Original Article

Comparison of the postoperative in-hospital versus at-home recovery quality and circadian rhythm status in preschool kids after adenotonsillectomy: a cohort and observational study

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Background: At present, minimally invasive surgery is often used in paediatric patients as a day surgery to promote rapid post-operative recovery. Obstructive Sleep Apnea Syndrome (OSAS) Patients recovery in the hospital or at home after surgery may differ in terms of recovery quality and circadian rhythm status because of sleep disruption; however, this remains unknown. Pediatric patients usually unable to explain their feelings effectively, and objective indicators to measure recovery situation in different environments are promising. This study was conducted to compare the impact of in-hospital and at-home postoperative recovery quality (primary outcome) and circadian rhythm (as measured via the salivary melatonin level) (secondary outcome) in preschool-age patients.

Methods: This was a cohort, non-randomized and exploratory observational study. A total of 61 children aged 4 to 6 years who were scheduled to receive adenotonsillectomy were recruited and assigned to recover either in the hospital (Hospital group) or at home (Home group) after surgery. There were no differences in the patient characteristics and perioperative variables between the Hospital and Home groups at baseline. They received the treatment and anesthesia in the same way. The patients' preoperative and up to 28 days post-surgery OSA-18 questionnaires were harvested. Moreover, their pre- and post-surgery salivary melatonin concentrations, body temperature, three-night postoperative sleep diaries, pain scales, emergence agitation, and other adverse effects were recorded.

Results: There were no significant differences in the postoperative recovery quality, as assessed by the OSA-18 questionnaire, body temperature, sleep quality, pain scales, and other adverse events (such as respiratory depression, sinus bradycardia, sinus tachycardia, hypertension, hypotension, nausea, and vomiting) between the two groups. The preoperative morning saliva melatonin secretion was decreased in both groups on the first postoperative morning ($P<0.05$), while a significantly greater decrease was found in the Home group on postoperative day 1 ($P<0.05$) and day 2 ($P<0.05$).

Conclusions: The postoperative recovery quality of preschool kids in the hospital is as good as at home based on OSA-18 evaluation scale. However, the clinical importance of the significant decrease in morning saliva melatonin levels with at-home postoperative recovery remains unknown and warrants further study.

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Introduction

At present, paediatric procedures including minimally invasive procedures, such as tensile and/or adenoid hypertrophy and inguinal hernia, can now be carried out as day surgeries to promote postoperative recovery (1-3). In addition to reducing the cost of care, research has revealed that the home environment makes patients feel more comfortable compared to the hospital environment and facilitates rest and sleep after surgery (4,5). During hospitalization, the in-hospital environment is unfamiliar and involves routine activating changes, noise, light, vital signs checks, and, which can all affect sleep and postoperative recovery (6,7). Obstructive sleep apnea is the main symptom of children with tonsil or adenoid hypertrophy. Sleep apnea affects the sleep structure of children and abnormal melatonin secretion, which seriously affect the growth and intellectual development of child (8,9).

Melatonin is an endogenous indoleamine secreted by the pineal gland and an important physiological sleep regulator in diurnal species. As an endogenously produced indoleamine, melatonin exerts various biological functions, including the regulation of the circadian biological rhythm and sleep as well as anti-cancer, anti-inflammatory, and antioxidant effects (10). Circadian biological rhythm misalignment is closely associated with an increased risk of various diseases, such as neurological diseases, sleep disorders, metabolic syndrome, epigenetic regulation, cardiovascular diseases, immune diseases, and cancer (11,12). Circadian rhythm-related genes help to guide personalized cancer immunotherapy strategies (13). Moreover, melatonin plays a critical role in pregnancy and fetal and postnatal development. Pineal dysfunction and delayed/disrupted melatonin production are likely to cause impaired mental development disorders including autism (14).

The neuroprotective effects of melatonin are particularly important in developing children (15). Melatonin is circadian rhythm-dependently synthesized from the amino acid precursor tryptophan, and its most important factor regulating is the light/dark cycle. Typically, melatonin levels peak at 60–200 pg/mL between 2 a.m. and decline to 0–20 pg/mL during the day (16). It is now evident that bright light exposure at night suppresses melatonin (17). In addition, some disease conditions such as diabetic neuropathy, Alzheimer's disease (AD), and certain drugs (e.g., β-blockers, nonsteroidal anti-inflammatory drugs, and anaesthetics) inhibit the nocturnal production of melatonin and are associated with disturbed sleep (18,19).

We hypothesize that the quality of postoperative recovery and the levels of melatonin are differently affected by the hospital versus home environments. We performed the current cohort study to compare the postoperative recovery quality and saliva melatonin changes in preschool children who recovered in the hospital versus at home after adenotonsillectomy. We present the following article in accordance with the TREND reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-138/rc).

Highlight box

Key findings

- The in-hospital postoperative recovery quality of preschool kids is as good as at home. Meanwhile, the morning saliva melatonin levels significantly decreased with at-home recovery.

What is known and what is new?

- Minimally invasive surgery is often used in paediatric patients as a day surgery to promote rapid postoperative recovery.
- We analysed the in-hospital versus at-home recovery quality of children using an OSA-18 questionnaire and measured the circadian rhythm status via saliva melatonin testing.

What are the implications, and what should change now?

- Hospital and at-home environments have a low impact on postoperative recovery quality. However, the clinical importance of the significant decrease in morning saliva melatonin levels with at-home recovery remains unknown and warrants further study.

Methods

Ethics

Ethical approval for this study (No. 201937101) was provided by the Ethical Committee of Guangzhou Women and Children's Medical Centre, Guangzhou, China (Chairperson Prof. Qingfeng Li) on the 24th of July 2019. This cohort observational study was conducted at the Guangzhou Women and Children's Medical Centre, which is the largest children's hospital in South China, in two discontinuous periods due to the coronavirus pandemic (August to October 2019 and April to June 2020). Written informed consent was obtained from the patients or their legal guardians before enrolment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Participants and group allocation

Pediatric patients were recruited from the Guangdong province located in the tropical and subtropical regions of China, where the average temperature during this trial was 25 ℃ and the day and night were of equal length. All patients visited the otolaryngology surgery clinic a week before surgery and completed a standardized preoperative questionnaire as well as pre-anaesthetic and surgical assessments (*Figure 1*). All parents underwent routine preoperative educational induction, including how to fill in the questionnaire form and perform basic vital sign measurements. The eligibility criteria were as follows: (I) American Society of Anesthesiologists (ASA) classification I-II; and (II) patients aged 4–6 years old with adenoidal and/or tensile hypertrophy (degrees 1 and 2). The exclusion criteria were as follows: (I) patients with upper respiratory infection within 2 weeks; (II) patients who were allergic to the saliva collector materials and those with other systemic/organ diseases (especially neurodevelopmental disabilities) or neuropathological diseases; and (III) parents or patients who refused to cooperate with saliva collection or participate in the study. All patients received same treatment before discharged to ward or back home after surgery.

Anaesthesia and surgery

Non-invasive blood pressure, heart rate, electrocardiogram, blood pulse oxygen saturation, $P_{ET}CO_2$, and electroencephalography (BIS) were performed and monitored before induction and throughout the entire surgical procedure. Propofol (2 $mg{\cdot}kg^{-1}$), fentanyl (0.3 $\mu g{\cdot}kg^{-1}$), and cisatracurium (0.2 $mg{\cdot}kg^{-1}$) were intravenously administered for the induction and facilitated intubation. Then, general anaesthesia was maintained with continuous propofol (4 $mg{\cdot}kg^{-1}$ h^{-1}, i.v.) infusion and inhalation of 2–3% sevoflurane delivered at a flow rate of 2 L/min in enriched air (50% oxygen). The depth of anaesthesia was adjusted to maintain the BIS value between 40 and 60. Following the surgery, patients recovered in the post-anaesthesia care unit (PACU) for postoperative care, including extubation. Patients were discharged from the PICU when their Modified Aldrete score was greater than nine. Patients were then transferred to the paediatric ward or back home according to allocation. Parents were given the same postoperative instructions, but one group went back home and the other stayed in the hospital overnight. We collected the effects of different postoperative environments on sleep diaries, melatonin secretion and 18-item obstructive sleep apnea (OSA-18) scores.

Outcome measures

The primary outcome was the postoperative recovery quality assessed using the OSA-18 scale questionnaire preoperatively and on the 28th day after surgery. The OSA-18 scale was reported to discriminate the OSA severity and improvements after treatment (20), and its Chinese version was also validated (21,22). It contains 18 questions scored on a Likert-type scale to collect data on 5 subscales: sleep disturbances, physical symptoms, emotional distress, daytime functions, and caregiver concerns. A score of ≥60 indicates the presence of OSAS in children (23). The secondary outcome was the perioperative saliva melatonin concentration (24,25). The saliva specimens were collected in a seated posture for a total of 4 days at 11 time points: (I) the day before surgery at 9:00 a.m. (T1), 7:00 p.m. (T2), and 9:00 p.m. (T3); (II) on the day of surgery at 7:00 a.m. (T4), 5 minutes after intubation (T5), 7:00 p.m. (T6), and 9:00 p.m. (T7); (III) postoperative day one: 7:00 a.m. (T8), 7:00 p.m. (T9), and 9:00 p.m. (T10); and (IV) on postoperative day two at 7:00 a.m. (T11) (*Figure 1*). The saliva samples were collected into a saliva collector under a dim light (Cortico-Salivette®51.1534.500) and stored in the frozen layer of the refrigerator (−20 ℃).

Next, the samples were used to detect the melatonin level using an ELISA kit (German IBL: RE54041) according to the manufacturer's instructions. In addition, the patients' family members were instructed to maintain a sleep diary, which mainly included recording the time of falling asleep and performing a sleep quality assessment. The Face, Legs, Activity, Cry, and Consolability (FLACC) scale (26) was also measured at 2 h and 4 h after surgery, and the

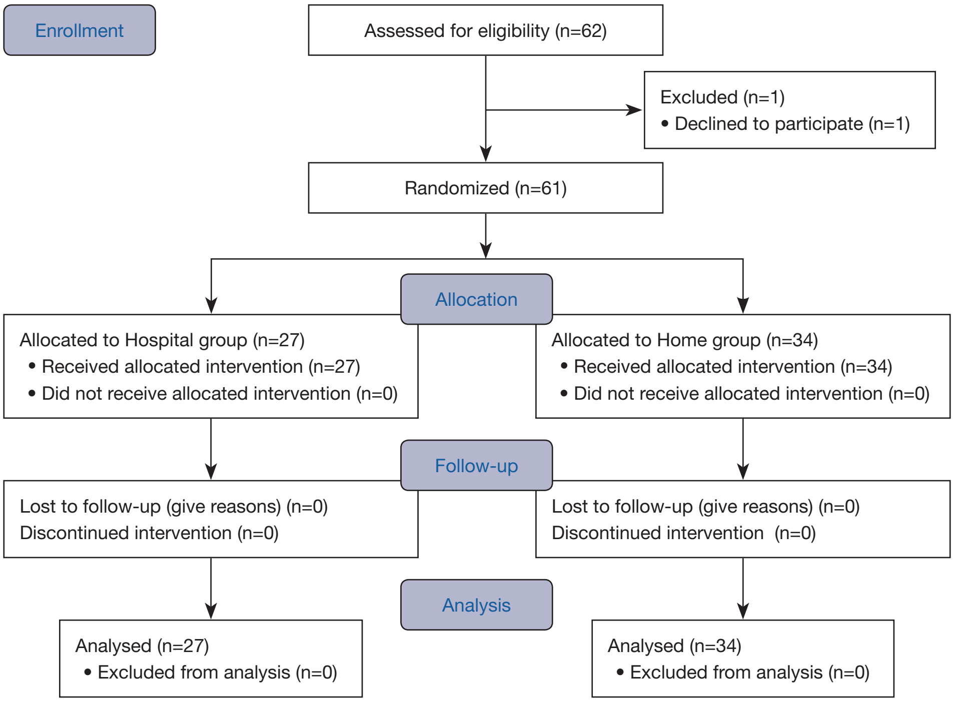

Figure 1 Study flow chart.

Riker Sedation-Agitation Scale (SAS) was also recorded. Furthermore, demographic data, respiratory and circulation parameters during the operation, duration of anaesthesia and surgery, time of extubation, postoperative complications up to 1 month after surgery, and any other perioperative adverse events were also recorded. A biostatistician, surgeons, anaesthesiologists, and postoperative follow-up medical staff were blinded to the treatment group assignment throughout the study period.

Statistical analysis

Power analysis

This was a cohort, non-randomized and exploratory observational study. Since it was an exploratory clinical study, we did not perform sample size estimates. Data were expressed as the means (SD) for continuous variables conforming to a normal distribution, or as the medians and interquartile ranges (IQRs) for variables with a skewed distribution. The *t*-test or Mann-Whitney test was applied to analyse the control between the two groups using Stata 16.0 software (Statacorp, College Station, TX, USA). A box-plot was used to describe the changes of melatonin at different time points. P<0.05 was considered statistically significant.

Results

Sixty-two patients aged 4–6 years old diagnosed with adenoidal and/or tensile hypertrophy (degrees 1 and 2) who were scheduled to undergo adenotonsillectomy at the Guangzhou Women and Children's Medical Center from August 12 to October 30, 2019, and April 1 to June 30, 2020, were initially enrolled in this study. One patient declined to participate, and thus, 61 patients were finally included. Among these patients, 27 (17 males and 10 females) recovered in the hospital (Hospital group) and 34 (22 males and 12 females) were discharged to recover at home (Home group) after surgery. All patients and their parents cooperated well with the sample and data collection, and no patients dropped out of the study. There were no differences in the patient characteristics (age, gender, BMI, heart rate and blood pressure) and perioperative variables (duration of anesthesia, surgery and intubation) (*Table 1*) between the Hospital and Home groups at baseline. This reflects the fact that they received the same treatment and that anesthesia and surgery affected them in the same way. Also, the perioperative body temperatures of patients were

Table 1 Baseline characteristics of the study participants

Variable	Hospital group (n=27)	Home group (n=34)	P value
Age (years)	5.24 (0.79)	5.15 (0.84)	0.676†
Male sex, n (%)	17 (63.0)	22 (64.7)	0.888‡
BMI	16.7 (2.40)	16.7 (2.09)	0.993†
DBP (mmHg)	91.0 (2.80)	90.8 (2.88)	0.780†
SBP (mmHg)	51.1 (4.28)	51.8 (5.69)	0.607†
HR (bpm)	93.3 (3.27)	94.5 (4.10)	0.208†
Anaesthesia time (min)	38.9 (10.7)	35.5 (11.8)	0.254†
Surgery time (min)	21.9 (8.22)	21.1 (9.93)	0.749†
Extubation time (min), median (IQR)	25.0 (20.0–40.0)	22.5 (20.0–30.0)	0.079⁋

Data were expressed as the mean (IQR), mean (SD), or n (%). Hospital group, recovery in hospital after surgery; Home group, recovery at home after surgery. †, two-sample *t*-test was used. ‡, Chi-square test was used. ⁋, Wilcoxon rank sum test was used. BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate.

Table 2 OSA-18 scoring scale before and at 28 days after surgery

OSA-18	Hospital group (n=27)	Home group (n=34)
Sleep disturbance		
Preoperatively	18.4 (1.50)	19.6 (2.40)
28-day postoperatively	6.00 (2.42)	4.65 (1.10)
Physical symptoms		
Preoperatively	16.9 (1.26)	18.5 (2.31)
28-day postoperatively	5.48 (1.93)	4.59 (0.96)
Emotional symptoms		
Preoperatively	6.37 (2.24)	6.53 (2.12)
28-day postoperatively	3.70 (1.17)	3.00 (0.00)
Daytime function		
Preoperatively	7.48 (1.40)	10.6 (2.13)
28-day postoperatively	3.78 (1.31)	3.00 (0.00)
Caregiver concerns		
Preoperatively	16.0 (14.0–17.0)†	16.0 (16.0–18.0)†
28-day postoperatively	4.00 (4.00–5.00)†	4.00 (4.00–4.00)†
Total score		
Preoperatively	65.0 (3.17)	72.0 (5.37)
28-day postoperatively	24.2 (6.10)	19.6 (2.57)

Data were expressed as mean (IQR)†, mean (SD). Hospital group, recovery in hospital after surgery; Home group, recovery at home after surgery. OSA-18, 18-item obstructive sleep apnea.

comparable between the two groups, which were slightly high in both groups but did not exceed 37.4 ℃ (data not shown).

The OSA-18 total symptom scores (TSS) were comparable between the two groups [65.0 (3.17) in the Hospital group and 72.0 (5.37) in the Home group] before surgery the 60. A TSS between 60 and 80 was considered to be correlated with a moderate impact on health-related quality of life. In contrast, the TSS at 28 days postoperatively decreased to normal levels in both groups [24.2 (6.10) in the Hospital group and 19.6 (2.57) in the Home group] (*Table 2*).

Melatonin secretion was decreased in both groups on the first morning postoperatively, and the decrease in the Home group was significantly higher than that in the Hospital group. On the second morning after surgery, the melatonin level returned to normal in the Hospital group but remained lower in the Home group (*Table 3* and *Figure 2*).

There were no significant differences in sleep duration and frequency of waking from dreams before and perioperative nights (*Table 4*). All of the patients had good analgesia postoperative and FLACC scores between 0 and 2 points, indicating that the postoperative pain in the two groups was comfortable. One child in the Hospital group presented with sedation and lethargy immediately after extubation, with a SAS score of 3, while the remaining patients in the two groups were in a quiet cooperative

Table 3 The melatonin saliva levels (pg/mL) at different time points perioperatively

Date	Time points	Hospital group (n=27)	Home group (n=34)	P value*
Day 1	T1 (9 am)	1.80 (0.78–4.06)	1.18 (0.56–2.18)	0.141
	T2 (7 pm)	1.29 (0.85–2.53)	0.55 (0.36–0.98)	<0.001
	T3 (9 pm)	0.99 (0.56–1.30)	0.94 (0.48–2.14)	0.964
Day 2	T4 (7 am)	5.78 (3.26–11.6)	7.41 (4.11–13.6)	0.299
	T5 (9 am)	2.60 (0.88–3.91)	1.30 (0.85–3.20)	0.331
	T6 (7 pm)	1.12 (0.57–3.40)	0.58 (0.32–3.15)	0.137
	T7 (9 pm)	1.50 (0.63–4.14)	1.74 (0.50–2.66)	0.755
Day 3	T8 (7 am)	2.92 (1.36–10.5)	1.79 (0.94–4.30)	0.073
	T9 (7 pm)	1.53 (0.48–2.41)	0.66 (0.34–1.56)	0.140
	T10 (9 pm)	1.87 (0.97–3.19)	1.29 (0.50–2.38)	0.307
Day 4	T11 (7 am)	4.72 (2.30–9.50)	1.54 (0.93–6.01)	0.021
Comparison	Δ (T8-T4)	−1.07 (−4.38 to 9.50)	−4.88 (−7.59 to −1.61)	0.017
	Δ (T11-T4)	−0.96 (−3.45 to 2.35)	−5.13 (−7.93 to 1.39)	0.004

Data were expressed as the mean (IQR)*. Day 1: day before surgery; Day 2: surgery day; Day 3: 1-day after surgery; Day 4: 2-day after surgery. Hospital group, recovery in hospital after surgery; Home group, recovery at home after surgery.

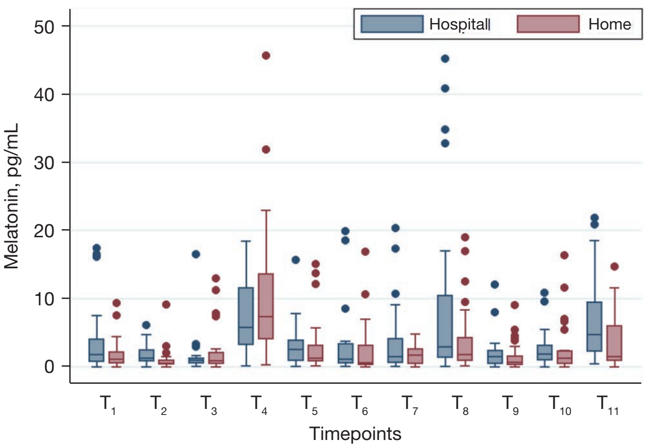

Figure 2 The distribution of melatonin over time in the two groups. A box-plot was used to describe the differences in melatonin at different time points in the two groups. Blue represents the Hospital group, red represents the Home group. The abscissa represents the time point of collection and the ordinate on behalf of the melatonin (pg/mL) content. The median (IQR) was used as the primary outcome measure. The melatonin level at the T8 and T4 time points were reduced in both groups but the decrease was more obvious in the Home group (P=0.017). Comparing the two groups at T11, the melatonin level in the Home group was significantly lower than that in Hospital group (P=0.021). Accordingly, the differences between T11 and T4 in the two groups were significant (P=0.004).

state. There were no other adverse events or related complications up to 28 days after surgery in both groups.

Discussion

In this prospective, single-center, observational cohort study, we found that there was no significant difference between patients who recovered in the hospital or at home after adenotonsillectomy surgery. Postoperatively, the morning saliva melatonin levels in the Home group decreased significantly. However, there were no differences in the other variables, including rehabilitation, postoperative pain score, sleep quality, the incidence of emergence agitation, and extubation time, between the two groups.

Most hospitals and departments have adopted multidisciplinary management and standardised care pathways to optimise patients preoperatively, minimise injury and stress perioperatively, and accelerate postoperative recovery (1). For children with Obstructive Sleep Apnea Syndrome (OSAS), sleep problems are the biggest problem. Parents often come to hospitals because of snoring. OSA-18 is one of the gold standards to measure the recovery quality, it's easy to finish, particular to measure such low-aged-OSAS group recovery situation. Instead of OSAS itself, the OSA-18 was first created for evaluating quality of life (23). Our data suggested

Table 4 The distributions of sleep diaries for three nights

Outcomes	Hospital group (n=27)	Home group (n=34)	P value*
Sleep duration (hours)			
Pre-operation	9.42 (0.96)	9.22 (0.86)	0.384
Operation day	9.45 (0.96)	9.01 (1.43)	0.178
Post-operation	9.86 (0.79)	9.37 (1.46)	0.119
Awake from dreams (frequency) pre-operation	0	0	
Operation	3 [2–3]	2 [0–3]	0.130
Post-operation	0	0	

Data were expressed as mean (SD). Hospital group, recovery in hospital after surgery; Home group, recovery at home after surgery. *, two-sample *t*-test was used.

that postoperative recovery in the hospital and home environments were comparable in pediatric patients who received adenotonsillectomy, as demonstrated by the OAS-18, a disease-specific quality-of-life questionnaire that is commonly used by pediatric otolaryngologists (21,27), as well as a sleep diary and other variables postoperatively.

An association was found between melatonin and age, sleep, and gender. Virtually melatonin secretion levels in children are lower from birth to the first 6 months of life, peaking at 3 years, and then gradually decreasing (28-30). Guangdong is located in the tropical/subtropical region of China, with average temperatures from August to October 2019 and April to June 2020 of 25 ℃, and the days and nights were of equal length during these periods. All patients in this study were recruited during this period to avoid a shift in the circadian phase due to seasonal bias. Different postoperative light exposure environments are particularly varied (31). The circadian rhythm of melatonin is mainly governed by the light and dark cycle via the circadian pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus (32). The pineal gland is innervated by sympathetic neurons from the SCN, which release norepinephrine, subsequently activates adenylyl cyclase, enhances AANAT activity, and creates melatonin. On the other hand, increased electrical activity in the SCN during the day inhibits the production of melatonin by causing the inhibitory neurotransmitter GABA to be released (18,33). The activation of $GABA_A$ receptors in the SCN can inhibit the expression of clock genes and thus affect melatonin secretion. Most general anaesthetics work by acting on GABA receptors, enhancing GABAergic inhibition and suppressing excitatory neurotransmission (34). Thus, general anaesthetic-induced sleep can affect the circadian rhythm phase and melatonin secretion (35). In fact, some research have shown that the circadian melatonin rhythm changes after surgery and that the concentration of night melatonin is lower on the first night following surgery, which may be associated to an irregular sleeping pattern (19,36,37). Older patients frequently experience postoperative circadian rhythm disorder, which may be a factor in the emergence of postoperative delirium (POD) (38). Interestingly, some clinical studies have suggested that there is no significant change in melatonin measured within 1 hour after anaesthesia (39). In this study, the effects of general anaesthetic on melatonin secretion were not observed. This inconsistency might be due to sampling times at which melatonin secretion is suppressed. We also collected evening saliva melatonin at 9 p.m. to evaluate the Dim Light Melatonin Onset (DLMO), which is considered to be the gold standard of the circadian phase (40). There is a substantial body of evidence showing that general anaesthesia can greatly affect the circadian clock via a few proposed mechanisms, such as anaesthetic agents acting on the expression of core circadian clock genes (41,42). Additional research found that anaesthesia medications, surgery, and environmental factors are likely to play a multifactorial role in the potential association between aberrant plasma melatonin secretion pattern to POD and the development of perioperative circadian rhythm problems (43,44). However, in this study, we did not find any significant difference in sleep disturbance and circadian rhythm disorders between the two groups, which may be due to shorter surgery and anaesthesia durations in the adenotonsillectomy procedures.

This study has some limitations that should be noted and considered. The sample size was relatively small, the subjects of this study were pediatric patients within a narrow age range of 4–6 years old, and the study was conducted at a single specialized tertiary medical center. Thus, the results are not representative and cannot be generalized to the wider population of day surgery cases.

Conclusions

In summary, we found that postoperative recovery in the hospital is as good as in the home environment. However, the clinical significance of decreased morning saliva melatonin levels postoperatively in the at-home recovery group of preschool children is unknown and needs further study to better our understanding.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TREND checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-138/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-138/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-138/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. This study was approved by institutional ethics board of the Guangzhou Women and Children's Medical Centre (No. 201937101). Written informed consent was obtained from the patients or their legal guardians before enrolment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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