Long-term quality of sleep after remifentanil-based anaesthesia: a randomized controlled trial

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Editor’s key points
- Sleep quality is important to patients and can be disrupted by hospital admission for surgery.
- Remifentanil was shown to have long-term effects on sleep quality in children.
- This study aimed to use patient self-report measures to assess sleep quality 6 months after surgery.
- Preoperative ‘good sleepers’ were affected most by remifentanil after 6 months.

Background. Clinical and pre-clinical data agree that opioids disrupt sleep architecture. Recently, remifentanil has been suggested to cause possible long-term disturbances of sleep quality. This randomized controlled clinical trial was designed to substantiate or refute a possible long-term effect of remifentanil on the quality of sleep.

Methods. One hundred patients undergoing elective surgery were randomized to receive either fentanyl or remifentanil-based anaesthesia. Before operation (T0) and 3 (T3) and 6 (T6) months after operation, the quality of sleep was assessed by the Pittsburgh Sleep Quality Index (PSQI).

Results. Overall, the quality of sleep for patients in the remifentanil or fentanyl group was not significantly different at any time point. Patients in the fentanyl group screened as good sleepers before operation showed no differences across time course of the study in PSQI scores. In contrast, good sleepers in the remifentanil group had significantly impaired sleep quality for at least 3 months after operation. Patients who were before operation screened as poor sleepers showed no significant changes in PSQI scores at T3 and T6 in both groups.

Conclusions. The intraoperative use of remifentanil in a general patient population does not significantly alter the quality of sleep in the postoperative period. However, it may result in a significant reduction in the quality of sleep in patients before operation considered good sleepers. These changes were not observed in the group of patients receiving fentanyl. The relevance of these findings in terms of patient recovery and quality-of-life warrants further investigation.

Trial Registration. ACTRN12610000362099.

Keywords: fentanyl; opioid, analgesic; postoperative complications/aetiology; remifentanil; sleep disorders

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usually heptically metabolized, remifentanil has an ester linkage, which undergoes rapid hydrolysis by non-specific tissue and plasma esterases. This means that accumulation does not occur with remifentanil and its context-sensitive half-life remains constant even after hours of infusion. Interestingly and despite its short half-life, remifentanil has also been reported to affect postoperative quality of sleep. A case-control study in children reported a significant impairment of sleep quality that was still detectable at 3 months after operation. The difference of effects between remifentanil and morphine, fentanyl, or sufentanil may be due to the fact that remifentanil has different effects on ACh levels in the cholinergic LD1 and terminal projection field areas within the mPRF that regulate arousal and REM sleep control and possibly other sleep-regulating regions of the basal forebrain involving adenosine and GABAergic transmission.

The aim of this trial was to compare potential long-term effects of remifentanil-based anaesthesia compared with fentanyl-based anaesthesia on the quality of sleep in the clinical setting of patients undergoing minor elective surgery. To our knowledge, this is the first randomized controlled, clinical trial that investigates such long-term effects on sleep quality.

### Methods

The trial was approved by the Royal Perth Hospital, Ethics Committee (protocol EC2010-019) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12610000362099). The study was designed as a parallel-group, double-blinded, randomized controlled trial.

After written informed consent, pain-free patients undergoing minor elective orthopaedic day surgery of the upper or lower limbs were randomly allocated to either a remifentanil or a fentanyl treatment group by sealed envelopes. The randomization scheme was generated using the method of randomly permuted blocks (http://www.randomization.com).

All patients underwent baseline Pittsburgh Sleep Quality Index (PSQI) assessment. The PSQI is a highly validated self-assessment tool that effectively measures the quality and patterns of sleep in the adult. It differentiates poor from good sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The patient self-rates each of these seven areas of sleep. Scoring of answers is based on a 0–3 scale, whereby ‘3’ reflects the negative extreme on the Likert scale. Since the PSQI also differentiates between good and poor sleepers with a high sensitivity and specificity, all subjects were categorized into good sleepers (PSQI global score <6) and poor sleepers (PSQI global score ≥6) according to their preoperative PSQI global scores.

Both the patients and the interviewer who conducted the PSQI before operation and during follow-ups were blinded to which treatment group the patient had been allocated.

Baseline data such as age, sex, height, weight, surgical procedure, co-morbidities, and usual medication were recorded. Study patients received no premedication.

Anaesthesia for patients in the remifentanil group was induced with propofol (3–5 mg kg\(^{-1}\)), remifentanil (0.4–1.0 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)), and, if required, either rocuronium (0.6–1.0 mg kg\(^{-1}\)) or cisatracurium (0.15–0.2 mg kg\(^{-1}\)) was used as a neuromuscular blocking agent. Anaesthesia was maintained using sevoflurane (end-tidal concentration 1.2–1.8 vol%) in oxygen/air (50/50) and continuous infusion of remifentanil (0.15–0.25 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). Owing to the extremely short half-life of remifentanil and thus reduced postoperative analgesic efficacy, a bolus of fentanyl (0.25–0.75 \(\mu\)g kg\(^{-1}\)) was administered 10 min before termination of the continuous infusion.

Patients in the fentanyl group were induced with propofol (2–5 mg kg\(^{-1}\)), fentanyl (50–300 \(\mu\)g), and neuromuscular blocking agent, as appropriate. Anaesthesia was maintained using sevoflurane (Fi 1.4–2.4 vol%) in oxygen/air (50/50). Individually titrated boluses of fentanyl (25–100 \(\mu\)g) were permitted as directed by clinical requirements at the attending anaesthesiologist’s discretion.

In both groups, depth of anaesthesia was measured using state entropy (SE) and response entropy (E-Entropy module, GE Healthcare, Australia) and titrated to achieve a target range for SE from 40 to 60 during the maintenance phase of anaesthesia.

After operation, patients in both groups received 1000 mg i.v. acetaminophen. Furthermore, i.v. fentanyl for postoperative analgesia according to the Royal Perth Hospital Fentanyl Protocol for Recovery Room, starting with two fentanyl doses of 20 \(\mu\)g each and then 0.5 \(\mu\)g kg\(^{-1}\) up to a total dose of 50 \(\mu\)g, if resting pain on a numeric rating scale (NRS) from 0 to 10 was >3. Additionally, it was left to the anaesthetist’s discretion to administer a single i.v. dose of parecoxib (40 mg) towards the end of the procedure.

A 5HT3 antagonist as a prophylactic medication to prevent postoperative nausea and vomiting (PONV) was administered towards the end of the procedure if considered appropriate by the anaesthetist running the case. Patients experiencing an episode of PONV in recovery were allowed to receive a single dose of a 5HT3 antagonist.

Study patients were not permitted to receive the following medication in the perioperative period: thiopental, clonidine, ketamine, gabapentinoids, \(\beta\)-blockers, benzodiazepines, steroids, metoclopramide, melatonin, anti-depressants, illicit drugs, and other stimulants. After operation, data regarding operation and anaesthetic details including dosages of all drugs administered were recorded in the database.

Patients were followed up at 3 and 6 months after operation via a telephone interview and the PSQI was repeated by the same blinded interviewer. Patients were asked to disclose any opioid medication during the study period. Patients who received any opioid other than the study medication during the trial were excluded.

Statistical analysis was performed using SPSS Statistics 18.0 (SPSS Inc., Chicago, IL, USA).
A sample size of 90 patients (45 in each group) was calculated based on previously published data\textsuperscript{11} for an anticipated difference in means of 0.3 and an anticipated standard deviation (SD) of 0.5 at a 1:1 ratio of controls to experiment subjects for independent groups with a type I error of 0.05 and a power of 80%. Given that patients needed to be followed up for 6 months, an anticipated drop-out rate of 10% was included and the number of study subjects was then rounded up to 100 (50 patients in each group).

Categorical variables are expressed as frequency and percentage, whereas continuous variables and PSQI scores are represented as means with SD. Before statistical testing, each continuous variable was analysed for its normal distribution using the Kolmogorov–Smirnov test. The non-parametric patients’ baseline characteristics and PSQI scores were assessed using the Wilcoxon test. The Friedman signed-rank test was used to compare the non-parametric time-dependent variables and the $\chi^2$ test for comparison of categorical variables. Analysis of all records was performed by blinded evaluators. The total follow-up period per patient was 6 months. The study flowchart is displayed in Figure 1.

**Results**

**Patient population and follow-up**

One hundred pain-free patients aged 34 (range 18–62) yr undergoing elective minor orthopaedic surgery were enrolled in the study. All patients were ambulatory cases with a maximum hospital stay of 23 h. All patients participated in the PSQI questionnaire before operation (T0). Fifty patients were randomly allocated to the remifentanil group and 50 patients were allocated to the fentanyl group. Patient characteristic data and average doses of intra- and postoperative medications are shown in Table 1. One patient in the remifentanil group and four patients in the fentanyl group received a single dose of i.v. parecoxib 40 mg before leaving the theatre.

At 3 months after operation (T3), 10 patients (20%) in the remifentanil and five patients (10%) in the fentanyl group were not contactable and lost to follow-up. At the 6 months follow-up (T6), a further seven patients in the remifentanil group and 10 patients in the fentanyl group were lost to follow-up. In total, 68 patients (68%) completed the study (Fig. 1).

At T3, two patients in the remifentanil group and one patient in the fentanyl group reported that pain was affecting their sleep quality but less than once a week (PSQI score 1). One patient in the remifentanil group and three patients in the fentanyl group reported pain affecting their quality of sleep once or twice a week (PSQI score 2) and one patient (remifentanil group) reported sleep quality to be affected by pain three or more times a week (PSQI score 3).

At T6, two patients (both from the fentanyl group) reported that pain affected their quality of sleep (less than once a week and once or twice a week, respectively).

**PSQI scores of the total population (good sleepers and poor sleepers)**

PSQI global scores for the total population were 4.55 (SD 2.75) at T0 vs 4.86 (SD 3.17) at T3 vs 4.23 (SD 3.14) at T6 (Fig. 2). Although there was a trend to higher global PSQI scores at T3, these differences were not statistically significant. Patients in the remifentanil group had a global PSQI score of 5.0 (SD 2.91).
at T0 vs 5.1 (SD 3.47) at T3 vs 4.47 (SD 3.70) at T6. Patients in the fentanyl group had a global PSQI score of 4.14 (SD 2.57) at T0 vs 4.64 (SD 2.89) at T3 vs 3.97 (SD 2.37) at T6. Differences between the groups and intergroup differences were not statistically significant at all time points investigated (Fig. 3).

Subgroup analysis
At T0, the PSQI identified 35 patients in the fentanyl group and 24 patients in the remifentanil group as good sleepers. Good sleepers in the fentanyl group had a PSQI global score of 2.82 (SD 1.53) at T0, 3.41 (SD 2.46) at T3, and 2.58 (SD 1.95) at T6. These changes were not significantly different between the three time points.

In contrast, patients who were categorized as poor sleepers before operation (T0) showed no significant changes in PSQI global and subscores at T3 and T6 in both the remifentanil and fentanyl groups (Fig. 4).

No patient required any opioids for extended pain therapy after hospital discharge. All patients were only exposed to opioids intraoperatively and in the immediate postoperative recovery period.

Discussion
The findings of the current study suggest that in a general population, the intraoperative use of remifentanil or fentanyl in a clinical setting in patients undergoing minor elective surgery does not significantly affect postoperative self-reported long-term quality of sleep. However, a subgroup analysis of patients who were before operation considered good sleepers showed that remifentanil but not fentanyl coincided with a significant reduction in postoperative sleep quality at 3 months follow-up.

Table 1. Patient characteristic data of study population in the two groups. All data are mean and (SD) or (range)

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl group</th>
<th>Remifentanil group</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>33 (18–62)</td>
<td>35 (18–61)</td>
</tr>
<tr>
<td>Body mass index (kg m⁻²)</td>
<td>25.8 (4.1)</td>
<td>26.6 (5.1)</td>
</tr>
<tr>
<td>Duration anaesthesia (min)</td>
<td>66.3 (28.2)</td>
<td>74.8 (32.9)</td>
</tr>
<tr>
<td>Duration surgery (min)</td>
<td>47.8 (27.8)</td>
<td>55.5 (28.6)</td>
</tr>
<tr>
<td>Induction dose fentanyl (µg)</td>
<td>132 (50–275)</td>
<td>—</td>
</tr>
<tr>
<td>∑ fentanyl intraoperatively (µg)</td>
<td>178 (100–425)</td>
<td>41 (0–150)</td>
</tr>
<tr>
<td>∑ remifentanil perioperatively (mg)</td>
<td>—</td>
<td>1.0 (0.9)</td>
</tr>
<tr>
<td>∑ fentanyl after operation (µg)</td>
<td>30 (0–200)</td>
<td>32 (0–200)</td>
</tr>
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</table>

Fig 2. Comparison of PSQI scores of the total population before operation and 3 and 6 months after surgery. The box plots show the median (bold bars), the inter-quartile range, and the 5th and the 95th percentiles (whiskers).
The quality of sleep in the acute postoperative period is known to be disturbed. Sleep is highly fragmented and there is an absence of REM sleep for the first few nights after operation. Although opioids have long been known to disrupt sleep, still most medical students and residents receive no formal training about sleep. The clinical significance of sleep is devalued and this is partially accepted by both doctors and patients. However, possible long-term sequelae are highly undesirable in routine clinical application. Although the function of sleep is largely unknown, ‘quality of sleep’ is an important clinical measure for multiple reasons: complaints about diminished quality of life through impaired quality of sleep is a common reason for patients to attend their physician. Patients with impaired

**Fig 3** Comparison of PQSI scores of the total population before operation and 3 and 6 months after surgery of patients with intraoperative fentanyl (blue box) or remifentanil (green box). The box plots show the median (bold bars), the inter-quartile range, and the 5th and the 95th percentiles (whiskers). There was statistically no significance in the scores between fentanyl and remifentanil (Mann–Whitney U-test).

**Fig 4** Comparison of PQSI scores before operation and 3 and 6 months after surgery of patients identified as ‘poor sleepers’ before operation (PQSI global score > 5). Intraoperative fentanyl (blue box) or remifentanil (green box). PQSI scores of poor sleepers before operation and 3 and 6 months after operation were not significantly different. Bold line, median; box, inter-quartile range; whiskers, 5th and 95th percentiles.
quality of sleep suffer both physically and mentally with sleep quality linked to neurological and psychological problems, impaired immune function, and diseases like irritable bowel syndrome. In addition, a lack of sleep quality has been shown to be directly associated with mortality. Furthermore, there is a growing appreciation of the fact that sleep deprivation leads to decreased pain perception thresholds.

To our knowledge, this is the first randomized controlled clinical trial investigating the potential long-term effects of different intraoperative opioids on the quality of sleep. In our study, patients who were considered good sleepers (as measured by the PSQI global score) before hospital admission experienced a significant reduction in their quality of sleep for at least 3 months after operation if they had received remifentanil intraoperatively. Specifically, the components quality, efficiency, and latency of sleep were affected. Preoperative good sleepers with significantly increased PSQI global scores at 3 months follow-up returned to average preoperative values at 6 months.

In contrast, preoperative good sleepers who had received fentanyl intraoperatively did not experience long-term sleep impairment. For patients who were poor sleepers before operation, no significant changes in sleep quality were observed after operation. According to the original publication of the PSQI tool, a differentiation between good and poor sleepers is possible and desirable as these groups may be affected differently by interventions.

Furthermore, our results are backed by a study by Rehberg and colleagues. In a non-randomized case-control study, the authors investigated the possible long-term influence of remifentanil on postoperative quality of sleep in children who underwent scoliosis surgery. They found a significantly impaired quality of sleep for up to 6 postoperative months in children receiving remifentanil but did not observe this problem in a matched sufentanil group. Interestingly and in contrast to our results suggesting an effect of remifentanil only in patients with undisturbed sleep before operation, the authors observed postoperative sleep impairment in all children and across the band of preoperative sleep quality. This may be due to the fact that children per se have a much better quality of sleep when compared with adults, hence the percentage of ‘good’ sleepers in their population could have been significantly higher.

A further study by Steinmetz and colleagues investigated the quality of sleep pre- and 2 weeks after operation in 39 children receiving either propofol–remifentanil or sevoflurane–fentanyl anaesthesia for surgical repair of cleft lip–gum–palate. The authors observed a non-significant trend towards increased sleep disturbances in the propofol–remifentanil group. The authors concluded that sevoflurane seemed to be associated with less impairment of postoperative sleep when compared with propofol. The possible role of the different opioids in the two groups was not discussed but in the light of our and previous data, the observed trend might be well related to the opioid given during anaesthesia.

The underlying reason for a remifentanil effect on postoperative sleep quality is not fully understood and was not the subject of our investigation. However, in an in vivo study in cats, Mortazavi and colleagues used microdialysis catheters to test the effect of opioids on ACh release from

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T3</th>
<th>T6</th>
<th>T0 vs T3 P-value</th>
<th>T0 vs T6 P-value</th>
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<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>0.73 (0.57)</td>
<td>0.85 (0.59)</td>
<td>0.73 (0.55)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Latency</td>
<td>0.73 (0.57)</td>
<td>0.98 (1.03)</td>
<td>0.77 (0.97)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration</td>
<td>0.32 (0.56)</td>
<td>0.44 (0.75)</td>
<td>0.23 (0.43)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Efficiency</td>
<td>0.18 (0.39)</td>
<td>0.29 (0.46)</td>
<td>0.32 (0.48)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Disturbing</td>
<td>1.08 (0.47)</td>
<td>1.0 (0.56)</td>
<td>0.82 (0.50)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Medication</td>
<td>0.05 (0.37)</td>
<td>0.08 (0.32)</td>
<td>0.14 (0.64)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tiredness</td>
<td>0.62 (0.76)</td>
<td>0.59 (0.70)</td>
<td>0.64 (0.90)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total PSQI</td>
<td>2.82 (1.53)</td>
<td>3.41 (2.46)</td>
<td>2.58 (1.95)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quality</td>
<td>0.81 (0.65)</td>
<td>0.99 (0.71)</td>
<td>0.69 (0.48)</td>
<td>0.016*</td>
<td>n.s.</td>
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<tr>
<td>Latency</td>
<td>0.81 (0.65)</td>
<td>1.15 (1.12)</td>
<td>0.58 (0.84)</td>
<td>0.006*</td>
<td>n.s.</td>
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<tr>
<td>Duration</td>
<td>0.48 (0.78)</td>
<td>0.57 (0.89)</td>
<td>0.11 (0.32)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Efficiency</td>
<td>0.25 (0.44)</td>
<td>0.41 (0.50)</td>
<td>0.16 (0.38)</td>
<td>0.019*</td>
<td>n.s.</td>
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<tr>
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<td>1.17 (0.53)</td>
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<td>0.68 (0.48)</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>Medication</td>
<td>0.09 (0.47)</td>
<td>0.12 (0.49)</td>
<td>0</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tiredness</td>
<td>0.49 (0.62)</td>
<td>0.55 (0.62)</td>
<td>0.37 (0.50)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total PSQI</td>
<td>3.11 (1.39)</td>
<td>4.6 (2.98)</td>
<td>3.64 (2.4)</td>
<td>0.024*</td>
<td>n.s.</td>
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neurones in the mPRF and in the LDT. The mPRF LDT network is part of a system controlling arousal and the REM phase of sleep.3,6,26,27 Similar to pontine reticular sites in the human brain,28,29 Interestingly, morphine sulphate decreased ACh in the mPRF and LDT up to 30%, while remifentanil delivered by continuous infusion did not alter ACh release, indicating a significant difference in the effect of a traditional opioid compared with the synthetic opioid.3 These findings demonstrate the potential for distinct differences in the cerebral effects between different opioids.

Opioids in general induce significant changes in brain physiology and cell integrity and long-term effects on repeated exposure, single exposure, or both have been described.30,31 By choosing to exclude chronic opioid users and including only minor orthopaedic and plastic surgery cases, we circumvented the problem of opioid requirements beyond the time of hospital discharge.

The clinical significance of our findings may be much greater than the obvious implications: postoperative changes of mental capacity have been described extensively in the elderly patient population.32,33 While cognitive deficit is clearly related to age, some data suggest that postoperative sleep disturbances may be a significant co-factor contributing to the development of postoperative cognitive dysfunction.18,34,35 As our study included younger patients and did not aim to investigate age-related differences, this subject will need further investigation.

Our study has limitations. We cannot fully exclude that other factors such as a surgical stress response have an unrecognized effect on the quality of sleep after operation; however, we randomized patients undergoing similar procedures into two groups, hence reducing a possible influence of surgical factors.

Secondly, even though we were able to contact more than 80% of all patients for the 3 months follow-up, the contact rate at 6 months was reduced. Secondly, patients in the remifentanil group received fentanyl in the post-anesthetic care unit (PACU). Enabling PACU staff to treat postoperative pain with potent opioids was a medical but also an ethical requirement, and we did not want to introduce a third opioid.

Sleep represents a complex phenomenon that is difficult to define and measure objectively. The exact components that define ‘sleep quality’ and their relative importance may vary between individuals. Our study did not formally measure how quality of life and everyday activity levels were affected by the reduced quality of sleep. From the telephone interviews, we learned that many patients noticed postoperative changes in their sleep pattern but did not necessarily attribute a poor quality of sleep to the previous anaesthetic, but rather to environmental or socio-economic reasons (‘weather’, ‘family’, ‘stress’, ‘job’). Although factors like stress or anxiety can be significant co-factors influencing sleep quality, the PSQI is able to adjust for these influences.12

First, the PSQI is asking for global estimates spanning 1 month and hence it is not sensitive to daily variability and secondly, the PSQI assigns ordinal scores to quantitative and qualitative information, allowing for the generation of a global score. Although there are a multitude of different tests available, which assess sleep in all its dimensions, we chose to rely on the PSQI as a single test. The PSQI has established itself as the main tool for the assessment of quality of sleep in multiple dimensions. It has a high degree of internal homogeneity, for example, each component measures part of a coherent overall construct. Furthermore, the consistency of the PSQI is higher than with any other test available, which was an important issue since we were repeatedly interviewing patients over the 6 month period. Lastly, it is a simple test to use and has the proven ability to identify cases and controls, or good and poor sleepers with high consistency and validity.12

Conclusion

For the general population, the intraoperative continuous use of remifentanil does not appear to significantly alter the quality of sleep for up to 6 months after operation. However, a subgroup analysis suggests that the intraoperative use of remifentanil in PSQI-identified preoperative ‘good sleepers’ may result in a significant reduction in postoperative quality of sleep for at least 3 months. The mechanism behind the observed changes is unclear, especially as the complex interplay between different classes of opioids and brain structures is only poorly understood. This study did not investigate the impact of sleep deprivation on patient satisfaction, cognitive function, quality of life, or postoperative morbidity, and these issues will need to be further investigated. The current results encourage further studies designed to objectively quantify the effects of intraoperative opioids on sleep in humans.

Authors’ contributions

M.W. is the principal investigator, conceived this study, participated in the design, and drafted the manuscript. D.M.P. participated in the study design, drafting the manuscript, and is the trial statistician. G.C. and H.G. participated in the design, collected data, and helped draft the manuscript. T.L. participated in the design of the study, helped draft the manuscript, and was responsible for trial set-up and coordination.

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Declaration of interest

None declared.

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