American Journal of Hospital Medicine
Promoting research and education in the field of hospital medicine. ISSN 2474-7017 (online)

Clinical Research

The Effect of Medication Prophylaxis on the Incidence of Delirium in Elderly Patients Undergoing Orthopedic Surgery: A Meta-Analysis

October 5, 2015 Clinical Research, October-December 2015
Keywords Delirium

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Citation – Manandhar N, Naqvi S. The Effect of Medication Prophylaxis on the Incidence of Delirium in Elderly Patients Undergoing Orthopedic Surgery: A Meta-Analysis. Journal of Academic Hospital Medicine 2015, Volume 7, Issue 4

Abstract

: Delirium is common in the post-operative period in patients who have undergone orthopedic surgery, and the elderly are especially vulnerable. It leads to increased costs, longer hospital stays and higher rates of discharge to inpatient institutions. Various medications are being utilized to prevent the development of delirium, but there are only a few small studies investigating these agents in randomized controlled trials. This meta-analysis examined whether delirium could be prevented with pharmaceutical agents.

: A search was performed for randomized controlled trials from the last ten years, which used medications for delirium prophylaxis in the study population of elderly patients undergoing orthopedic surgery. A random-effects model was used to calculate odds ratios for the incidence of delirium as well as length of hospital stay, a secondary outcome.

: 943 patients from four trials were included in the meta-analysis, and results did not show significance in incidence of delirium in patients who received medication compared to those who were given placebo (OR 0.52, 95% CI 0.21, 1.31). Data for secondary outcome of length of hospital stay also did not show a significant difference (mean difference -1.4, 90% CI -3.30, 0.51).

: Prophylactic medication in elderly patients undergoing orthopedic surgery does not decrease the incidence of delirium or length of hospital stay. These results may be in part due to a high level of heterogeneity and small

sample sizes. More randomized controlled trials are needed to examine delirium prophylaxis, as an effective pharmaceutical agent could lead to better outcomes for patients.

1. **Background**

Delirium is characterized by disturbances of consciousness, attention, cognition, and perception. It develops over a short period of time and tends to fluctuate during the course of the day (APA, 2013). It is diagnosed based on the patient's clinical history as well as the observation of key features and assessment of the patient's cognition. While some patients exhibit signs of psychosis, others present with confusion and depressed mood. It is estimated that among the thirteen million patients aged 65 and older who were hospitalized in 2002, 10% – 52% had delirium during their hospitalization (Cole, Primeau, & McCusker, 1996). Delirium can lead to increased morbidity and mortality, and it has also been associated with longer hospital stays as well as higher rates of institutionalization upon discharge. The cost of managing delirium has been estimated at over $100 billion (Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008). Delirium can have multiple etiologies and can occur in a wide variety of settings. Risk factors include sex, age, infections, surgery and adverse drug reactions (Lonergan, Britton, Luxenberg, & Wyller, 2007). Patients hospitalized for medical indications can develop delirium as a complication of their acute and/or chronic disease. While surgical patients are often managed to obtain optimal physical status before their procedures, they can develop delirium with analgesic and anesthetic agents as contributing factors. Patients with delirium in the post-operative period (DPP) may not have an identifiable etiology. The postoperative course can be complicated by dehydration, hypotension, hypercapnia, urinary tract infections, pain etc (Contín, Perez-Jara, Alonso-Contín, Enguix, & Ramos, 2005). In addition, sleep deprivation in the hospital setting and psychosocial factors may also play a role in precipitating delirium. Specifically, patients undergoing orthopedic surgery have high rates of delirium – 22% in hip replacements and 32% in knee replacements (Contín et al., 2005). They may be lucid in the post-anesthesia care unit but typically develop fluctuating mental status between post-operative days 1 and 3 (Deiner & Silverstein, 2009). Patients with DPP are more likely to achieve complete recovery than those with other forms of delirium.

Delirium is widespread, but the pathophysiology is not yet clearly understood. It is hypothesized that delirium occurs due to an imbalance in neurotransmitters. Specifically, decreased cholinergic transmission and increased release of dopamine have been implicated in its pathogenesis. Alterations in GABA, serotonin, cortisol, and beta-endorphins are also thought to contribute to delirium (White, 2002). There has been growing interest in preventing DPP over the past decade. Although the FDA has not approved any pharmaceutical intervention for the prevention or treatment of delirium, clinicians often employ first or second generation antipsychotics and cholinergic agents. Cholinesterase inhibitors such as donepezil increase the available acetylcholine and have been used in a few trials to investigate the treatment of delirium (Overshott, Karim, & Burns, 2008). Haloperidol, a D2 dopamine receptor antagonist, is the most utilized and studied medication for the management of delirium. Haloperidol blocks dopamine and thus increases the levels of acetylcholine. Although low doses are generally considered safe, higher doses can lead to extrapyramidal effects and cardiac conduction defects. Atypical antipsychotics are currently being studied as alternatives to haloperidol. They are associated with a lower incidence of extrapyramidal adverse effects due to sparing of the dopaminergic blockade (Lonergan et al., 2007). However, they can lead to anticholinergic effects in the elderly. Studies involving these medications have been relatively small with inadequate sample sizes and inconsistent interventions (Boustani et al., 2007). A meta-analysis can combine the data in these studies to reach better statistical power. The aim of this meta-analysis was to see if pharmaceutical intervention would affect the incidence of delirium in elderly patients undergoing elective orthopedic surgeries and also to examine secondary outcomes such as length of hospital stay.

1. **Methods**

<u>Search Strategy</u>

The meta-analysis was conducted using PubMed, Medline, Scopus, and the Cochrane Library. The search terms utilized were delirium, elderly, prophylaxis, orthopedic, surgery, knee, hip, and joint. The search was limited to the English language and only included randomized controlled trials conducted in the last ten years. Only trials examining the use of pharmaceutical agents for delirium prophylaxis were considered. There were two trials

found investigating donepezil, one trial involving olanzapine, and one trial that utilized haloperidol. The meta-analysis was limited to the elderly population. The search was performed by one of the authors (N.M.).

Data Extraction and Analysis

The data was extracted and entered into RevMan for analysis. A random effects model was used, and odds ratios as well as 95% confidence intervals were calculated for the dichotomous outcomes. Forest plots were also used in the data analysis. Heterogeneity was calculated with the I^2 statistic.

1. **Results**

Study Characteristics

Four randomized controlled trials with a total of 943 patients were included in the meta-analysis. All of them were parallel group trials. Kalisvaart et al. randomized 430 elderly patients. They were given haloperidol 1.5 mg/day preoperatively and continued up to 3 days postoperatively. Each patient also received geriatric consultation. 15.1% of the haloperidol patients became delirious while 16.5% of those receiving placebo experienced delirium (RR 0.91, 95% CI 0.6-1.3). This study did not demonstrate a significant difference between the two groups. However, haloperidol did affect secondary outcomes, as it significantly reduced the length of hospital stay compared to placebo (17.1 +/- 11.1 vs. 22.6+/-16.7 respectively, 95% CI 1.4-2.3, P <0.001).

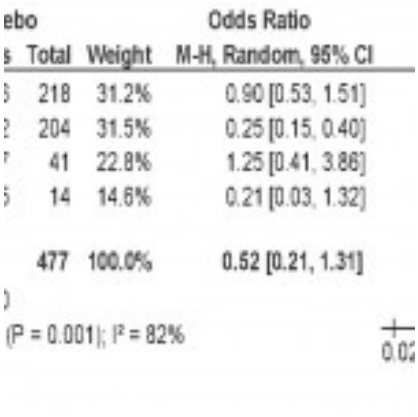
Larsen et al. randomized 400 patients and administered either 5 mg olanzapine or placebo once preoperatively and a second time postoperatively. They found a significant decrease in the incidence of delirium with olanzapine vs. placebo (14.3% vs. 40.2% respectively, 95% CI 17.6-34.2, p<0.0001). While various secondary outcomes were measured, length of hospital stay was not among one of them.

Liptzin et al. asked 80 patients to self-administer either donepezil 10mg or placebo for 14 days preoperatively and 14 days postoperatively. The authors found no significant difference in the incidence of delirium between the two groups (20.5% donepezil and 17.1% placebo, with 90% CI 0.6-2.6, p =0.69). Differences in length of hospital stay were also insignificant.

In the randomized controlled trial by Sampson et al., 33 patients received 10 mg donepezil 5mg immediately after surgery and for three days afterwards. There was no significant difference in delirium incidence between the two groups (9.5% donepezil vs. 35.7% placebo, RR 0.29, 95% CI 0.06, 1.3). Donepezil also did not decrease secondary outcomes such as length of inpatient stay.

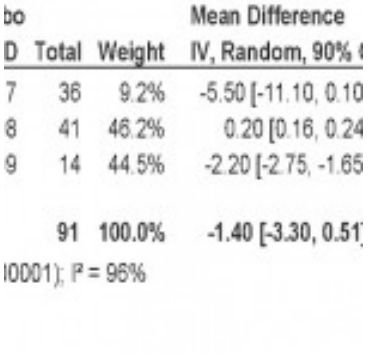
Meta-analysis

The pooled analysis of the four randomized controlled trials showed the difference of incidence of delirium to be insignificant with administration of a pharmaceutical agent versus placebo (OR 0.52, 95% CI 0.21, 1.31). The total incidence of delirium with medication prophylaxis was 15% compared to 27.3% with placebo. Some of the studies also measured secondary outcomes such as length of hospital stay, and this data were also aggregated. Although there were no significant differences for this outcome in the meta-analysis, there was a trend showing decreased length of hospital stay with the administration of medication, Comparison of three of the trials which reported length of hospital stay showed a mean difference of -1.4 with 90% CI of -3.30 to 0.51. The studies showed significant heterogeneity with I^2 of 82%, which could be secondary to the variability among the studies.



Primary Outcome: Incidence of Delirium

Figure 1. Primary Outcome: Incidence of Delirium



Secondary Outcome: Length of Hospital Stay

Figure 2. Secondary Outcome: Length of Hospital Stay

Discussion

Overall, data from the four randomized controlled trials together did not demonstrate that medication prophylaxis affects the incidence of delirium in a significant manner. Significant findings were also not revealed by pooling data for length of hospital stay. It is important to note that I^2 was calculated to be 82% for the primary outcome, indicating a high level of variability in the four trials analyzed. The heterogeneity can be seen with the number of days of intervention, which ranged from 1 day in the Larsen et al. trial to 28 days in the Liptzin et al. trial. In addition, the doses of the medications also varied greatly. Both studies involving donepezil utilized 10 mg per day, and the investigators in the Larsen et al. study administered a total of 10 mg olanzapine per day. However, the patients in the haloperidol study received a low dose of 1.5 mg per day. While this prevented extrapyramidal effects in the study population, the low dose may have been the reason differences in incidence were not seen between the medication and placebo group. There was also great variation in the size of the study populations among the four trials. While the Kalisvaart et al. and the Larsen et al. studies had adequate numbers of patients (430 and 400 respectively), the other trials had small study populations. The Liptzin et al. and Sampson et al. trials were both pilot studies and were comprised of 80 patients and 33 patients respectively. This

could have led to a type II error. These studies were included in the meta-analysis in order to increase the power of the investigation.

There are increasing numbers of elderly patients undergoing orthopedic surgery, and they need special monitoring for delirium due to multiple co-morbidities. Age was a filter used to select the trials for this meta-analysis, as this study was limited to whether delirium prophylaxis would be effective for the elderly population. In the United States, elderly is defined as age > 65. While two of the studies had patients with mean age over 70 years, the patients in the Liptzin et al. study had a mean age of 66.8 for the interventional group and 67.6 for the control group. Similarly, the Sampson et al study had a mean age of 69.7 in the medication group and 65.1 in the placebo group. The patients in the trials who were relatively younger may not have been as susceptible to delirium, which makes them less representative of the typical elderly patient undergoing surgery. Some of the studies sought to eliminate the co-morbidities that place the elderly at higher risk for delirium. For example, the investigators in the Sampson et al. study collected blood and urine cultures on patients prior to the initiation of the study to account for infection as a contributing cause. While this removes confounding factors, it also makes the patient population less representative. This may be the reason that some investigators (Liptzin et al, Sampson et al.) noted that their patients only developed a mild form of dementia.

There were other individual differences in the study designs of the four randomized controlled trials. In the Kalisvaart et al. trial, all patients received geriatric consultation in addition to placebo or haloperidol. This was not performed in the other studies. Geriatric consultation for elderly patients is being increasingly utilized and should be encouraged, as non-pharmacological management can decrease delirium by 13% (Cole et al., 1996). However, this intervention could have led to the low incidence of delirium seen in both groups. It also could have decreased external validity, as the true incidence of delirium could be higher in a population which does not receive such support. An important fault in the Liptzin et al. study is that patients self-administered the medication, and thus, patient compliance could not be ensured. In fact, a fourth of the patients did not adhere to taking the medication for the full duration of the study. The Larsen et al. trial was somewhat compromised by 6 of the patients developing alcohol withdrawal. Thus in these trials, the data may not have been accurate and could have negatively affected the meta-analysis.

The effects of three different medications – haloperidol, donepezil, and olanzapine were investigated in this meta-analysis. In almost all of the studies, the medications were very well tolerated, with no serious adverse effects. Larsen et al. postulate that the lack of difference in the secondary outcomes in their study could have been due to olanzapine causing anticholinergic effects. Since these medications are increasingly administered to elderly patients, care must be taken to administer the lowest effective dose while monitoring for adverse effects. Even though the meta-analysis did not reveal a significant decrease in the development of delirium, there were trends seen in all of the trials. Since the medications are generally safe, physicians should consider administering prophylaxis. The incidence of delirium is higher in the elderly and even higher in the elderly undergoing orthopedic surgeries compared to surgeries in general (Rogers et al., 1989). Successful prophylaxis for delirium in these patients could lead to a decrease in patient morbidity and also lead to significant savings in healthcare costs. All three medications are currently used widely in the treatment of delirium. In order to further investigate these pharmaceutical agents for prophylaxis, these trials should be replicated with a larger patient populations.

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