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Original Contribution

Perioperative risks of narcolepsy in patients undergoing general anesthesia: A case-control study

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ABSTRACT

Study objective: To compare the perioperative outcomes between patients with narcolepsy and matched controls undergoing anesthetic management.
Design: Retrospective 2:1 matched study design.
Setting: Large tertiary medical center.
Patients: Narcoleptic patients who underwent general anesthesia from January 1, 2011, through September 30, 2015, were matched with controls by age, sex, and type and year of surgery.
Measurements: Medical records were reviewed for episodes of respiratory depression during phase I recovery and for other meaningful perioperative outcomes.
Main results: The perioperative courses of 76 narcoleptic patients and their controls were examined. Compared to controls, narcoleptic patients were more often prescribed central nervous system stimulants (73.7% vs 4.0%, $P < 0.001$) and antidepressants (46.1% vs 27.6%, $P = 0.007$) and more often had obstructive sleep apnea (40.8% vs 19.1%, $P < 0.001$). The intraoperative course was similar. The number of episodes of respiratory depression was not different between patients and controls (5 [6.6%] vs 12 [7.9%], respectively; $P = 0.80$). Narcoleptic patients had a higher frequency of emergency response team activations (5 of 76 [6.6%]; 95% CI, 2.2%–14.7%) compared to controls (2 of 152 [1.3%]; 95% CI, 0.2%–4.7%) ($P = 0.04$). Hemodynamic instability was the indication for all emergency response team activations except 1, which was for a narcoleptic patient who had excessive postoperative sedation and respiratory depression.
Conclusions: Narcoleptic patients had similar intraoperative courses as the matched controls, including phase I anesthetic recovery. However, they had a higher rate of emergency response team activations than the controls, which suggests that patients with narcolepsy may be at increased perioperative risk.

1. Introduction

Narcolepsy is an uncommon sleep disorder characterized by severe, excessive daytime sleepiness (EDS) and disordered regulation of rapid eye movement (REM) sleep [1,2]. The disorder may be accompanied by other conditions: cataplexy (loss of muscle tone triggered by a strong positive emotion, such as laughter), hypnagogic (at sleep onset) and hypnopompic (during awakening) hallucinations, and sleep paralysis (feeling of being conscious but unable to move while going to sleep or awakening). Etiologic contributions include autoimmune-mediated loss of neurons that produce hypocretin (orexin), a neuropeptide that promotes wakefulness and suppression of REM sleep [1], and a genetic contribution by the HLA-DQB1*06:02 allele [2]. A diagnosis of narcolepsy requires at least 3 months of daily periods with an irrepressible need to sleep or daytime lapses into sleep and a positive multiple sleep latency test with a mean sleep latency of 8 min or less and at least 2 sleep-onset REM periods, or 1 sleep-onset REM period on multiple sleep latency tests and 1 on overnight polysomnography. The disease is further classified as type 1, with a definite presence of cataplexy or a cerebrospinal fluid (CSF) hypocretin-1 concentration of 110 pg/mL or less, or type 2, in which cataplexy is absent and the CSF hypocretin-1 concentration is >110 pg/mL (if measured) [3]. For both types, treatment consists of behavior modifications and wakefulness-promoting medications (e.g., central nervous system [CNS] stimulants) [2]. Antidepressants and sodium oxybate may decrease the frequency of episodes

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; EHR, electronic health record; ERT, emergency response team; OSA, obstructive sleep apnea; REM, rapid eye movement.

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of cataplexy [2]. Obstructive sleep apnea (OSA) is a frequent comorbid sleep disorder of narcoleptic patients, especially in older patients [4].

Few articles have presented case reports [5–21] and case series [22,23] related to the anesthetic management of narcoleptic patients. Short-term or long-term amphetamine use may interfere with anesthesia management. However, many impressions and recommendations are based on circumstantial evidence (i.e., on reports of isolated occurrences of perioperative adverse events in patients taking these medications). Long-term amphetamine use has been reported to result in a diminished anesthetic requirement [24], which is thought to be related to catecholamine depletion in the CNS. Furthermore, Samuels et al. [25] speculated that chronic catecholamine depletion may lead to an inability to respond to the stress of anesthetic induction. In contrast, short-term amphetamine use was thought to increase anesthetic requirements and arterial blood pressure [24]. Further, patients with narcolepsy may have substantial autonomic impairment [26]. Therefore, both the pathophysiologic processes associated with narcolepsy and its treatment can increase the risk of perioperative complications. Most likely, these complications are respiratory or hemodynamic (or both).

Our institution has a unique protocol for monitoring for postoperative respiratory depression during phase I recovery while patients are in the postanesthesia care unit. During their recovery there, patients are continuously monitored by registered nurses for signs of apnea, hypoventilation, oxyhemoglobin desaturation, and discrepant patient self-report of severe pain while being moderately or profoundly sedated [27,28]. These episodes have been linked to both increased postoperative respiratory complications and increased resource use [28,29]. It is unknown whether patients with narcolepsy are at increased risk for respiratory depression during phase I recovery. Our primary aim was to perform a case-control matched analysis that compared the clinical outcomes of surgical narcoleptic patients with controls who did not have a diagnosis of narcolepsy and were matched for age, sex, and procedure.

2. Methods

This study was approved by the Mayo Clinic Institutional Review Board in Rochester, Minnesota (15-008165; approved November 25, 2015). Consistent with Minnesota statute 144.295, we included only patients who had provided authorization for research use of their medical records.

This study used a retrospective case-control design that assessed potential factors associated with morbidity and mortality and anesthetic complications in narcoleptic patients undergoing general anesthesia. The institutional medical database from January 1, 2011, through September 30, 2015, was electronically searched to identify patients with a history of narcolepsy who underwent general anesthesia. Each of these narcoleptic patients was matched with 2 controls by sex, age (within 5 years), surgical procedure, and year of surgery.

Electronic health records (EHRs) for narcoleptic patients and matched controls underwent abstraction for demographic variables; outpatient use of CNS stimulant drugs or antidepressants (or both); comorbid conditions; preoperative, intraoperative, and postoperative variables; and postoperative course and complications. EHRs of narcoleptic patients were also reviewed for the definite presence of cataplexy. Measurements of hypocretin-1 concentration in the CSF were not performed at our institution during the study time frame. Comorbid conditions included presence of cardiovascular disease, pulmonary disease, OSA, other central nervous system diseases, and diabetes mellitus. Preoperative use of opioids, benzodiazepines, or gabapentinoids was also recorded. Overall physical status was assessed from the Charlson Comorbidity Index score.

The presence of OSA was determined by review of the medical records and the preoperative nursing check-in records. Consistent with 2006 American Society of Anesthesiologists guidelines, during the nursing check-in process all patients are queried if they have a history of OSA [30]. Furthermore, patients who do not have a known history of OSA undergo OSA screening with Flemons criteria [31]. Responses to this query and screening process are entered into the EHR and were abstracted for this study [28].

The anesthetic and surgical records were reviewed for general anesthesia duration, type of procedure, perioperative medications, blood transfusion, fluid administration, and perioperative complications. Respiratory depression events during phase I recovery were abstracted [28]. Complications included hemodynamic instability or systemic arterial hypotension, adverse respiratory events, and other severe perioperative complications. Postoperative complications were reported if they occurred within 30 days postoperatively. Information was obtained from the EHRs from the index hospitalization, rehospitalization, and outpatient visits.

Any postoperative activation of the emergency response team (ERT) [32] was noted, and details of the activating circumstances were abstracted and described. ERTs have been introduced by hospitals to evaluate and manage hospitalized patients whose condition is acutely deteriorating, and they are designed to deliver emergent care to patients who are assessed by health care workers as "acutely deteriorating." Postoperative complications included myocardial infarction, respiratory failure (requiring tracheal reintubation or noninvasive positive pressure ventilation), thromboembolic events (pulmonary embolism or deep vein thrombosis), and death. Intensive care unit admissions were recorded. Total hospital length of stay was recorded.

Data were summarized as mean (SD) or median (interquartile range) for continuous variables and frequency (percentage) for nominal variables. Analysis included comparison of narcoleptic patients and controls with the 2-sample *t*-test for continuous variables and the Fisher exact test for categorical variables. *P* values of 0.05 or less were considered significant.

3. Results

For this study, 76 narcoleptic patients who had a procedure performed under general anesthesia were identified and matched with 152 controls. The numbers of patients and controls, respectively, who underwent each type of surgical procedure were as follows: abdominal/gastrointestinal (32, 64), orthopedic (15, 30); urologic (8, 16); otorhinolaryngologic (6, 12); thoracic (6, 12); neurosurgical (3, 6); gynecologic (2, 4); spinal (2, 4); oral and maxillofacial (1, 2); and ophthalmologic (1, 2). Among the narcoleptic patients, 6 (7.9%) had a type 1 diagnosis according to their history of cataplexy, and the others were presumed to have type 2, even though CSF results were not available (Appendix 1). Twenty-five narcoleptic patients were prescribed modafinil or armodafinil, 34 were prescribed an amphetamine or methylphenidate (3 of these patients were prescribed both), and 20 were not prescribed any of these medications at the time of surgery (Appendix 2). Table 1 compares clinical, surgical, and anesthetic factors for narcoleptic patients and non-narcoleptic controls. The narcoleptic patients and controls had similar rates of intraoperative vasoactive medication administration and fluid administration (Table 1). Table 2 compares postoperative outcomes between the 2 groups. Phase I recovery, including the incidence of episodes of respiratory depression (6.6% vs 7.9%, $P = 0.80$), was similar for narcoleptic patients and controls. The frequency of ERT activations was higher among narcoleptic patients (5 of 76 [6.6%]; 95% CI, 2.2%–14.7%) compared to controls (2 of 152 [1.3%]; 95% CI, 0.2%–4.7%) ($P = 0.04$). Table 3 summarizes details for patients with ERT activation for both narcoleptic patients and controls. All ERT activations were for hemodynamic reasons, except for 1 instance when a narcoleptic patient had respiratory depression and hypotension.

That patient was a 36-year-old woman who had narcolepsy without cataplexy. CNS stimulants had not been prescribed for her. Her medical history included type 1 diabetes mellitus, restless leg syndrome, intracranial cavernous angioma, and chronic migraine complicated with aura and aphasia. Her therapy for migraine prophylaxis included amitriptyline, atenolol, gabapentin, and topiramate, and she was also taking

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