## Postoperative Obstructive Sleep Apnea and Delirium?

We read with interest the recent article by Flink *et al.*[1] in which the authors evaluated the frequency of postoperative delirium (POD) in 106 elderly patients aged 65 yr or older after elective knee replacement. The screening for POD was thorough and well-conducted with recognized screening tools, with an incidence of 25% on days 2–3 postoperatively. The pathophysiologic mechanisms are multiple, including anemia, electrolyte disturbances, infection, pain, and benzodiazepine and opioid use.[2]

Patients with obstructive sleep apnea are at an increased risk of postoperative complications in general, and this is especially true when combined with opioid-based analgesia in the postoperative period.[2,3] It is therefore unfortunate that this otherwise well-conducted study did not include data on pain, opioid use, and other sedatives, because this may worsen the adverse effects of obstructive sleep apnea. In addition, there was little specific information on the anesthetic technique *per se*.

The incidence of POD of 25% seems high in an elective, nondemented surgical population. Our group recently found no cases of POD in a similar population of patients undergoing knee and hip replacement.[4] However, our patients received multimodal optimized care with reduced opioid use and only moderate postoperative pain, combined with short length of stay (mean 2.6 days). We believe that future studies evaluating the complex cognitive outcome of POD with multiple pathophysiologic mechanisms should include an optimized multimodal enhanced recovery program (the fast-track methodology)[3–5] to provide a better understanding of POD and preventive techniques.

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*In Reply:*

We thank Drs. Krenk and Kehlet for their comments on our study,[1] and we appreciate their concerns. The type of anesthesia used for our patients is listed in tables 1 and 2 of our article. There was no effect of type of anesthesia on postoperative delirium. In the majority of our patients (89 of 106, 84%) a femoral nerve catheter was inserted before surgery, through which they received a constant infusion of local anesthetic postoperatively. An additional seven patients received postop epidural analgesia. Regional analgesia in both instances was supplemented with oral celecoxib and pregabalin, and opioid as needed.

The incidence of postoperative delirium in our patient population is similar to that reported by others in knee arthroplasty patients.[2] In contrast, Dr. Krenk's impressive study of fast-track hip and knee arthroplasty (of which we were unaware before our article submission) revealed no postoperative delirium.[3] However, there are significant differences between the studies. In particular, delirium in our study was diagnosed not only on the basis of nursing, physical therapy, and physician notes (as in Dr. Krenk's study), but also by using Confusion Assessment Method and Delirium Rating Scale-Revised-98 administered by a dedicated, specifically trained nurse, and reviewed by a psychiatrist. Most of our cases were mild, thus we probably detected many cases that might not have been noted by ward nurses with many other responsibilities. We agree with Drs. Krenk and Kehlet that opioids can enhance postoperative complications in obstructive sleep apnea patients. Despite implementation of fairly consistent regional analgesia to minimize such effects, we still observed an effect of obstructive sleep apnea. Indeed, it is likely that some patients with apnea went undiagnosed or were not known. These false negatives would tend to weaken the observed effect in our analysis, suggesting that an even stronger effect of obstructive sleep apnea on delirium might exist.

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# Should We Use Psychostimulant Drugs to Boost the Emergence from General Anesthesia?

*To the Editor:*

Recently, Chemali *et al.*[1] showed that psychostimulants can accelerate the emergence from propofol anesthesia as evidenced by a faster recovery of the righting reflex and by signs of electroencephalogram activation after the injection of methylphenidate during propofol infusion. The authors believe that methylphenidate can be safely used in a clinical setting to facilitate the awakening from prolonged propofol anesthesia or in patients overly sedated by propofol. In our view, the use of psychostimulants such as methylphenidate as emergence drugs may lead to undesirable consequences, especially in the abovementioned subsets of patients.

It has been recently suggested that sequential activation of consciousness, connectedness to the environment, and responsiveness may be prerequisites for the smooth and uneventful emergence from anesthesia.[2] Switching on the connectedness or responsiveness before the consciousness is fully recovered from the effect of GABAergic drugs may be a cause of cognitive dysfunction or even delirium on emergence.[2,3] Although connectedness to external stimuli is likely to rely on norepinephrinergic signaling,[4] responsiveness probably requires the engagement of the basal ganglia and is subject to dopaminergic modulation in the striatum.[5] Methylphenidate can increase extracellular levels of both norepinephrine and dopamine in cortical and subcortical areas.[6–9] We believe that administering methylphenidate during propofol infusion or immediately after its termination and before the anesthetic is eliminated and consciousness sufficiently restored would interrupt the natural sequential switching-on of consciousness–connectedness–responsiveness and may result in postoperative cognitive dysfunction.

We also suspect that accelerated emergence in otherwise uncomplicated anesthesia cases may be unpleasant, similar to sudden and forced awakening from sleep.[10] The authors themselves noticed that the electroencephalogram pattern after methylphenidate injection during propofol infusion was not exactly a return to a normal awake state: rather, the electroencephalogram showed signs of overactivation.[1] Administration of methylphenidate at doses comparable to those used in this study causes an increase in locomotion in rats.[11,12] If the authors had examined the behavior of rats awakened from anesthesia by methylphenidate and compared it with that of animals allowed to naturally awaken from propofol, they would probably have found increased locomotor activity in the former group. The human equivalent of rat hyperlocomotion may be restlessness and agitation, both of which are undesirable and can complicate the postoperative period.

Finally, many stimulant drugs with a dopaminergic mechanism of action, including methylphenidate, lead to the so-called rebound hypersomnolence, evidenced by a period of enhanced compensatory sleep after drug-induced waking.[13,14] For methylphenidate, rebound hypersomnolence occurs at about 3 h after its intraperitoneal administration in rats.[14] It is unclear whether this phenomenon could be potentiated by residual sedation after propofol anesthesia. However, such potentiation is likely to occur and may have detrimental effects in overly sedated patients and, therefore, should be examined before the drug is used in humans.

In conclusion, the results of the study by Chemali *et al.* certainly enrich our knowledge about the mechanisms of anesthesia and prepare us for possible drug interactions in patients on methylphenidate scheduled for surgery. However, before proceeding to examine the ability of methylphenidate to accelerate the emergence from propofol anesthesia in patients, especially in those with increased drug-induced GABAergic tone, it seems prudent to investigate the effects of methylphenidate on postanesthetic cognitive function in animals. Meanwhile, we can still rely on the natural emergence from anesthesia caused by physiologic elimination of the anesthetic drug. Fortunately, with the ever-improving pharmacokinetic profiles of modern anesthetic drugs, we do not have to wait too long.

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