Effects of melatonin on postoperative sleep quality: a systematic review, meta-analysis, and trial sequential analysis

Effets de la mélatonine sur la qualité du sommeil postopératoire : une revue systématique, méta-analyse et analyse séquentielle des études

Akito Tsukinaga, PhD · Takahiro Mihara, PhD [ORCID] **· Teppei Takeshima, PhD · Makoto Tomita, PhD · Takahisa Goto, PhD**

Abstract

Purpose Postoperative sleep disturbances are common. Although several studies have examined the effect of melatonin on postoperative sleep disturbances, the results have not reached any definitive conclusion. We sought to conduct a systematic review to compare the effects of melatonin and melatonin agonists on postoperative sleep quality with those of placebo or no treatment in adult patients who underwent surgery under general or regional anesthesia.

Methods We searched MEDLINE, Cochrane Central Register of Controlled Trials, Embase, Web of Science, ClinicalTrials.gov, and the UMIN Clinical Trials Registry up to 18 April 2022. Randomized clinical trials examining the effects of melatonin or melatonin agonists in patients

A. Tsukinaga, PhD · T. Mihara, PhD (✉)
Department of Health Data Science, Yokohama City University Graduate School of Data Science, Yokohama 236-8511, Japan
e-mail: meta.analysis.r@gmail.com

Department of Anesthesiology, School of Medicine, Yokohama City University, Yokohama, Japan

T. Takeshima, PhD · M. Tomita, PhD
Department of Health Data Science, Yokohama City University Graduate School of Data Science, Yokohama 236-8511, Japan

T. Goto, PhD
Department of Anesthesiology, School of Medicine, Yokohama City University, Yokohama, Japan

undergoing general or regional anesthesia with sedation for any surgery were eligible for inclusion. The primary outcome was sleep quality measured using a visual analog scale (VAS). The secondary outcomes were postoperative sleep duration, sleepiness, pain, opioid consumption, quality of recovery, and adverse events. A random-effects model was used to combine the results. We assessed study quality with the Cochrane Risk of Bias Tool version 2. We applied a trial sequential analysis to assess the precision of the combined results.

Results Eight studies (516 participants) were analyzed for sleep quality. Of those, four studies used only a short duration of melatonin, either on the night before and the day of surgery or only on the day of surgery. A random-effects meta-analysis showed that melatonin did not improve sleep quality measured by VAS compared with placebo (mean difference, -0.75 mm; 95% confidence interval, -4.86 to 3.35), with low heterogeneity (I^2, 5%). Trial sequential analysis revealed that the accrued information size (n = 516) reached the estimated required information size (n = 295). We downgraded the certainty of the evidence because of the high risk of bias. The effect on postoperative adverse events was comparable between the melatonin and control groups.

Conclusion Our results indicate that melatonin supplementation does not improve postoperative sleep quality measured with the VAS compared with placebo in adult patients (GRADE: moderate).

Study registration PROSPERO (CRD42020180167); registered 27 October 2022.

Résumé

Objectif Les troubles du sommeil postopératoires sont fréquents. Bien que plusieurs études aient examiné l'effet

Springer

de la mélatonine sur les troubles du sommeil postopératoires, les résultats n'ont abouti à aucune conclusion définitive. Nous avons tenté de réaliser une revue systématique afin de comparer les effets de la mélatonine et des agonistes de la mélatonine sur la qualité du sommeil postopératoire à ceux d'un placebo ou de l'absence de traitement chez des patients adultes ayant bénéficié d'une intervention chirurgicale sous anesthésie générale ou régionale.

Méthode *Nous avons effectué des recherches dans les bases de données MEDLINE, le registre Cochrane des essais contrôlés, Embase, Web of Science, ClinicalTrials.gov et le registre des essais cliniques UMIN pour en tirer les manuscrits publiés jusqu'au 18 avril 2022. Les études cliniques randomisées examinant les effets de la mélatonine ou des agonistes de la mélatonine chez des patients bénéficiant d'une anesthésie générale ou régionale avec sédation pour toute intervention chirurgicale étaient éligibles pour l'inclusion. Le critère d'évaluation principal était la qualité du sommeil mesurée à l'aide d'une échelle visuelle analogique (EVA). Les critères d'évaluation secondaires étaient la durée du sommeil postopératoire, la somnolence, la douleur, la consommation d'opioïdes, la qualité de la récupération et les événements indésirables. Un modèle à effets aléatoires a été utilisé pour combiner les résultats. Nous avons évalué la qualité des études en utilisant l'outil de risque de biais de Cochrane version 2.0. Nous avons appliqué une analyse séquentielle des études pour évaluer la précision des résultats combinés.*

Résultats *Huit études (516 participants) ont été analysées pour déterminer la qualité du sommeil. Parmi celles-ci, quatre études n'ont utilisé la mélatonine que pour une courte durée, c'est-à-dire soit la nuit précédant et le jour de la chirurgie, soit le jour de la chirurgie seulement. Une méta-analyse à effets aléatoires a montré que la mélatonine n'améliorait pas la qualité du sommeil mesurée par une EVA comparativement au placebo (différence moyenne, -0,75 mm; intervalle de confiance à 95 %, -4,86 à 3,35), avec une faible hétérogénéité (I^2, 5 %). L'analyse séquentielle des études a révélé que la taille de l'information accumulée (n = 516) avait atteint la taille estimative de l'information requise (n = 295). Nous avons abaissé le niveau de confiance des données probantes en raison du risque élevé de biais. L'effet sur les événements indésirables postopératoires était comparable entre le groupe mélatonine et les groupes témoin.*

Conclusion *Nos résultats indiquent que la supplémentation en mélatonine n'améliore pas la qualité du sommeil postopératoire mesurée avec une EVA par rapport au placebo chez les patients adultes (GRADE : modérée).*

Postoperative sleep disturbances are common. Several studies have reported its incidence as ranging from 19.5% to 70%.[1–4] Although pain is one of the most important contributing factors to postoperative sleep disturbance, patients with low postoperative pain levels also suffer from poor sleep quality.[5,6] Postoperative sleep disturbance is also associated with subsequent cognitive dysfunction,[7] and there is expert consensus that postoperative sleep quality is one of the patient outcomes to be studied during the postoperative period.[8] In response, the importance of its prevention is drawing attention.

Melatonin is a central circadian regulator, primarily produced by the pineal gland, and a normal melatonin rhythm is partly instrumental in the regulation of the sleep–wake cycle.[9] The circadian rhythm of melatonin secretion is disturbed after surgery,[10,11] and this disturbance is thought to contribute to postoperative sleep disturbance.[12] Therefore, melatonin administration may modify the circadian rhythm and improve postoperative sleep disturbance. Furthermore, melatonin is known to have an excellent safety profile[13] and has no major adverse effects, such as respiratory depression. Therefore, melatonin has been researched in nonperioperative settings such as insomnia,[14] jet lag,[15] and shift work.[16] In the perioperative period, melatonin is reportedly effective in decreasing preoperative anxiety,[17] emergence agitation,[18] and postoperative delirium.[19] Since ramelteon, one of the melatonin agonists, has a six-fold higher affinity for MT1 receptors and a three-fold higher affinity for MT2 receptors than that of melatonin,[20,21] ramelteon may be more effective than melatonin in improving sleep quality.

Few studies investigating the preventive effect of melatonin administration on postoperative sleep quality have reached any definitive conclusion.[22–24] Therefore, a systematic review and meta-analysis of these small studies could add value to our current knowledge of postoperative melatonin administration. Zhang *et al.* conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) and suggested that melatonin intervention did not significantly influence sleep quality compared with a control group.[25] Nevertheless, since they limited the surgery to laparoscopic cholecystectomy and analyzed only two RCTs for sleep quality, their studies may be underpowered.

The primary purpose of this systematic review was to compare the effects of melatonin or melatonin agonists on postoperative sleep quality with those of no treatment or placebo in adult patients who underwent surgery under general or regional anesthesia. Secondarily, we sought to assess the effects on pain, opioid consumption, quality of recovery, and any adverse events.

Methods and analysis

The manuscript was prepared following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[26] The protocol for this systematic review was registered in PROSPERO on 27 October 2020, with registration number CRD42020180167 and published elsewhere.[27]

Eligibility criteria

We included all RCTs that tested the effect of melatonin or melatonin agonists on postoperative sleep quality in adult patients ($\geq$ 18 yr) undergoing general or regional anesthesia with sedation for any surgery. We excluded patients who received surgical intervention under regional anesthesia without sedation. We excluded data from case reports, observational studies, reviews, and animal studies. Eligibility was not restricted by language, type of surgery, or type of anesthesia.

The intervention of interest was the perioperative (seven days before and after the date of surgery) administration of melatonin or melatonin agonists. There were no restrictions on dosing, frequency, timing, route of administration, or therapy duration. No treatment or placebo was included as the control intervention.

Information sources and search strategy

We conducted a search in MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Web of Science. The final search was conducted on 18 April 2022. We also searched the reference lists of relevant articles. Furthermore, we conducted a search of ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform, and the University Hospital Medical Information Network (UMIN) Clinical Trials Registry. We searched the gray literature using Web of Science. The literature search was limited to studies with human participants. The search strategy, combining free text and Medical Subject Headings terms for PubMed, is shown in Electronic Supplementary Material (ESM) eTable.

Study records

Two authors (A. T. and T. T.) independently scanned the titles and abstracts of the reports identified using the search strategies described above. When eligibility was determined based on the title or abstract, the full paper was retrieved. Potentially relevant studies chosen by at least one author were retrieved and evaluated in full-text versions. Articles that met the inclusion criteria were assessed independently by two authors, and any discrepancies were resolved through discussion.

Two authors (A. T. and T. T.) extracted data independently and in duplicate from each eligible study. The reviewers resolved disagreements through discussion. We contacted the authors of the study to resolve any uncertainties.

Outcomes and prioritization

PRIMARY OUTCOME

The primary outcome was sleep quality measured using a visual analog scale (VAS) (0 mm = best conceivable sleep and 100 mm = worst conceivable sleep) during the early postoperative period. We defined the early postoperative period as the period between the first postoperative night and the fourth night after surgery. If the outcomes were measured several times during the early postoperative period, we considered the mean of these values as our primary outcome. Although we defined the early postoperative period as the interval between the day after surgery and three days after surgery (i.e., between the second postoperative night and the fourth night after surgery) in the protocol,[27] we changed the definition as described above because almost all included studies assessed sleep quality from the first night after surgery.

SECONDARY OUTCOMES

The secondary outcomes were as follows:

1. Total sleep time (minutes);
2. Sleepiness during the daytime was measured using VAS, the Karolinska Sleepiness Scale (KSS),[28] or the Stanford Sleepiness Scale (SSS);[29]
3. Quality of recovery assessed by the QoR-40[30] or QoR-15 measures;[31]
4. Opioid consumption (expressed as cumulative dose [mg] of intravenous morphine or morphine equivalent);
5. Pain as assessed using validated assessment tool scores, such as a VAS, numerical rating scale (NRS), and verbal categorical rating scale; and

6. Any adverse events such as dizziness, desaturation event, or delayed recovery.

Risk of bias in individual studies

We assessed the risk of bias using the Cochrane Risk of Bias Tool version 2 (RoB 2) for randomized controlled trials.[32] The RoB 2.0 assessment for individually randomized trials (including crossover trials) has five domains and one overall risk of bias domain, as follows:

1. Bias arising from the randomization process;
2. Bias due to deviations from intended interventions;
3. Bias due to missing outcome data;
4. Bias in the measurement of outcomes;
5. Bias for selection of the reported result; and
6. Overall risk of bias

The risk of bias was assessed as "low," "some concern," or "high" in each domain.

Data synthesis

We summarized continuous data using mean differences (MDs) or standardized mean differences (SMDs) with a 95% confidence interval (CI), and dichotomous data as risk ratio (RR) with 95% CI. If the 95% CI included a value of 0 or 1 for continuous or dichotomous data, respectively, we considered the difference not statistically significant. We contacted the original authors of the study to obtain the relevant missing data. Heterogeneity was quantified using the I^2 and Cochran's Q statistics. We considered significant heterogeneity to exist when the I^2 statistic exceeded 50%. We conducted a subgroup analysis to explore the possible causes of the high heterogeneity. We used a random-effects model (DerSimonian and Laird methods[33]) considering clinical and methodological heterogeneity to combine the results.

We conducted a subgroup analysis according to the following predefined factors when the I^2 statistic exceeded 50%: 1) type of anesthesia (regional anesthesia, inhaled general anesthesia, or total intravenous general anesthesia); 2) type of surgery; 3) timing of surgery (daytime *vs* nighttime); 4) drug type (melatonin *vs* melatonin agonists); 5) dose of melatonin/melatonin agonists; 6) age; or 7) type of control (placebo *vs* no treatment). Subgroup analyses were not performed if there were fewer than three studies. Sensitivity analysis excluding studies with a high risk of bias was performed for the primary outcome.

Trial sequential analysis (TSA) was performed to correct for random error and repetitive testing of accumulating and sparse data[34] using TSA viewer version 0.9.5.10 β (www.ctu.dk/tsa).[35] The risk of type 1 error was maintained at 5%, with a power of 90%. We considered a 10-mm reduction in MD for the primary outcome clinically meaningful. We used diversity (D^2) as an estimator of heterogeneity for the required information size calculation.[36] We assumed D^2 is 30% or a model variance-based value if it is higher than 30%. If the cumulative z-curve did not cross the TSA monitoring boundaries, we downgraded the certainty of the evidence owing to imprecision in the results.

Statistical analyses were performed using R software, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and the "meta" package was used to perform the meta-analysis.

Reporting bias and publication bias

To determine whether reporting bias was present, we determined whether the RCT protocol was published before patients were recruited for the study. For studies published after July 1, 2005, we screened the Clinical Trial Register at ClinicalTrials.gov (https://clinicaltrials.gov/), the WHO International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform), and the UMIN Clinical Trials Registry (https://www.umin.ac.jp/ctr/). We evaluated whether selective reporting of outcomes was present (outcome reporting bias) by comparing the outcomes mentioned in the published study protocol or trial registry with the outcomes reported in the paper. The small study effect was assessed using a funnel plot and Egger's regression asymmetry test[37] and was considered positive if $P < 0.1$ in the regression asymmetry test.

Summary of evidence

We graded the certainty of the evidence of the main outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[38,39] with the GRADEpro guideline development tool (https://gradepro.org/). The certainty of the evidence was judged based on the presence or absence of the following variables: limitations in the study design, inconsistency, indirectness, imprecision of the results, and publication bias. The certainty of the evidence for the main outcomes was graded as very low, low, moderate, or high.

Results

Search selection and study characteristics

In the initial search of the databases, 2,526 articles were identified. We examined the full texts of 40 articles in detail. Of these, 19 trials were included in this systematic

review, and eight trials with 516 patients were included for quantitative synthesis of sleep quality. The PRISMA flow diagram detailing the disposition of the retrieved publications is shown in Fig. 1. The features of the randomized studies included in this meta-analysis are listed in Table 1. Oral or sublingual melatonin or ramelteon was used in 17 trials, intravenous melatonin was used in one trial, and a dermal melatonin patch was used in one trial. The doses of oral melatonin or ramelteon ranged from 5.0 to 12.0 mg, and 13 of the 19 studies used only a short duration of melatonin administration. Of these, six studies investigated melatonin administration on the night before and on the day of surgery, and seven studies assessed melatonin use during the day of the surgery, before surgery only (i.e., lack of nighttime dosing). The type of control was placebo except for one study where there was no

control. To date, there have been no studies on regional anesthesia under sedation.

Sleep quality assessed by VAS

Eight trials evaluated postoperative sleep quality using the VAS.[23,24,40–45] The time point of assessment of sleep quality varied between the included studies. The combined results are shown in Fig. 2. Melatonin did not improve VAS scores compared with placebo (MD, -0.75 mm; 95% CI, -4.86 to 3.35; I^2, 5%; Cochran's Q, 7.38). The CI was corrected to -5.46 to 3.97 by TSA. Trial sequential analysis revealed that the accrued information size ($n = 516$) reached the estimated required information size ($n = 295$) (ESM eFig. 1). We considered three trials to have some concerns of risk of bias, whereas five were at a high risk of bias (Fig. 3).
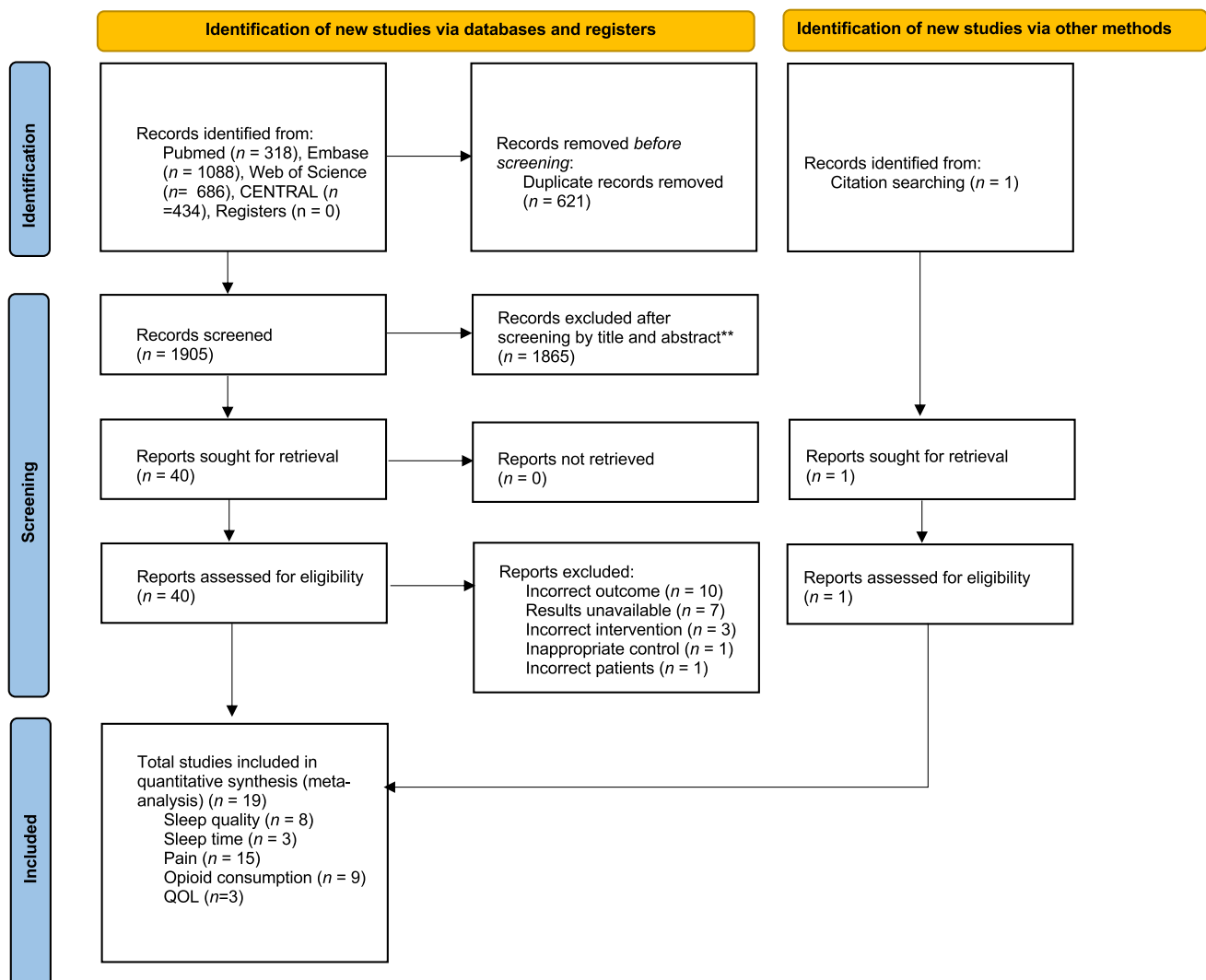

Fig. 1 PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis

Table 1 Features of the included studies measuring sleep quality using a visual analog scale

Author	Sample size, *n*	Age (yr), mean	Surgery	Intervention drug	Dose, route	Timing of melatonin administration	Timing of primary outcome data
Capuzzo 2006	138	72.6	Abdominal, thoracic, endocrinologic, vascular, or skin surgery	Melatonin	10 mg, oral	On the day of surgery (before surgery)	Not applicable
Caumo 2007	33	44.4	Abdominal hysterectomy	Melatonin	5 mg, oral	The night before and 1 hr before surgery	Not applicable
Caumo 2009	40	44.4	Abdominal hysterectomy	Melatonin	5 mg, oral	The night before and 1 hr before surgery	Not applicable
Gongenur 2009	121	45.5	Laparoscopic cholecystectomy	Melatonin	5 mg, oral	On the 3 nights after surgery	Average of postoperative 1st to 3rd night
Borazen 2009	52	57.5	Open prostatectomy	Melatonin	6 mg, oral	The night before surgery and again 1 hr before surgery	Postoperative 1st night
Andersen 2014	41	51.1	Laparoscopic cholecystectomy	Melatonin	10 mg, intravenous	At the time of surgical incision	Average of postoperative 1st to 3rd night
Yamaguchi 2014	53	76.8	Total knee arthroplasty	Ramelteon	8 mg, oral	From the night before surgery to the 2nd postoperative night	Not applicable
Hoseini 2015	44	38.8	Laparoscopic cholecystectomy	Melatonin	6 mg, oral	At 120 minutes before surgery	Not applicable
Kirksey 2015	37	65.8	Total knee arthroplasty	Melatonin	5 mg, oral	From the 3rd preoperative night to the 3rd postoperative night	Average of postoperative 1st to 3rd night
Seet 2015	73	22.9	Dental surgery	Melatonin	6 mg, oral	At 90 minutes before surgery	Postoperative 1st night
Esmat 2016	40	44.0	Laparoscopic cholecystectomy	Melatonin	7 mg/8 hr, dermal patch	Placed 2 hr preoperatively and removed 12 hr postoperatively	Not applicable
Madsen 2016	48	54.5	Breast cancer surgery	Melatonin	6 mg, oral	From the 3rd preoperative night to at least 1 week postoperatively	Average of postoperative 1st to 3rd night
Ivry 2016	44	40.7	Laparoscopic gastrectomy	Melatonin	5 mg, oral	On the night before surgery and again 2 hr before surgery	Postoperative 1st night
Vij 2018	100	42.1	Laparoscopic cholecystectomy	Melatonin	6 mg, oral	On the 3 nights after surgery	Postoperative 1st to 3rd night
Jaiswal 2019	117	57.1	Pulmonary thromboendarterectomy	Ramelteon	8 mg, oral	Starting the night prior to surgery and for a maximum of 6 nights while in the intensive care unit	Not applicable
Tunay 2019	110	47.4	Major abdominal surgery	Melatonin	6 mg, oral	1 hr before surgery	Not applicable
Barati 2020	70	64.2	On-pump coronary artery bypass graft	Melatonin	12 mg, sublingual	On the evening before surgery and 1 hr before surgery	Not applicable
Lotfy 2021	105	46.3	Inguinal hernia repair	Melatonin	3 or 6 mg, oral	On the day of surgery (before transfer to the theater)	Not applicable

Table 1 continued

Author	Sample size, n	Age (yr), mean	Surgery	Intervention drug	Dose, route	Timing of melatonin administration	Timing of primary outcome data
Nogueira 2021	14	Not available (from 18 to 60 yr old)	Zygomatic complex fractures	Melatonin	10 mg, oral	On the night before surgery and 1 hr before the start of surgery	Not applicable

Fig. 2 Meta-analysis of sleep quality measured by visual analogue scale. Graphs represent the mean differences (MDs) with 95% confidence intervals (CIs).
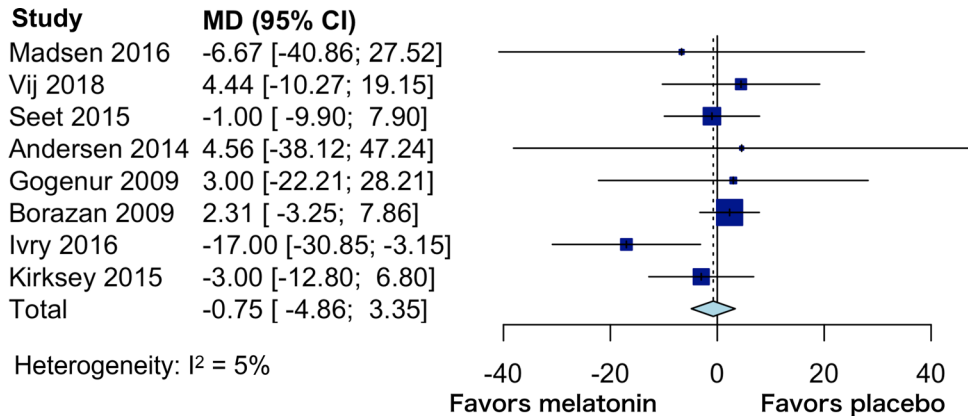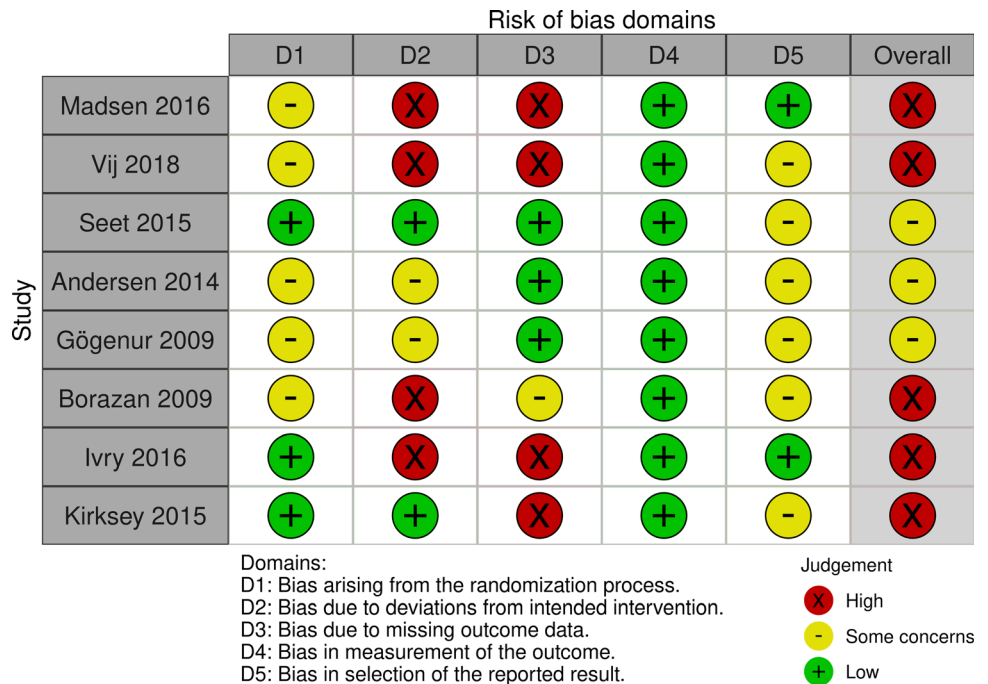

Fig. 3 Risk of bias in the included studies measuring sleep quality by visual analogue scale

Sensitivity analyses that removed studies with a high risk of bias showed consistent results with the primary meta-analyses (MD, -0.37 mm; 95% CI, -8.60 to 7.87, I^2, 0%; Cochran's Q, 0.14; ESM eFig. 2). We did not conduct a subgroup analysis because the I^2 statistic did not exceed 50%. We did not conduct an asymmetry test for the funnel plot because only eight trials were included. The overall GRADE certainty of the evidence was rated moderate (Table 2). The evidence was downgraded for the risk of bias.

Table 2 Evidence profile

Certainty assessment							Number of patients		Absolute effect (95% CI)	Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin or melatonin agonist	Placebo		
Sleep quality (assessed with: VAS from 0 to 100)										
8	Randomized trials	Serious	Not serious	Not serious	Not serious[a]	None	262	254	MD 0.21 mm higher (3.92 lower to 4.34 higher)	⊕⊕⊕◯ Moderate
Sleep time										
3	Randomized trials	Very serious	Serious[b]	Not serious	Serious[c]	None	66	59	MD 30.2 minutes higher (1.7 lower to 62 higher)	⊕◯◯◯ Very low
Pain (assessed with: VAS from 0 to 100)										
13	Randomized trials	Serious	Very serious	Not serious	Not serious	None	425	418	MD 6.8 mm lower (13.37 lower to 0.22 lower)	⊕◯◯◯ Very low
Opioid consumption (assessed with: morphine equivalent)										
9	Randomized trials	Serious	Very serious	Not serious	Very serious	None	276	274	MD 3.25 mg lower (4.5 lower to 2.01 lower)	⊕◯◯◯ Very low
QoR (assessed with: SMD)										
3	Randomized trials	Very serious	Not serious	Not serious	Very serious	None	65	61	SMD 0.26 SD higher (0.15 lower to 0.67 higher)	⊕◯◯◯ Very low

CI = confidence interval; MD = mean difference; QoR = quality of recovery; SMD = standardized mean difference

Sleep time

Three trials[41,44,45] evaluated perioperative sleep time on the preoperative night and on the first to third postoperative nights by actigraphy. Postoperative sleep time was defined as the difference from the preoperative sleep time and changed to a mean value of three days. The combined results are shown in ESM eFig. 3. Melatonin and ramelteon did not improve sleep time compared with placebo (MD, 30.2 min; 95% CI, -1.7 to 62.0; I^2, 47.5%; Cochran's Q, 3.81). We considered all trials to be at high risk of bias (ESM eFig. 4). The CI was corrected to -30.81 to 91.10 by TSA. The TSA showed that the estimated required information size was 382; however, the accrued information size was only 125 (32.7%). The z-curve did not cross the TSA monitoring boundary or reach the required information size (ESM eFig. 5). This indicates that sufficient data were not accumulated to conclusively determine whether melatonin improves sleep duration. The overall GRADE certainty of the evidence was rated very low (Table 2). The evidence was downgraded for the risk of bias, inconsistency, and imprecision.

Sleepiness

Five trials evaluated postoperative sleepiness using the VAS,[45,46] KSS,[40,44] and SSS.[41] We did not combine these results because the measurements differed in nature; the VAS score measures only sleepiness whereas the KSS and the SSS contain several conditions (alert/vital/active, relaxed, and sleepy) that are not always considered sequential. Moreover, the absolute scores for the relaxation state considered the best condition differed between the KSS and the SSS. In studies measuring sleepiness with KSS, the MD was 0.00 (95% CI, -2.70 to 2.70)[43] and -0.78 (95% CI, -4.51 to 2.95).[40] In studies measuring sleepiness with VAS, the MD was 0.51 (95% CI, -1.16 to 2.18)[46] and 0.56 (95% CI, -0.24 to 1.36).[45] In a study measuring sleepiness with SSS,[41] the MD was 0.00 (95% CI, -0.39 to 0.39) (ESM eFig. 6). We considered three studies to be at a high risk of bias and two studies to be at some concerns of risk of bias (ESM eFig. 7).

Pain

Fifteen trials evaluated postoperative pain using a VAS[23,24,41–51] and NRS.[52,53] Each score until postoperative day 3 was converted to the mean value. We considered an NRS score (measured from 0 to 10) as equivalent to the VAS, and synthesized a ten-fold value of the NRS with the VAS. The combined results are presented in Fig. 4. Melatonin improved pain compared with placebo

(MD, -6.89 mm; 95% CI, -11.50 to -2.28; I^2, 86%; Cochran's Q, 103.32). We considered seven, six, and two studies to be at high risk of bias, some concerns of risk of bias, and low risk of bias, respectively (ESM eFig. 8). The CI was corrected to -11.89 -1.88 by TSA. Trial sequential analysis revealed that the accrued information size ($n = 962$) reached the estimated required information size ($n = 562$) (ESM eFig. 9). The overall GRADE certainty of the evidence was rated very low (Table 2). In post hoc analysis, we performed subgroup analyses according to the 1) type of anesthesia (inhaled vs total intravenous general anesthesia), 2) type of surgery (major vs minor surgery), and 3) age (> 50 vs < 50 yr), which were preplanned for the subgroup analyses of the primary outcome. The interaction P values were 0.82, 0.10, and 0.43 for the type of anesthesia, type of surgery, and age, respectively.
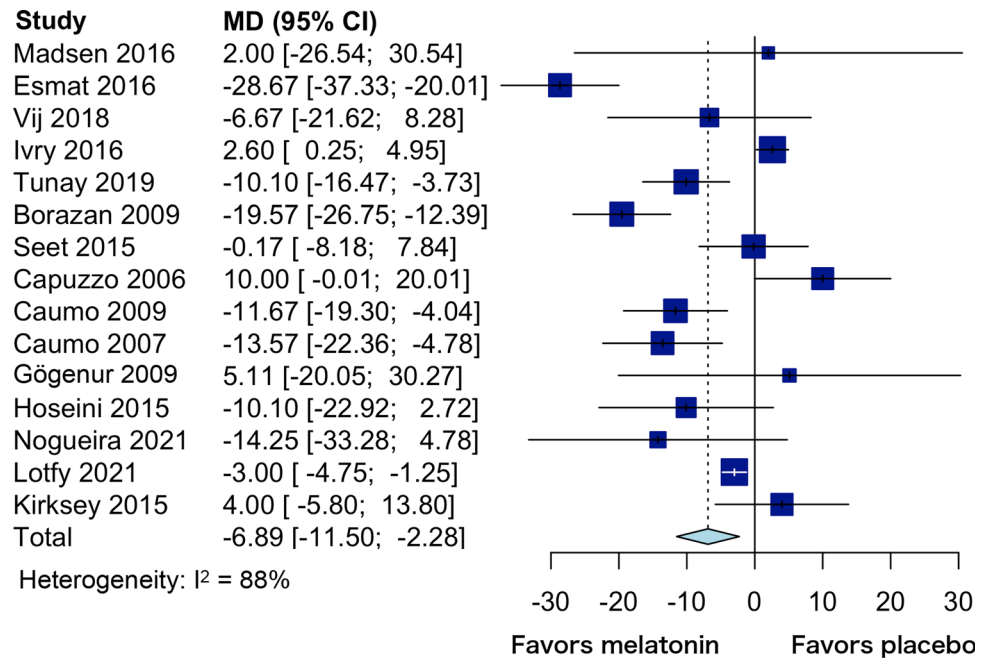
Opioid consumption

Nine trials[23,24,40,41,46,47,49,50,54] evaluated postoperative opioid use. One study[40] was excluded from the analysis because it had no opioid use in the control group. We recalculated accumulated morphine consumption. The combined results are shown in ESM eFig. 10. Melatonin and ramelteon reduced opioid consumption compared with placebo (SMD, -3.25 mg; 95% CI, -4.50 to -2.01; I^2, 97%; Cochran's Q, 221.40). We considered 3, 5, and 1 as high, some concern, and low risk of bias, respectively (ESM eFig. 11). Trial sequential analysis showed that the accrued information size ($n = 550$) reached only 2.1% of the estimated required information size; thus, we could not calculate the TSA-adjusted CI. The z-curve did not cross the TSA monitoring boundary or reach the required information size (ESM eFig. 12). The overall GRADE certainty of the evidence was rated very low (Table 2).

Quality of recovery

Three trials evaluated the postoperative quality of recovery by the QoR-40[41,55] or QoR-15 measures.[43] The combined results are shown in ESM eFig. 13. Melatonin did not improve postoperative quality of recovery compared with placebo (SMD, 0.26; 95% CI, -0.15 to 0.67; I^2, 25%; Cochran's Q, 2.66). All trials were considered to have a high risk of bias (ESM eFig. 14). The CI was corrected to -0.78 to 1.31 by TSA. The TSA showed that the estimated required information size was 667; however, the accrued information size was only 126 (18.9%). The z-curve did not cross the TSA monitoring boundary or reach the required information size (ESM eFig. 15). The overall GRADE certainty of the evidence was rated very low (Table 2).

Fig. 4 Forest plot of postoperative pain measured using the visual analog scale. Graphs represent the mean differences (MDs) with 95% confidence intervals (CIs).

Study	MD (95% CI)
Madsen 2016	2.00 [-26.54; 30.54]
Esmat 2016	-28.67 [-37.33; -20.01]
Vij 2018	-6.67 [-21.62; 8.28]
Ivry 2016	2.60 [0.25; 4.95]
Tunay 2019	-10.10 [-16.47; -3.73]
Borazan 2009	-19.57 [-26.75; -12.39]
Seet 2015	-0.17 [-8.18; 7.84]
Capuzzo 2006	10.00 [-0.01; 20.01]
Caumo 2009	-11.67 [-19.30; -4.04]
Caumo 2007	-13.57 [-22.36; -4.78]
Gögenur 2009	5.11 [-20.05; 30.27]
Hoseini 2015	-10.10 [-22.92; 2.72]
Nogueira 2021	-14.25 [-33.28; 4.78]
Lotfy 2021	-3.00 [-4.75; -1.25]
Kirksey 2015	4.00 [-5.80; 13.80]
Total	-6.89 [-11.50; -2.28]

Heterogeneity: $I^2 = 88\%$

Favors melatonin   Favors placebo

Adverse events and other outcomes

Six trials evaluated postoperative nausea and vomiting (PONV) using VAS,[46,47,50] NRS,[48] or a dichotomous variable.[23,41] The results of one study[50] were not used for the synthesis because the original data were not available. Visual analog scale scores ranged from 0 (absence of symptoms) to 10 (maximum symptoms). Melatonin did not affect the incidence and severity of PONV (RR, 1.20; 95% CI, 0.63 to 2.28; I^2, 45%; Cochran's Q, 1.82 and MD, -1.91 mm; 95% CI, -4.84 to 1.02; I^2, 0%; Cochran's Q, 0.03) compared with placebo (ESM eFigs 16 and 17).

Three trials[23,41,56] evaluated dizziness; the combined results are shown in ESM eFig. 18. Melatonin did not affect the incidence of dizziness compared with placebo (RR, 0.78; 95% CI, 0.60 to 1.02; I^2, 0%; Cochran's Q, 1.91).

Two trials[23,56] evaluated headaches; the combined results are shown in ESM eFig. 19. Melatonin did not affect the incidence of headaches compared with placebo (RR, 1.21; 95% CI, 0.78 to 1.88; I^2, 0%; Cochran's Q, 0.16).

Included studies did not report any other secondary outcomes preplanned in the published protocol.[27]

Discussion

Our systematic review's results indicate that melatonin supplementation does not improve postoperative sleep quality measured with the VAS compared with placebo in adult patients (GRADE: moderate). Trial sequential analysis indicated sufficient precision for the conclusion, but we downgraded the certainty of evidence because of the high risk of bias. Furthermore, melatonin may not improve sleep time, daytime sleepiness, or quality of recovery (GRADE: very low). Nevertheless, melatonin may reduce postoperative pain scores (GRADE: very low) and opioid consumption (GRADE: very low).

Compared with placebo, moderate evidence indicates that melatonin has no positive effect on postoperative sleep disturbance in adult patients. In the CI of the present results, the minimum and maximum values were less than the clinically minimally important difference (10 mm of VAS), indicating reasonably strong evidence. There are several possible reasons for the finding that melatonin did not improve postoperative sleep disturbance. First, the doses of melatonin intervention ranged from 5 to 10 mg, which may be inadequate for improving postoperative sleep disturbances. In healthy volunteers, the same dose mediates the circadian rhythm and improves sleep disturbances.[57,58] In contrast, this dose might be insufficient to shift the circadian rhythm in the perioperative period. The effects of melatonin, such as circadian phase-shifting and hypnotic effects,[59] have also been reported to be dose-dependent. Therefore, a higher dose might mediate circadian rhythm and improve sleep disturbances. Second, the duration of melatonin administration was short in four of eight studies, only during the day of the surgery before surgery[40,42] or the day before surgery and during the day of surgery before surgery.[24,43] The half-life of both oral and intravenous

melatonin is 45 min;[60] therefore, melatonin administration before surgery only might not affect postoperative sleep disturbances. Although four studies[23,41,44,45] administering melatonin in the postoperative period might positively affect sleep disturbance, we could not interpret its effect from the forest plot (Fig. 2). Third, even if the dose or duration is sufficient and melatonin shifts the circadian rhythm, it might not have a clinical impact on postoperative sleep disturbances. A prior systematic review found that melatonin or ramelteon compared with placebo was not efficacious for insomnia disorders.[14] Fourth, factors other than circadian rhythm may be related to postoperative sleep disturbances. Natural sleep has been recognized to be controlled by the combined actions of two different but related mechanisms: the sleep homeostat and the circadian rhythm.[61] Even if melatonin improves disturbed circadian rhythm, postoperative sleep disturbance may remain because of disturbed sleep homeostasis. Slow-wave sleep during nonrapid eye movement is a classical marker of sleep homeostatic processes. Several factors arising from perioperative periods, such as surgical endocrine[62,63] and cytokine response,[64,65] anesthesia,[66] and opioids,[67] disturb rapid eye movement sleep and slow-wave sleep. Moreover, daytime surgery might disturb sleep homeostasis more significantly and lead to sleep disturbance than nighttime surgery might.

A prior systematic review,[25] which included RCTs on laparoscopic cholecystectomy, synthesized only two RCTs and found that melatonin had no substantial effects; the present results appear to be largely in line with this small study. Because the present study did not restrict the type of surgery and synthesized more studies, our results can be adapted to larger populations with more robust evidence than the previous systematic review.

Melatonin decreased postoperative pain scores, which was in line with a prior study.[68] Previous studies suggested that melatonin may mediate antinociceptive antihyperalgesia through central[69] and peripheral[70] effects. Melatonin may also affect the opioid and gamma-aminobutyric acid systems.[70–72] Therefore, the present finding that melatonin decreased postoperative pain scores is biologically plausible. To clarify the reason for high heterogeneity, we conducted post hoc subgroup analyses, but could not determine any possible reasons for the high heterogeneity. Moreover, the difference in VAS scores was associated with very low certainty of evidence. Therefore, our study could not conclude that melatonin was clinically effective at improving postoperative pain.

The results of sleep time were in line with the results of the primary outcome. Although there were no statistically significant differences in sleep time, the TSA result indicates that further studies are needed. Melatonin might be biologically effective in reducing sleep disturbance and improving sleep time (MD, 30 min; 95% CI, -1.7 to 62.0), but this might not be enough to improve the patient's subjective assessment of sleep quality as measured by the VAS. Postoperative sleepiness and quality of recovery are concepts that encompass sleep disturbances. Although we did not combine the results of the studies assessing sleepiness, individual studies seemed to have no positive effect on sleepiness. Melatonin did not improve the quality of recovery, which was similar to the primary outcome. Nevertheless, all secondary outcomes had a very low level of evidence, and it was difficult to obtain plausible imprecation.

The present study has several limitations. First, many studies had a high risk of bias. The reasons for the high risk of bias are as follows: 1) An intention-to-treat analysis was not performed; 2) the number of missing outcomes was significant and it could not be considered that "missing" was completely at random; and 3) there was no protocol, and it was difficult to determine whether the reported results were selected. If patients with low melatonin efficacy were missing or if the authors failed to report unfavorable results, the direction of bias would favor melatonin. Nevertheless, our systematic review concluded that melatonin had no effect. Moreover, we did not detect inconsistency, indirectness, imprecision, or publication bias. Therefore, we downgraded the overall GRADE certainty of the evidence by only one level and rated it as moderate for the primary outcome. Second, melatonin was the only intervention drug among the included studies that assessed sleep quality. Since ramelteon has a six-fold higher affinity for MT1 receptors and a three-fold higher affinity for MT2 receptors than melatonin does,[20,21] ramelteon may be more effective than melatonin in improving sleep quality. Therefore, our results cannot be extrapolated to melatonin agonists, and further RCTs are needed to know the effects of these drugs.

In conclusion, the findings from this systematic review indicate that melatonin supplementation does not reduce sleep disturbances after general anesthesia but may reduce postoperative pain scores and opioid consumption. Further RCTs with a low risk of bias are needed to assess the effect of melatonin or melatonin agonists on postoperative sleep disturbances.

References

1. *Hou H, Wu S, Qiu Y, Song F, Deng L*. The effects of morning/afternoon surgeries on the early postoperative sleep quality of patients undergoing general anesthesia. BMC Anesthesiol 2022; 22: 286. https://doi.org/10.1186/s12871-022-01828-w

2. *Wang SJ, Shen SY, Lin B, Wang F, Yang HY*. Factors affecting postoperative sleep quality of patients undergoing flap transfer for head and neck reconstruction. Oral Oncol 2022; 127: 105804. https://doi.org/10.1016/j.oraloncology.2022.105804

3. *Duan G, Wang K, Peng T, Wu Z, Li H*. The effects of intraoperative dexmedetomidine use and its different dose on postoperative sleep disturbance in patients who have undergone non-cardiac major surgery: a real-world cohort study. Nat Sci Sleep 2020; 12: 209–19. https://doi.org/10.2147/nss.s239706

4. *Cai J, Chen Y, Hao X, et al*. Effect of intraoperative dexmedetomidine dose on postoperative first night sleep quality in elderly surgery patients: a retrospective study with propensity score-matched analysis. Front Med (Lausanne) 2020; 7: 528. https://doi.org/10.3389/fmed.2020.00528

5. *Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO*. Postoperative sleep disturbance: influences of opioids and pain in humans. Sleep 2001; 24: 39–44. https://doi.org/10.1093/sleep/24.1.39

6. *Kain ZN, Caldwell-Andrews AA*. Sleeping characteristics of adults undergoing outpatient elective surgery: a cohort study. J Clin Anesth 2003; 15: 505–9. https://doi.org/10.1016/j.jclinane.2003.02.002

7. *Gögenur I, Middleton B, Burgdorf S, Rasmussen LS, Skene DJ, Rosenberg J*. Impact of sleep and circadian disturbances in urinary 6-sulphatoxymelatonin levels, on cognitive function after major surgery. J Pineal Res 2007; 43: 179–84. https://doi.org/10.1111/j.1600-079x.2007.00460.x

8. *Myles PS, Boney O, Botti M, et al*. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. Br J Anaesth 2018; 120: 705–11. https://doi.org/10.1016/j.bja.2017.12.037

9. *Shochat T, Haimov I, Lavie P*. Melatonin–the key to the gate of sleep. Ann Med 1998; 30: 109–14. https://doi.org/10.3109/07853899808999392

10. *Mihara T, Kikuchi T, Kamiya Y, et al*. Day or night administration of ketamine and pentobarbital differentially affect circadian rhythms of pineal melatonin secretion and locomotor activity in rats. Anesth Analg 2012; 115: 805–13. https://doi.org/10.1213/ane.0b013e3182632bcb

11. *Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO*. Melatonin secretion after surgery. Lancet 2000; 356: 1244–5. https://doi.org/10.1016/s0140-6736(00)02795-1

12. *Leardi S, Tavone E, Cianca G, et al*. The role of melatonin in the immediate postoperative period in elderly patients [Italian]. Minerva Chir 2000; 55: 745–50.

13. *Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F*. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. Anesthesiology 2010; 113: 968–76. https://doi.org/10.1097/aln.0b013e3181e7d626

14. *De Crescenzo F, D'Alò GL, Ostinelli EG, et al*. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet 2022; 400: 170–84. https://doi.org/10.1016/s0140-6736(22)00878-9

15. *Herxheimer A, Petrie KJ*. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2002; https://doi.org/10.1002/14651858.cd001520

16. *Liira J, Verbeek JH, Costa G, et al*. Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. Cochrane Database Syst Rev 2014; https://doi.org/10.1002/14651858.cd009776.pub2

17. *Madsen BK, Zetner D, Møller AM, Rosenberg J*. Melatonin for preoperative and postoperative anxiety in adults. Cochrane Database Syst Rev 2020; 12: CD009861. https://doi.org/10.1002/14651858.cd009861.pub3

18. *Mihara T, Nakamura N, Ka K, Oba MS, Goto T*. Effects of melatonin premedication to prevent emergence agitation after general anaesthesia in children: a systematic review and meta-analysis with trial sequential analysis. Eur J Anaesthesiol 2015; 32: 862–71. https://doi.org/10.1097/eja.0000000000000323

19. *Han Y, Wu J, Qin Z, et al*. Melatonin and its analogues for the prevention of postoperative delirium: a systematic review and meta-analysis. J Pineal Res 2020; 68: e12644. https://doi.org/10.1111/jpi.12644

20. *Miyamoto M*. Pharmacology of ramelteon, a selective MT1/MT2 receptor agonist: a novel therapeutic drug for sleep disorders. CNS Neurosci Ther 2009; 15: 32–51. https://doi.org/10.1111/j.1755-5949.2008.00066.x

21. *Hardeland R*. Melatonin in aging and disease - multiple consequences of reduced secretion, options and limits of treatment. Aging Dis 2012; 3: 194–225.

22. *Hansen MV, Madsen MT, Andersen LT, et al*. Effect of melatonin on cognitive function and sleep in relation to breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Int J Breast Cancer 2014; 2014: 416531. https://doi.org/10.1155/2014/416531

23. *Gögenur I, Kücükakin B, Bisgaard T, et al*. The effect of melatonin on sleep quality after laparoscopic cholecystectomy: a randomized, placebo-controlled trial. Anesth Analg 2009; 108: 1152–6. https://doi.org/10.1213/ane.0b013e31819a6cf0

24. *Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S*. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. J Anesth 2010; 24: 155–60. https://doi.org/10.1007/s00540-010-0891-8

25. *Zhang J, Wang Y, Xu H, Yang J*. The influence of melatonin on sleep quality after laparoscopic cholecystectomy: a meta-analysis of randomized controlled trials. Surg Laparosc Endosc Percutan Tech 2019; 29: 1–6. https://doi.org/10.1097/sle.0000000000000601

26. *Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097. https://doi.org/10.1371/journal.pmed.1000097

27. *Tsukinaga A, Mihara T, Takeshima T, Tomita M, Goto T, Yamanaka T*. Effect of melatonin and melatonin agonists on postoperative sleep quality in adult patients: a protocol for systematic review and meta-analysis with trial sequential analysis. BMJ Open 2021; 11: e047858. https://doi.org/10.1136/bmjopen-2020-047858

28. Kaida K, Takahashi M, Akerstedt T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. Clin Neurophysiol 2006; 117: 1574–81. https://doi.org/10.1016/j.clinph.2006.03.011

29. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology 1973; 10: 431–6. https://doi.org/10.1111/j.1469-8986.1973.tb00801.x

30. Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth 2000; 84: 11–5. https://doi.org/10.1093/oxfordjournals.bja.a013366

31. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology 2013; 118: 1332–40. https://doi.org/10.1097/aln.0b013e318289b84b

32. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. https://doi.org/10.1136/bmj.l4898

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88. https://doi.org/10.1016/0197-2456(86)90046-2

34. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA), 2011. Available from URL: https://ctu.dk/wp-content/uploads/2021/03/2017-10-10-TSA-Manual-ENG_ER.pdf (accessed January 2023).

35. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008; 61: 64–75. https://doi.org/10.1016/j.jclinepi.2007.03.013

36. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol 2009; 9: 86. https://doi.org/10.1186/1471-2288-9-86

37. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–34. https://doi.org/10.1136/bmj.315.7109.629

38. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490. https://doi.org/10.1136/bmj.328.7454.1490

39. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–6. https://doi.org/10.1136/bmj.39489.470347.ad

40. Andersen LP, Kücükakin B, Werner MU, Rosenberg J, Gögenur I. Absence of analgesic effect of intravenous melatonin administration during daytime after laparoscopic cholecystectomy: a randomized trial. J Clin Anesth 2014; 26: 545–50. https://doi.org/10.1016/j.jclinane.2014.03.008

41. Kirksey MA, Yoo D, Danninger T, Stundner O, Ma Y, Memtsoudis SG. Impact of melatonin on sleep and pain after total knee arthroplasty under regional anesthesia with sedation: a double-blind, randomized, placebo-controlled pilot study. J Arthroplasty 2015; 30: 2370–5. https://doi.org/10.1016/j.arth.2015.06.034

42. Seet E, Liaw CM, Tay S, Su C. Melatonin premedication versus placebo in wisdom teeth extraction: a randomised controlled trial. Singapore Med J 2015; 56: 666–71. https://doi.org/10.11622/smedj.2015186

43. Ivry M, Goitein D, Welly W, Berkenstadt H. Melatonin premedication improves quality of recovery following bariatric surgery – a double blind placebo controlled prospective study. Surg Obes Relat Dis 2017; 13: 502–6. https://doi.org/10.1016/j.soard.2016.11.001

44. Madsen MT, Hansen MV, Andersen LT, et al. Effect of melatonin on sleep in the perioperative period after breast cancer surgery: a randomized, double-blind, placebo-controlled trial. J Clin Sleep Med 2016; 12: 225–33. https://doi.org/10.5664/jcsm.5490

45. Vij V, Dahiya D, Kaman L, Behera A. Efficacy of melatonin on sleep quality after laparoscopic cholecystectomy. Indian J Pharmacol 2018; 50: 236–41. https://doi.org/10.4103/ijp.ijp_250_18

46. Caumo W, Torres F, Moreira NL Jr, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg 2007; 105: 1263–71. https://doi.org/10.1213/01.ane.0000282834.78456.90

47. Caumo W, Levandovski R, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. J Pain 2009; 10: 100–8. https://doi.org/10.1016/j.jpain.2008.08.007

48. Hosseini VS, Yekta RA, Marashi S, Marashi SM. The efficacy of melatonin, clonidine and gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy: a randomized clinical trial. AACC 2015; 1: 120–5

49. Esmat IM, Kassim DY. Comparative study between transdermal nicotine and melatonin patches on postoperative pain relief after laparoscopic cholecystectomy, a double-blind, placebo-controlled trial. Egypt J Anaesth 2016; 32: 299–307. https://doi.org/10.1016/j.egja.2016.05.002

50. Tunay DL, Ilgınel MT, Ünlügenç H, Tunay M, Karacaer F, Biricik E. Comparison of the effects of preoperative melatonin or vitamin C administration on postoperative analgesia. Bosn J Basic Med Sci 2020; 20: 117–24. https://doi.org/10.17305/bjbms.2019.4379

51. de Carvalho Nogueira EF, de Carvalho Melo V, Catunda IS, Afonso Ferreira JC, de Aguiar Soares Carneiro SC, do Egito Vasconcelos BC. Evaluation of the effects of exogenous melatonin in zygomatic complex fractures. J Maxillofac Oral Surg 2022; 21: 923–8. https://doi.org/10.1007/s12663-021-01568-3

52. Lotfy M, Ayaad M. Preoperative oral melatonin can reduce preoperative anxiety and postoperative analgesia in a dose-dependent manner. Ain-Shams J Anesthesiol 2021; 13: 32. https://doi.org/10.1186/s42077-021-00146-6

53. Capuzzo M, Zanardi B, Schiffino E, et al. Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. Anesth Analg 2006; 103: 121–3. https://doi.org/10.1213/01.ane.0000222476.62547.ed

54. Jaiswal SJ, Vyas AD, Heisel AJ, et al. Ramelteon for prevention of postoperative delirium: a randomized controlled trial in patients undergoing elective pulmonary thromboendarterectomy. Crit Care Med 2019; 47: 1751–8. https://doi.org/10.1097/ccm.0000000000004004

55. Yamaguchi Y, Mihara T, Taguri M, Yamaguchi O, Goto T. Melatonin receptor agonist for the prevention of postoperative delirium in elderly patients: a randomized, double-blind, placebo-controlled trial. Int Care Med 2014; 40: S246.

56. Barati S, Jahangirifard A, Ahmadi ZH, Tavakoli-Ardakani M, Dastan F. The effects of melatonin on the oxidative stress and duration of atrial fibrillation after coronary artery bypass graft surgery: a randomized controlled trial. Endocr Metab Immune Disord Drug Targets 2021; 21: 1142–9. https://doi.org/10.2174/1871530320666200728152307

57. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. Brain Res 1995; 688: 77–85. https://doi.org/10.1016/0006-8993(95)96872-i

58. Sharkey KM, Eastman CI. Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work

study. Am J Physiol Regul Integr Comp Physiol 2002; 282: R454–63. https://doi.org/10.1152/ajpregu.00135.2001

59. *Naguib M, Hammond DL, Schmid PG 3rd, et al.* Pharmacological effects of intravenous melatonin: comparative studies with thiopental and propofol. Br J Anaesth 2003; 90: 504–7. https://doi.org/10.1093/bja/aeg092

60. *Harpsøe NG, Andersen LP, Gögenur I, Rosenberg J.* Clinical pharmacokinetics of melatonin: a systematic review. Eur J Clin Pharmacol 2015; 71: 901–9. https://doi.org/10.1007/s00228-015-1873-4

61. *Dijk DJ, Lockley SW.* Integration of human sleep-wake regulation and circadian rhythmicity. J Appl Physiol 2002; 92: 852–62. https://doi.org/10.1152/japplphysiol.00924.2001

62. *Friess E, U VB, Wiedemann K, Lauer CJ, Holsboer F.* Effects of pulsatile cortisol infusion on sleep-EEG and nocturnal growth hormone release in healthy men. J Sleep Res 1994; 3: 73–9. https://doi.org/10.1111/j.1365-2869.1994.tb00110.x

63. *Bohlhalter S, Murck H, Holsboer F, Steiger A.* Cortisol enhances non-REM sleep and growth hormone secretion in elderly subjects. Neurobiol Aging 1997; 18: 423–9. https://doi.org/10.1016/s0197-4580(97)00036-5

64. *Høgevold HE, Lyberg T, Kähler H, Haug E, Reikerås O.* Changes in plasma IL-1beta, TNF-alpha and IL-6 after total hip replacement surgery in general or regional anaesthesia. Cytokine 2000; 12: 1156–9. https://doi.org/10.1006/cyto.2000.0675

65. *Späth-Schwalbe E, Hansen K, Schmidt F, et al.* Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. J Clin Endocrinol Metab 1998; 83: 1573–9. https://doi.org/10.1210/jcem.83.5.4795

66. *Lehmkuhl P, Prass D, Pichlmayr I.* General anesthesia and postnarcotic sleep disorders. Neuropsychobiology 1987; 18: 37–42. https://doi.org/10.1159/000118390

67. *Kay DC, Eisenstein RB, Jasinski DR.* Morphine effects on human REM state, waking state and NREM sleep. Psychopharmacologia 1969; 14: 404–16. https://doi.org/10.1007/bf00403581

68. *Oh SN, Myung SK, Jho HJ.* Analgesic efficacy of melatonin: a meta-analysis of randomized, double-blind, placebo-controlled trials. J Clin Med 2020; 9: 1553 https://doi.org/10.3390/jcm9051553

69. *Dubocovich ML.* Melatonin receptors in the central nervous system. Adv Exp Med Biol 1991; 294: 255–65. https://doi.org/10.1007/978-1-4684-5952-4_23

70. *Ambriz-Tututi M, Rocha-González HI, Cruz SL, Granados-Soto V.* Melatonin: a hormone that modulates pain. Life Sci 2009; 84: 489–98. https://doi.org/10.1016/j.lfs.2009.01.024

71. *Mantovani M, Kaster MP, Pertile R, Calixto JB, Rodrigues AL, Santos AR.* Mechanisms involved in the antinociception caused by melatonin in mice. J Pineal Res 2006; 41: 382–9. https://doi.org/10.1111/j.1600-079x.2006.00380.x

72. *Golombek DA, Escolar E, Burin LJ, De Brito Sánchez MG, Cardinali DP.* Time-dependent melatonin analgesia in mice: inhibition by opiate or benzodiazepine antagonism. Eur J Pharmacol 1991; 194: 25–30. https://doi.org/10.1016/0014-2999(91)90119-b