



# Influence of general anesthesia on the postoperative sleep cycle in patients undergoing surgery and dental treatment: a scoping review on the incidence of postoperative sleep disturbance

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General anesthesia may influence the postoperative sleep cycle; however, no clinical studies have fully evaluated whether anesthesia causes sleep disturbances during the postoperative period. In this scoping review, we explored the changes in postoperative sleep cycles during surgical procedures or dental treatment under general anesthesia. We compared and evaluated the influence of general anesthesia on sleep cycles and sleep disturbances during the postoperative period in adult and pediatric patients undergoing surgery and/or dental treatment. Literature was retrieved by searching eight public databases. Randomized clinical trials, observational studies, observational case-control studies, and cohort studies were included. Primary outcomes included the incidence of sleep, circadian cycle alterations, and/or sleep disturbances. The search strategy yielded six studies after duplicates were removed. Finally, six clinical trials with 1,044 patients were included. In conclusion, general anesthesia may cause sleep disturbances based on alterations in sleep or the circadian cycle in the postoperative period in patients scheduled for elective surgery.

**Keywords:** Circadian Rhythm; General Anesthesia; Sleep Cycle; Sleep Disturbance.



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## INTRODUCTION

Maintenance of the circadian sleep-wake cycle is essential for regulating the fundamental physiological processes of cognitive function, memory consolidation, the immune system, and growth hormone secretion. Sleep cycles may be altered by general anesthesia in patients who undergo surgery or dental treatment under general anesthesia. This is associated with a significant increase

in rapid eye movement (REM) sleep a few days after general anesthesia since REM sleep is inhibited during general anesthesia [1-5]. Recently, we postulated that general anesthesia could cause sleep disturbances during the postoperative period in patients with disabilities [6]. Furthermore, based on logistic regression, Wang et al. [7] determined that the number of exposures to general anesthesia is a potential factor in sleep disturbances among children. They concluded that more frequent anesthesia exposure leads to worsened sleep quality and

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a higher incidence of sleep disorders and that a longer duration of cumulative anesthesia exposure could also lead to worse sleep quality.

Interestingly, several studies have indicated that sleep disturbances may worsen if patients suffer from sleep disorders before general anesthesia. For instance, postoperative behavioral changes caused by general anesthetics were recognized in two patients with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder [8]. They reported significant behavioral changes, including ongoing marked insomnia, significant loss of appetite, prolonged daytime somnolence, and aggressive behavioral withdrawal from social interactions. This report indicates that secondary causes of sleep disturbances after general anesthesia may predispose these patients to serious adverse events in the acute and late postoperative periods after general anesthesia [9]. Symptoms of insomnia due to reduced total daytime sleep, commonly experienced in ASD [10-13], could be a major factor in sleep cycle disturbance after general anesthesia. Although general anesthesia should be scheduled because ordinary dental treatments are deemed difficult in patients with ASD owing to reports of extreme noncooperation, several complications (e.g., increased hyperactivity, worsened self-harming behavior, and sleep disturbances) can occur after general anesthesia.

However, evidence proving the influence of general anesthesia on the incidence of sleep disturbance is lacking, and this issue remains uncertain and controversial, with minimal randomized clinical trials and basic clinical observational research being conducted, in addition to case reports. Some well-designed clinical trials have investigated the mechanisms by which general anesthesia may cause sleep cycle disturbances in patients after general anesthesia. In this scoping review, we aimed to determine the influence of general anesthesia on postoperative sleep cycles and sleep disturbances based on previously published literature.

Currently, the occurrence of sleep disturbance after general anesthesia during the postoperative period in

patients undergoing elective surgery and/or dental treatments remains controversial. The purpose of this study was to compare the incidence of sleep disturbance after general and non-general anesthesia in patients undergoing elective surgery and/or dental treatment. To the best of our knowledge, this is the first scoping review of this topic.

## METHODS

This scoping review was performed per PRISMA-ScR guidelines [14]. The principal investigator searched for English-language articles published before September 1, 2022, using the PubMed and Cochrane databases. We searched for MeSH terms in the PubMed and Cochrane databases. The search terms used were “sleep disturbances” OR “sleep disorder” OR “sleep” OR “sleep quality” OR “sleep-wake timing” OR “circadian rhythm,” “general anesthesia” OR “anesthesia” OR “intravenous anesthesia” OR “sedation” and “adult patients” OR “pediatric patients.” Restrictive conditions for all search formulas were obtained by searching titles, abstracts, and keywords. Language restrictions were not imposed. A literature search was performed using EndNote X9 (Thomson Reuters, New York, NY, USA). After excluding duplicate and non-clinical studies, we screened the titles and abstracts of the retrieved articles. We then screened the full texts and included six studies. When the results of the investigators diverged, the opinions of the co-investigator were adopted. The studies included in the scoping review met the following criteria: clinical randomized trials (RCTs), clinical observational studies, observational studies, observational case-control studies, prospective cohort studies, and comparisons of general and non-general anesthesia (subarachnoid anesthesia, sedation, or regional anesthesia). Studies with the following characteristics were excluded: animal studies, study protocols, reviews, guidelines, conference abstracts, case reports, and studies with inconsistent inclusion criteria. Three investigators independently completed the

**Table 1.** Study characteristics of clinical study included in the scoping analysis

Source	Country	Design	Primary outcome	Randomization groups	No. of patients randomized	Journal	Procedure	Sedation	Patients	Significant
Ayuse T, et al. 2019 [6]	Japan	An observational study	Sleep cycle	One arm of GA	16	Special Care in Dentistry	Dental procedure	GA	Intellectual disability patients	P < 0.0001 primary outcome Sleep cycle were significantly extended on postoperative day.
Song Y, et al. 2021 [15]	China	A prospective cohort trial	circadian rhythm disruption	Treatment group, GA (n = 69) vs subarachnoid anaesthesia (69)	138	EBioMedicine	Hip fracture surgery	Single dose subarachnoid spinal anaesthesia and intravenous propofol, sevoflurane, etomidate and sufentanil.	elderly patients	P < 0.05 primary outcome, poor sleep quality on surgery day in GA group
Wang Y, et al. 2022 [7]	China	A cohort study	SDSC total score	Treatment group, GA (n = 458) vs no GA (230)	688	Sleep and Biological Rhythms	Plastic surgery	Midazolaplusufentanil and intravenous propofol, sevoflurane, remifentanil.	pediatric patients	P < 0.0001 primary outcome The SDSC score were higher in the GA group
Selvadurai S, et al. 2018 [17]	Canada	An observational case-control study	sleep cycle (sleep efficiency, total sleep time, wake time after sleep onset and sleep latency)	One arm of GA	31	Sleep	Urologic and otolaryngologic surgery	Sevoflurane, opiates (remifentanil or fentanyl morphine)	pediatric patients	No significant differences were found in all the parameters
Tran J, et al. 2018 [18]	USA	An observational case-control study	sleep disturbance recorded in anesthesia record and interview on telephone	One arm of GA	77 (40 healthy and 37 ASD children)	Frontiers in Oral Health	Dental surgery	Sevoflurane or ketamine (im) for induction and propofol for maintenance	pediatric patients	No significant differences in sleep disturbance
van Zuylen ML, et al. 2022 [16]	Netherlands	An observational study	diurnal phase shift the night after surgery (sleep-wake pattern (circadian timing system))	One arm of GA	94	Anaesthesia	Elective surgery	??	adult patients >aged 18	P < 0.001 primary outcome. The phase advance of 40 minutes compared in the night after surgery

ASD, autism spectrum disorder; GA, general anesthesia; n, number; SDSC, sleep disorder scale for children; USA, United States of America.

data extraction. Table 1 shows the characteristics of randomized clinical research, including RCTs, clinical observational studies, observational case-control studies, and cohort studies. These data include the source of the study, year, primary outcome, other outcome(s), randomization groups, number of randomized patients, published journals, and target procedures. An independent librarian was responsible for resolving disputes during the data extraction process. The primary outcome of this scoping review was the incidence of sleep disturbances or alteration of the circadian rhythm during the postoperative period after general anesthesia.

## RESULTS

Upon searching for clinical research articles written in English in the international databases of PubMed and

Cochrane, six articles were identified. Among several databases, we selected PubMed and Cochrane because it is possible to search. Six articles were identified by searching the PubMed and Cochrane databases. We analyzed six clinical trials (randomized clinical trials [RCT]: one, clinical observational studies: two, observational case-control study: one, cohort study characteristics: two). By screening abstracts, titles, and keywords, we obtained six studies related to sleep disturbance after general anesthesia. After screening full texts, six studies were included. The literature retrieval process is summarized in Table 1.

Ayuse et al. [6] has postulated that general anesthesia could cause sleep disturbances in the postoperative period in handicapped patients [6]. They found that the percentage of deep sleep significantly decreased on postoperative day 1, whereas that of light sleep increased. Sleep cycles were also significantly extended on

postoperative day 1. These findings reveal that the sleep cycle may be affected on the first day following general anesthesia in patients with disabilities. Song et al. [15] suggested that circadian disruption in patients scheduled for hip fracture surgery was greater in the general anesthesia group than in the subarachnoid anesthesia group. Wang et al. [7] indicated that children who underwent plastic surgery between the ages of 6 and 15 years with multiple exposures to general anesthesia may have worse sleep quality and a higher incidence of sleep disorders. Furthermore, van Zuylen et al. [16] concluded that there is a perioperative phase advance at the midpoint of sleep, indicating that general anesthesia disturbs the circadian timing system. However, several studies have opposing findings regarding general anesthesia, which has no significant influence on sleep quality. Selvadural et al. [17] indicated that general anesthesia did not result in disturbed sleep or associated negative behavioral changes in otherwise healthy children undergoing elective surgeries of low complexity. Tran et al. [18] also suggested that there was no significant difference in sleep disturbance in any of the surveys performed after general anesthesia upon the evaluation of anesthesia records and interviews with patients.

## DISCUSSION

In this scoping review, six clinical studies were identified that tested the influence of general anesthesia on the sleep cycle of circadian rhythms. There might be an incidence of sleep disturbance after general anesthesia in certain patient populations and types of surgery. Although the factors that affect sleep disturbance after general anesthesia remain unknown, perioperative circadian rhythms should be carefully managed and maintained, especially in patients with sleep disorders before general anesthesia. Moody et al. [5] suggested that general anesthesia and natural sleep share the common feature of reversible unconsciousness and that sleep is primarily driven by the withdrawal of subcortical

excitation to the cortex; however, anesthetics can directly act on both subcortical and cortical targets. Although some anesthetics appear to activate specific sleep-active regions to induce unconsciousness, not all sleep-active regions play a significant role in anesthesia. Anesthetics also inhibit cortical neurons, and each class of anesthetic drugs likely produces a distinct combination of subcortical and cortical effects that lead to unconsciousness. Conversely, arousal circuits that promote wakefulness are involved in anesthetic emergence, and their activation can induce emergence and accelerate the recovery of consciousness. Song et al. [4] revealed cross-relationships between cerebellar function and the sleep-wake cycle, which might lead to sleep disturbances in patients with cerebellar malfunction. There may have been inconsistent conclusions regarding the clinical studies listed in this scoping review. Therefore, it might be necessary to test the influence of general anesthesia on the sleep cycle or circadian rhythms in randomized clinical trials using accurate evaluation methods such as actigraphy, matt-type devices, or EEG monitoring, including the most recent sophisticated devices for monitoring the sleep cycle or circadian rhythms.

### 1. Sleep disorders after general anesthesia

The risk of sleep disturbance after general anesthesia, characterized by increased rebound REM sleep, has been reported by Knill et al. [1,19-21]. The percentage of REM sleep increased after abdominal surgery. Chung et al. reported changes in the sleep cycle on the first day after general anesthesia in patients with obstructive sleep apnea. There are several ways to prevent sleep disturbances after general anesthesia, such as reducing postoperative stress, appropriate pain management, and maintaining an early return to activities of daily living at home through early discharge from the hospital. Patients scheduled for surgery under general anesthesia have reduced sleep efficiency on the first night after surgery [1,2,9,20,22]. Sleep efficiency and REM sleep are suppressed on the first night after general anesthesia in pediatric patients undergoing

tonsillectomy [23]. Furthermore, REM rebound was observed on the third night after surgery due to the significant inhibition of REM sleep phases [1,2]. It should be noted that the type of anesthetic agent used may affect sleep architecture. Total intravenous anesthesia with propofol and remifentanyl was maintained during general anesthesia. Although propofol has been reported to abolish REM sleep [24], it has not been associated with a rebound increase during the REM sleep phase [25]. Notably, opioids may suppress slow-wave sleep and REM sleep via the  $\mu$  receptor [20,26,27]. Several factors have been suggested to cause sleep disturbances after general anesthesia, including inflammation (wound pain and opioid requirements) and psychological and environmental factors (ambient noise, nursing interventions, and light) [27]. One major risk factor is severe pain perception due to regional wounds after treatment, particularly after tooth extraction [11]. However, the influence of pain on sleep disturbance was negligible because an adequate acetaminophen injection was administered during general anesthesia, if needed, in the case of tooth extraction. Furthermore, an increased incidence of insomnia reduces sleep efficiency and REM sleep [9]. It has been postulated that general anesthesia may affect the postoperative sleep architecture and/or circadian rhythm [28]. However, it is not fully understood why general anesthesia may affect the sleep architecture or circadian cycle regulated by the central nervous system and the possible occurrence of postoperative behavioral changes. To elucidate the clinical relevance of postoperative sleep disturbance after general anesthesia in patients with ASD, it may be necessary to alter cognitive function and behavioral science. We also suggest that it is necessary to establish a preventive pharmacological protocol for postoperative sleep disturbance after general anesthesia.

## **2. Sleep disorders specific to patients with intellectual disabilities, including ASD or attention-deficit/hyperactivity disorder**

Considering behavioral management for dental

treatment with sedation or general anesthesia, unlike healthy adults, patients with ASD often encounter communication difficulties even during the preoperative phase. These patients may experience stress not only because they are anesthetized but also because a visit to the hospital may seem daunting. A report suggested that patients with ASD have sleep disorders even under normal living conditions, and a strong association between sleep disorders and self-harming behaviors has been reported [29]. We assumed that the symptoms of daytime insomnia due to reduced total sleep, commonly experienced in ASD [10,11], could be a major factor in sleep disturbance. In addition, sleep efficiency declines with age [30]. If patients with ASD become older, we would expect baseline changes in sleep architecture before planning for general anesthesia. In our previous study [6], the sleep cycle began 5 days before general anesthesia. Daily measurements of sleep patterns can serve as preoperative control values. Therefore, even though the patient's sleep cycle was already modulated, patient-specific preoperative values could be used as control values to compare the changes in the sleep cycle after general anesthesia. Notably, local anesthesia can exacerbate pre-existing sleep disorders [31]. It has been reported that minimizing agitation and excitement during emergence from local anesthesia using additional sedative agents could be effective in reducing sleep disturbance after general anesthesia in patients with ASD. This is important because patients with ASD are highly sensitive to discomfort and anxiety. The importance of communicating with parents and/or caregivers has also been emphasized. Therefore, special care is necessary for these patients when separating them from their parent(s) in the operating room and outpatient centers. The timing of hospital arrival and discharge after the hospital stay is also crucial. We should minimize the measurements of vital signs performed by nursing staff in the ward or recovery room, considering the environmental changes in hospital rooms compared with the familiar environment of homes. Anxiolysis could also be effective with necessitating effective premedication, such as

preoperative sedation. Sleep disturbances may strongly interact with oral medications, such as antiepileptic and/or antipsychotic drugs, in patients with ASD. In this study, nine patients were taking antiepileptics, antidepressants, or psychotropic drugs. Therefore, we hypothesized that the daily use of these drugs for the maintenance of mental health could have a major influence on sleep quality. Patients with ASD and intellectual disabilities often have preexisting sleep disorders [12,32-37]. Symptoms of insomnia, including increased sleep onset latency, increased wake after sleep onset episodes, and reduced total sleep time, are common causes of ASD [10,11]. In this study, most patients were on medication, such as antiepileptic and antipsychotic medications. Considering the possible influence of general anesthesia on sleep disturbance in patients with ASD, it may be necessary to investigate the characteristics of the patient's sleep architecture through a screening test, in addition to evaluating the systemic screening of the patient's general condition. To achieve this, a lightweight, small, wrist-type actigraph or sleep-monitoring mat device that is acceptable to patients is required. If a patient presents with a significant preoperative sleep disorder, treatment with endogenous sleep aids, such as melatonin agonists, can be considered as an alternative preventive treatment [38]. If insomnia occurs before general anesthesia, normalization of sleep with various sleep regulators is necessary. The use of sedative drugs may be appropriate to prevent postoperative acute agitation after general anesthesia, which may lead to secondary postoperative sleep disturbances [39]. In our opinion, preoperative treatment of insomnia by the administration of these medicines could be clinically relevant. Moreover, the risk of sleep disorders due to increased orexin levels after general anesthesia has been reported. In addition to insomnia treatment, active preventive measures, such as orexin normalization by the administration of an orexin antagonist (suvorexant), could be effective in the future. Furthermore, careful perioperative management including preoperative instructions, hospitalization, and postoperative follow-up is necessary.

### 3. How to prevent sleep disturbance after general anesthesia

It should be noted how sleep disturbance could be prevented after general anesthesia if there is a possibility of circadian disruption in a specific population of patients. Several projects testing pharmacological interventions to prevent sleep disturbance by normalizing the sleep-wake cycle before general anesthesia have been announced. Melatonin agonists may be candidates for preventing the incidence of postoperative sleep disturbance [40]. Ayuse et al. [38] planned an RCT to test the preventive effect of ramelteon on sleep disturbance after general anesthesia. Further clinical trials are required to investigate the preventive effects of several pharmacological interventions, including melatonin agonists.

### 4. Conclusion

There is considerable evidence that general anesthesia may influence circadian rhythms or sleep efficiency, leading to sleep disturbances in both pediatric and adult patients. Notably, perioperative anesthetic management, including maintaining sleep cycles, might be important for patients with sleep disorders prior to general anesthesia, such as older patients with cerebellar or cognitive malfunction, and intellectually disabled patients with ASD or attention-deficit/hyperactivity disorder.

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