Melatonin for Treatment and Prevention of Postoperative Delirium

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Postoperative delirium is a common problem associated with increased morbidity and mortality, prolonged hospital stay, additional tests and consultations and therefore, increased cost (1,2). The reported incidence of delirium or confusion after surgery ranges from 8% to 78% (2,3–5), depending on methods and population studied. The elderly seem to be at significantly increased risk for this complication.

Sleep-wake cycle disruption has been associated with delirium and behavioral changes (5) and sleep deprivation can even result in psychosis (6). Environmental changes (i.e., hospital stay), medications, and general anesthesia can affect the sleep-wake cycle (3,4). Plasma melatonin levels, which play an important role in the regulation of the sleep-wake cycle, are decreased after surgery (18) and in hospitalized patients (7,11).

We report the successful use of melatonin in treating severe postoperative delirium unresponsive to antipsychotics or benzodiazepines in one patient. In another patient with a history of postoperative delirium, melatonin was used to prevent another episode of delirium after repeat lower extremity surgery.

Case 1

A 53-yr-old male with a history of Crohn's disease had a hip pinning procedure under general anesthesia for a hip fracture. Preoperative medications included Lomotil (atropine/ diphenoxylate) (Searle & Co., Skokie, IL) and low-molecular weight heparin. He was last treated with steroids more than 2 yr ago. The patient was receiving IV patient controlled analgesia for 3 days preoperatively using between 30 and 42 mg/d of morphine and was alert and oriented without confusion. Postoperatively, he continued to use morphine at 19–28 mg/d for 2 days, followed by oxycodone or codeine over the next 3 days. His behavior was appropriate until 2 days postoperatively, when the patient became confused and disoriented for most of the day and was not sleeping and very agitated at night. He required restraints at times and received lorazepam 2 mg IV for agitation the first night without help. The next 3 nights, haloperidol 1.5–4.5 mg IV was tried without improvement. Serum electrolytes and an arterial blood gas did not reveal any metabolic or oxygenation problems, and a computed tomography scan of the head was normal. A psychiatric consult confirmed the diagnosis of delirium. As other interventions had not helped, melatonin was given on the fourth night postoperatively. A 2-mg slow release formulation was used, and the patient slept better that night and was oriented without confusion the next day. He received melatonin at about 9 PM for three additional nights and had no further episodes of delirium.

Case 2

A 78-yr-old male with a history of coronary artery disease and transient ischemic attacks underwent a hip pinning procedure for a hip fracture under epidural anesthesia. His medications included isosorbide and propranolol, and he received 2 mg of morphine via the epidural and 1 mg of midazolam IV for a 2-h surgery. He required a total of 7 mg of morphine IV over the next 3 days.

The patient was alert and oriented preoperatively and did not have a history of dementia. He began experiencing confusion during the daytime beginning the day after surgery; this persisted for 4 days along with confusion and mild agitation for the first 5 nights. Sleep was disturbed, and he required a restraint vest at times. He was not febrile and there were no lab abnormalities to explain the change in mental status. Seven days postoperatively, he began sleeping better and was less confused.

The patient presented 3 yr later for open debridement of an infected knee joint. The patient was on the same medications preoperatively with the addition of the antibiotic, vancomycin. Melatonin was given preemptively the night after surgery in hopes of preventing postoperative delirium after repeat orthopedic surgery. Anesthesia consisted of a femoral and sciatic nerve block, 100 μ g IV fentanyl and a propofol infusion for the 1.5-h surgery. Oxycodone was given for 2 days postoperatively. During this hospitalization, he received melatonin 2 mg for 3 nights postoperatively and slept well. He remained alert and oriented without confusion during the 5-day hospitalization.

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Discussion

The incidence of postoperative delirium in patients undergoing surgery for hip fracture by spinal or general anesthesia is reported at 16%-41%, beginning usually one or two days after surgery and persisting up to six days in one study and more than one month in another study (3,8,9). An international study that included 1183 patients undergoing noncardiac surgery reported 9% of patients developing postoperative delirium with these patients being 2 ½ times more likely to have a cardiac event, 3 times more likely to have a respiratory event, and 7 times more likely to die during hospitalization (2). The patients with delirium also stayed in the hospital an average of five additional days.

Sleep disorders and disruption of rapid eyemovement sleep after surgery may result from increased cortisol secretion and disruption of circadian rhythm (13). The elderly are more prone to sleep disorders, and this may be related to degeneration of the suprachiasmatic nuclei, which results in lower baseline serum melatonin levels (10). Serum melatonin levels decrease after surgery (18) and after administration of certain opioids (12), possibly contributing to disruption of the sleep-wake cycle postoperatively.

Melatonin or bright light synchronize or reset the internal circadian rhythm and sleep-wake cycle (15). Melatonin can correct sleep disorders in the elderly (17) and can reduce jet lag from travel across time zones by resetting the internal clock (14). Morning light therapy was shown to normalize disturbed sleep and also improve behavior disorders in elderly patients with dementia (16). We hypothesize that melatonin can reset the sleep-wake cycle that is altered after surgery and may correct or prevent postoperative delirium in susceptible patients. A small dose, slow-release formulation of melatonin, similar to the preparation used in geriatric sleep studies, was used in these cases (17).

Melatonin was used by this author on a number of occasions to treat postoperative delirium, and one such case is presented in this report. In the second case, it is possible that a repeat episode of postoperative delirium was prevented with a short course of melatonin. In fact, a double-blind placebo controlled study is underway at our institution to determine whether melatonin can prevent postoperative delirium. In the meantime, it may be worthwhile to use this fairly benign drug to treat postoperative delirium or even prophylactically inpatients with a history of confusion after surgery.

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