 = 1 point, and >35 = 0 point)
Surgical risk (high = 1 point, low or intermediate = 0 point)
Surgery type (orthopedic and spine surgery = 1 point, others = 0 point)
TICS = telephone interview of cognitive status, CNS = central nervous system, mod = moderate

Given our previous work showing the association between pain and pain management with postoperative delirium, we conducted a pilot study to test the hypothesis that, in older patients undergoing major noncardiac surgery, the occurrence of postoperative delirium can be reduced through intensive pain management after surgery. We conducted a double blind, placebo-controlled pilot study using gabapentin as an add-on agent in the treatment of postoperative pain in older patients undergoing spinal surgery (14). In this study, the incidence of postoperative delirium as measured...
by the CAM was significantly higher in the placebo than in the gabapentin groups (42% vs. 0%, P= 0.045) (15). We are currently conducting a larger clinical trial to validate these results. This study provides support to our overall research objective that identification and modification of reversible risk factors may improve cognitive outcomes.

**Future studies**

Despite the strong association demonstrated between sleep disruption, high pain levels and high opioid use in delirious patients, prospective randomized studies are lacking which demonstrate that improvement of sleep-wake cycle, or intensive treatment of postoperative pain will lead to a reduction in postoperative delirium. These studies are critically needed to guide the ultimate prevention and treatment of in-hospitalized delirium.
References


