

CLINICAL ARTICLE

Improved Perioperative Sleep Quality or Quantity Reduces Pain after Total Hip or Knee Arthroplasty: A Systematic Review and Meta-Analysis

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Objective: To investigate the effects of improved perioperative sleep on pain, analgesic consumption, and postoperative nausea and vomiting (PONV) in patients who were undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA).

Methods: Original studies published from 1 January 1970 to 30 September 2020 were queried in three unique databases using a common search term. The searches sought randomized controlled trials (RCT) investigating the effectiveness of sleep quality or quantity interventions for pain control early after TKA or THA. Grey literature was also searched by screening trial registers. There was no limitation on published language and patients. Two reviewers then assessed studies for eligibility. Eligible studies should have primary outcomes including perioperative visual analogue scale (VAS) pain score and analgesic consumption; and secondary outcomes including side effects, such as PONV. Data extracted from the literature were abstracted into a comma-separated database spreadsheet using Microsoft Excel. A meta-analysis was then performed. Pooled statistics were calculated with weighting by inverse variance assuming a random effect model. I^2 was calculated as a quantifier of heterogeneity and interpreted according to the Cochrane manual. All data analysis was performed using Revman software.

Results: From a total of 1285 potential records identified in the electronic search, six studies eventually fulfilled the eligibility criteria. The six controlled RCTs consisted of 207 patients in the sleep-improving group and 209 patients in the control group. The severity of rest pain was significantly lower in the sleep-improving group compared with the control group at day 1 and day 3 postoperatively; the severity of active pain was significantly lower in the sleep-improving group compared with the control group at day 3 postoperatively. Data concerning analgesic drugs could not undergo a meta-analysis due to the difference of eligible studies. No significant difference was found in the incidence of PONV between the sleep-improving group and the control group.

Conclusion: Improved perioperative sleep, regardless of quality or quantity, could significantly reduce the pain level at the early stage after TKA or THA, thus the total amount of analgesic drugs consumed was decreased, without significant increase in the incidence of PONV.

Key words: Pain; Postoperative Nausea and Vomiting; Sleep; Total Hip Arthroplasty; Total Knee Arthroplasty

Introduction

Total knee and total hip arthroplasty (TKA and THA) are among the most successful operations performed successfully all over the world. Most of the candidates who undergo

these procedures usually suffer from chronic pain, which may be accompanied by unacceptable sleep quality or quantity¹⁻⁵. The patients may experience anxiety and depression, which increases the pain⁶. Moderate to severe pain is commonly

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reported in the postoperative period of TKA or THA patients, causing over-consumption of opioids or other analgesics. Current research is attempting to find ways of reducing postoperative pain through different types of analgesics or different drug-delivery methods⁷⁻⁹. Edwards *et al.*¹⁰ and Cremeans-Smith *et al.*¹¹ demonstrated that functional recovery and quality of life were, to some extent, affected by nocturnal pain; Woolhead *et al.*¹² also found that about 81% of patients suffered from night pain after TKA or THA. Sleep could be disrupted directly by pain, and in turn, poor quality or quantity of sleep might aggravate pain sensation. Büyükyılmaz *et al.*¹³ indicated the correlation between pain intensity and sleep quality existed. However, evidence-based medicine is not sufficient, and there is no reliable evidence for the specific measures and prognosis. The main purpose of this systematic review and meta-analysis is to fill the gap in this field.

Most of the body's systems are in an anabolic state to restore the skeletal and muscular systems during sleep, which are vital processes that maintain mood, memory, and cognitive performance. Many approaches might improve sleep quality or quantity, which could be generally divided into drug-using and non drug-using approaches. The drugs used to induce sleep—hypnotics and sedatives—are a class of psychoactive drugs whose primary function is to induce sleep and to be used in the treatment of insomnia or surgical anesthesia, such as benzodiazepines including estazolam, zolpidem, etc. Melatonin is a hormone that regulates sleep and wakefulness, the secretion of melatonin decreases with age. Exogenous melatonin as a medicine is used for the treatment of insomnia; however, scientific evidence is insufficient to demonstrate a benefit in this area. There are many anti-anxiety drugs, antidepressants, some GABA modulators, etc. that also have sedative effects which may influence patients' sleep, such as pregabalin, duloxetine, escitalopram, etc. But these kinds of drugs have analgesic effect at the same time, which may lead to a confusion of outcomes.

In turn, there were a few trials that aimed to find out the relationship between the perioperative sleep quality or quantity and pain level after TKA or THA, showing conflicting conclusions¹⁴⁻¹⁹. And yet the role of perioperative sleep alone in the postoperative pain and other outcomes has not been investigated through a systematic review. Any methods, either by the usage of hypnotics or simply by prolonging the duration of patients' sleep, could be considered as intending to improve the perioperative sleep. This result could be measured by the Pittsburgh Sleep Quality Index (PSQI)²⁰.

We hypothesized that patients who are undergoing TKA or THA may benefit from the improvement of perioperative sleep, regardless of quality or quantity, resulting in less pain and a better recovery without increased adverse effects. So, in this study, we aim to evaluate this situation from randomized controlled trials (RCTs) and make a further exploration of the efficacy and safety of perioperative sleep improvement in the reduction of postoperative pain and side effects from TKA or THA.

The purpose of TKA and THA is to restore a painless, stable, and functional joint, and severe postoperative pain could delay a patient's recovery. If postoperative pain could be relieved by a good sleep, which means lower consumption of analgesics and lower rate of side effects postoperatively such as nausea or vomiting, it would be a simple and cost-effective method of perioperative pain management.

Methods

This systematic review and meta-analysis was performed following the guidelines of the Cochrane Collaboration²¹ and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement²².

An electronic search for RCTs or controlled clinical trials, with no language limitation, was last performed on 1 September 2020 on the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (1970–September 2020), and EMBASE (1970–September 2020) using appropriate synonyms for sleep, total knee or hip arthroplasty or replacement, to identify published trials evaluating the association between the perioperative sleep improvement and the postoperative pain and side effects. Of all the literature, only RCTs were included.

Patients who underwent TKA or THA would try to improve sleep, regardless of quality or quantity, with or without hypnotics. Drugs with both sedative and analgesic effects were excluded. The primary outcomes measured were the perioperative visual analogue scale (VAS) pain scores and post-surgical analgesics consumption. The secondary outcomes are the incidence of side effects, such as postoperative nausea and vomiting (PONV).

Search methods for identification of studies:

#1 MeSH descriptor: [Arthroplasty, Replacement, Knee] explode all trees.

#2 MeSH descriptor: [Arthroplasty, Replacement, Hip] explode all trees.

#3 MeSH descriptor: [Arthroplasty, Replacement] explode all trees.

#4 Knee arthroplasty.

#5 Knee replacement.

#6 Total knee arthroplasty.

#7 Total knee replacement.

#8 Hip arthroplasty.

#9 Hip replacement.

#10 Total hip arthroplasty.

#11 Total hip replacement.

#12 Joint arthroplasty.

#13 Joint replacement.

#14 Total joint arthroplasty.

#15 Total joint replacement.

#16 Arthroplasty.

#17 Replacement.

#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17.

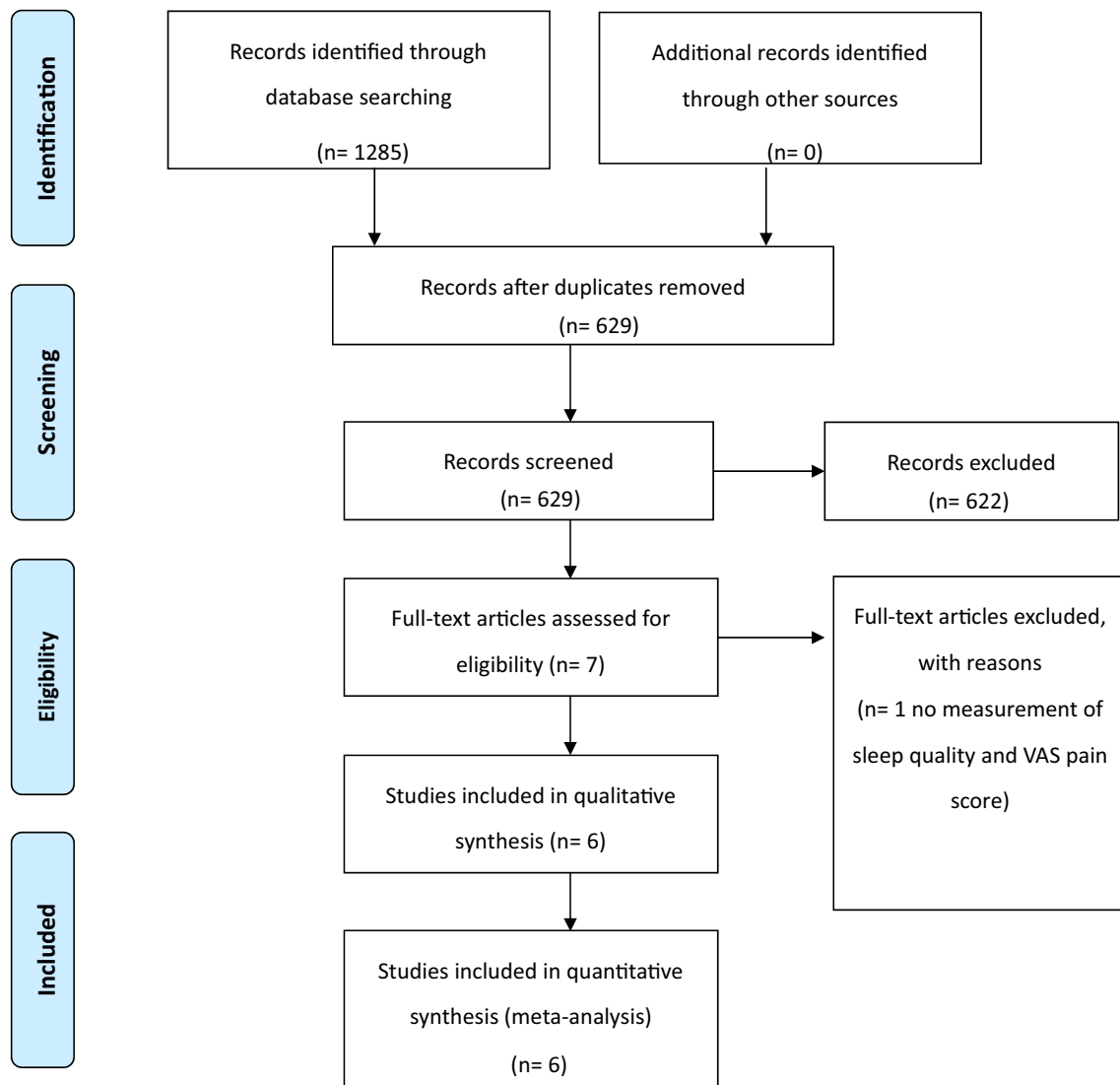


Fig. 1 PRISMA flow diagram.

- #19 MeSH descriptor: [Sleep] explode all trees.
- #20 Sleep.
- #21 #19 or #20.
- #22 Randomized and controlled and trial.
- #23 Controlled and clinical and trial.
- #24 Randomized.
- #25 Placebo.
- #26 Trial.
- #27 #22 or #23 or #24 or #25 or #26.
- #28 #21 and #27.

Selection of Studies

Two reviewers (SS and YW) imported all search results into Endnote X8 software. Titles and abstracts were perused using dropout trends. All duplicates, irrelevant, and non-trial articles were removed and medications which have both sedative

and analgesic effects were also excluded. Articles satisfying the inclusion and exclusion criteria were retrieved in full-text format for further analysis. If uncertainties remain, we would contact the corresponding study author (HQ). If the outcomes presented were not complete or appropriate, the authors were contacted to provide further details. Independent analysis of full-text articles resulted in the exclusion of further articles. Any discrepancies in selection were discussed and resolved. We recorded the selection process in sufficient detail and completed a PRISMA flow diagram (Fig. 1) (Moher 2009). No language restrictions were imposed.

Data Extraction and Management

Two review authors (SS and YW) extracted data (including methods, participants, interventions, comparisons, outcomes,

and other information) independently and entered them in our prespecified data collection form.

Assessment of Risk of Bias in Included Studies

Two review authors (SS and YW) assessed the risk of bias independently for each eligible study by using the “risk of bias” assessment tool. For the missing data, we contacted three study authors of the original report for important missing statistics, but had no effective responses; therefore, we just used the available data.

Data Synthesis

We used Review Manager 5.3 software to perform the pooled analysis for the outcomes from more than one study (RevMan2014). We defined $I^2 < 40\%$ as no statistical heterogeneity among studies, using a fixed-effect model; otherwise, if $I^2 > 40\%$, we used a random-effects model.

Variables to Observe

1. Perioperative visual analogue scale (VAS) pain scores: postoperative rest and active pain were measured respectively with VAS on day 1 and day 3 post-surgery.
2. Post-surgical analgesics consumption: the dosage of analgesic drugs used to relieve postoperative pain, excluding those possessing both sedative and analgesic effects.
3. Postoperative nausea and vomiting (PONV): the common complications when analgesics were applied.

Results

Results of the Search

A total of 1285 potential records were identified from the electronic search, including 656 duplicated articles. By the assessment of the titles, and reading the abstracts, 622 articles were excluded as irrelevant, and one article had no sleep quality or VAS scores mentioned, leaving six studies¹⁴⁻¹⁹ that eventually fulfilled the eligibility criteria. The six controlled RCTs consisted of 207 patients in the sleep-improving group and 209 patients in the control group. The publication time was between the years of 2014 and 2017. Five of the studies used hypnotics as the intervention and had a placebo-controlled group; only the Roehrs 2017 research used as a non-medication intervention, without placebo in the control group.

Description of Studies

The key characteristics of the included studies are illustrated in Table 1. All the relevant literature had relatively small sample sizes, from 18 to 141 patients. The statistical characteristics were extracted from two groups. All the literature included were RCTs. The average age of participants reported in the literature ranged at 55.4–74.6 years. Analgesic drugs were used in safe doses preoperatively and postoperatively.

Risk of Bias in Included Studies

The Cochrane Collaboration’s tool was used to evaluate the risk of bias in all included RCTs. The quality assessment of methodology is shown in Fig. 2. Two researchers, Kirksey 2015 and Liang 2017, had high risk of bias due to incomplete outcome data.

Sleep Quality Improvement

Fan, Liang, and Gong reported sleep quality or efficacy improved in the experiment group when using melatonin, alprazolam, and zolpidem, respectively; by contrast, Kirksey, Krenk, and Roehrs found sleep quality or efficacy had no significant difference between groups. Data was reported in quite different ways, which meant a meta-analysis could not be carried out.

Postoperative Rest Pain Score at Day 1

Three trials reported the details of postoperative VAS pain score on the first day post-surgery at rest. No significant heterogeneity was found ($\text{Chi}^2 = 2.89$, $\text{df} = 2$ [$P = 0.24$]; $I^2 = 31\%$) (Fig. 3). This result showed that the severity of rest pain was significantly lower in the sleep-improving group compared with the control group at day 1 postoperatively (SMD = -0.75 , 95% CI: -1.09 to -0.40 , Test for overall effect: $Z = 4.18$, $P < 0.0001$).

Postoperative Rest Pain Score at Day 3

Three trials reported the details of postoperative VAS pain score at day 3 post-surgery at rest (Fig. 4). Significant heterogeneity was found ($\text{Chi}^2 = 7.00$, $\text{df} = 2$ [$P = 0.03$]; $I^2 = 71\%$); therefore, a random model was performed. The result showed that the severity of rest pain was still significantly lower in the sleep-improving group compared with the control group at day 3 postoperatively (SMD = -0.91 , 95% CI: -1.48 to -0.33 , Test for overall effect: $Z = 3.08$, $P = 0.002$).

Postoperative Active Pain Score at Day 1

Three trials reported the details of postoperative active VAS pain score on day 1 post-surgery (Fig. 5). Significant heterogeneity was found ($\text{Chi}^2 = 6.81$, $\text{df} = 2$ [$P = 0.03$]; $I^2 = 71\%$); therefore, a random model was used. The result showed that the severity of active pain found in the sleep-improving group had no significant difference compared with the control group at day 1 postoperatively (SMD = -0.31 , 95% CI: -0.64 to 0.03 , Test for overall effect: $Z = 1.18$, $P = 0.24$).

Postoperative Active Pain Score at Day 3

Three trials reported the details of postoperative active VAS pain score on day 3 post-surgery (Fig. 6). No significant heterogeneity was found (Heterogeneity: $\text{Chi}^2 = 2.07$, $\text{df} = 2$ [$P = 0.36$]; $I^2 = 3\%$). The result showed that the severity of active pain was still significantly lower in the sleep-improving group compared with the control group at day 3 postoperatively (SMD = -0.49 , 95% CI: -0.88 to -0.09 , Test for overall effect: $Z = 2.42$, $P = 0.02$).

TABLE 1 Characteristics of the included studies

Clinical trials	Intervention/Controlled		Age (Mean)	Gender (% Male)	Anesthesia	Intervention	Time of Intervention	Research Type	Location
	Cases	Gender (% Male)							
Liang 2017	31/30	58/69	62.4/62.5		General anesthesia	Alprazolam	2 Weeks preoperatively, stop 1 day preoperatively	RCT	China
Gong 2015	71/70	13/17	64.8/66.1		Not mention	Zolpidem	1 to 14 days postoperatively	RCT	China
Kirksey 2015	19/18	26/67	70/61.4		CSEA	Melatonin	3 Days preoperatively to 3 days postoperatively	RCT	USA
Roehrs 2017	7.0/11	29/36	55.4/67.5		General anesthesia	EXT TIB (Non medication)	1 Week preoperatively	RCT	USA
Krenk 2014	10.0/10.0	50/30	70.9/70.5		Spinal anesthesia	Zolpidem	Single used first night postoperatively	RCT	Denmark
Fan 2017	69/70	36/40	74.5/74.6		Spinal anesthesia	Melatonin	1 Day preoperatively to 5 day postoperatively	RCT	China

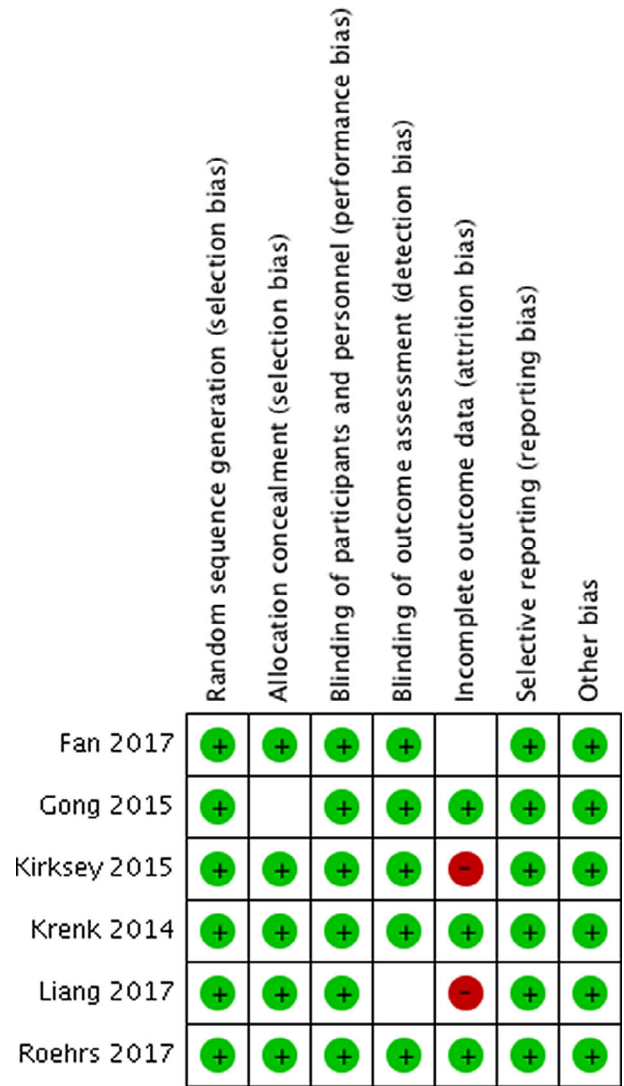


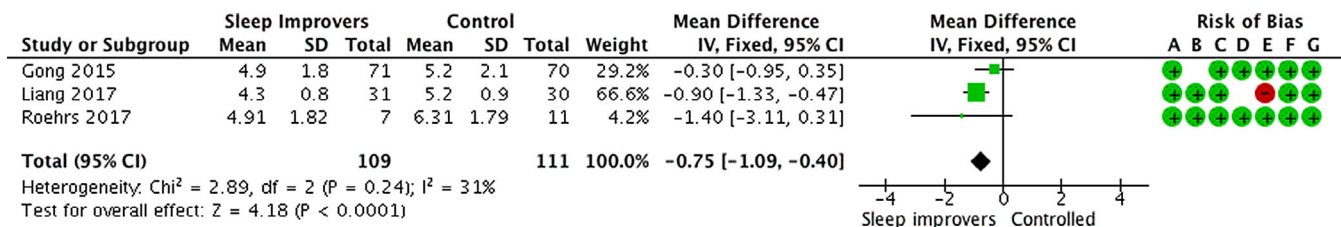
Fig. 2 Risk of bias in included studies. Kirksey 2015 and Liang 2017, had high risk of bias due to incomplete outcome data.

Postoperative Analgesic Consumption

Liang, Gong, and Roehrs reported that the analgesic consumption had a significant decrease in the treatment group; by contrast, Kirksey, Krenk found no significant difference in analgesic consumption between treatment group and control group. Data could not be analysed via meta-analysis due to the difference in analgesic drugs, which varied from morphine to NSAIDs.

Postoperative PONV Incidence

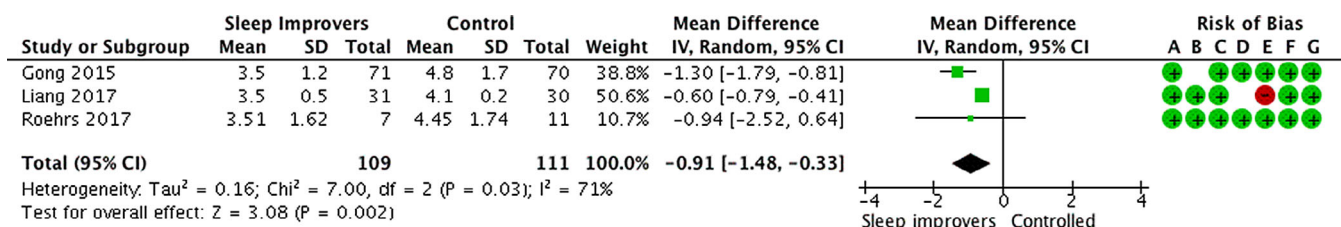
Three trials reported the details of postoperative PONV incidence. Significant heterogeneity was found (Heterogeneity: $\text{Chi}^2 = 4.41$, $\text{df} = 2$ [$P = 0.11$]; $I^2 = 55\%$); therefore, a random model was used. The result showed that no significant difference was found in the postoperative PONV incidence



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

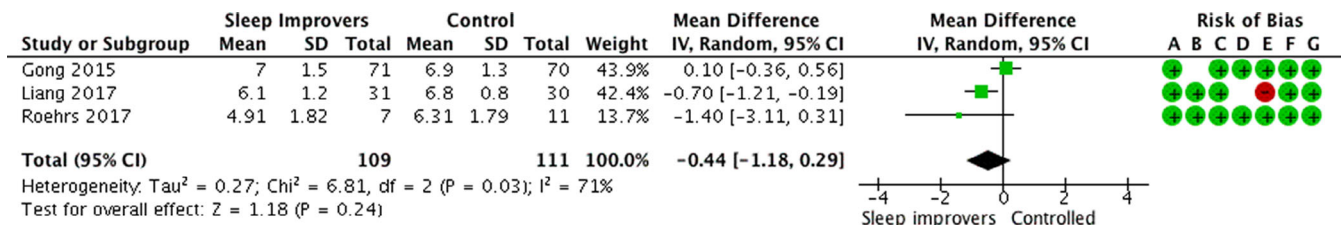
Fig. 3 Postoperative rest pain score at day 1. No significant heterogeneity was found.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Fig. 4 Postoperative rest pain score at day 3. Significant heterogeneity was found, the severity of rest pain was still significantly lower in the sleep-improving group compared with the control group at day 3 postoperatively.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Fig. 5 Postoperative active pain score at day 1. Significant heterogeneity was found, the severity of active pain found in the sleep-improving group had no significant difference compared with the control group at day 3 postoperatively.

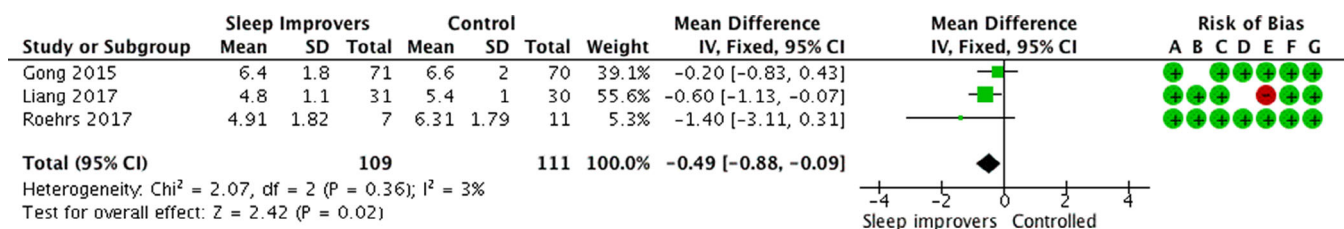


Fig. 6 Postoperative active pain score at day 3. No significant heterogeneity was found.

between the sleep-improving group and the control group (M-H = 0.67, 95% CI: 0.25 to 1.77, Test for overall effect: $Z = 0.81$, $P = 0.42$).

Discussion

The main findings of this systematic review and meta-analysis are: (i) improved sleep in the perioperative period of TKA or THA could reduce the pain level in the early stage after surgery; (ii) the postoperative analgesic consumption would be reduced by improved sleep in the perioperative period; and (iii) the approaches would not increase the incidence of PONV.

There is a growing attention to the significance of sleep. In 2017, the Nobel Prize in medicine was awarded to the study of the effect of circadian rhythms on the expression of *Drosophila* genes²³.

Sleep disturbance is a very common symptom in patient with osteoarthritis before TKA or THA, but the relationship between sleep and pain is rarely researched. Parmelee *et al.*³ confirmed that sleep disturbance in osteoarthritis patients had linkages with pain and depressive symptoms. The authors suggested that sleep could be a mediator of the relationships between pain, disability, and depression. Interventions to improve sleep may disrupt the cycle of poor sleep, pain, and depression, but the mechanism of this finding is still unclear.

Zolpidem, alprazolam, and melatonin are commonly used drugs in the clinical setting to induce sleep. In China, melatonin was approved as a health food by Chinese State Food and Drug Administration (CSFDA), not a drug. In all of the studies included in the systematic review, drugs were used in safe doses, even lower than the general dose. There were conflicting results among trails concerning sleep quality or quantity. Therefore, the application of these drugs did not increase the risk of cognitive disorder and falls. Among these drugs, melatonin has significant difference compared to the other two. According to research by Cronin *et al.*²⁴,

melatonin replacement might prevent melatonin suppression and associated sleep disturbance after surgery, which means the use of melatonin might be more physiological.

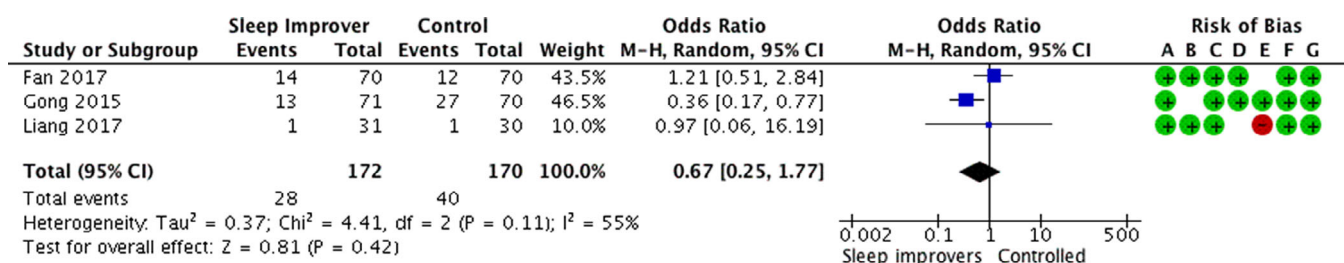
With the rapid increase in the amount of TKA and THA surgeries and the popularization of enhanced recovery after TKA or THA, the refinement of perioperative management of patients has become a current research focus. In China, a series of expert consensus have been released^{25,26}; among them there are recommendations for perioperative sleep management in patients undergoing TKA or THA.

Our meta-analysis of the pooled data evaluated the relevant literature systematically and created a profound understanding of the effectiveness and safety of perioperative improvement of sleep quality or quantity in the management of postoperative pain after TKA or THA.

To assess the effect of perioperative sleep improvement in relieving postoperative pain, VAS score was the most often used measurement in clinic. In part of the study, the postoperative VAS pain score at 24 and 72 h was used as the point of early-stage postoperative pain assessment. The overall results demonstrated that, compared with the controlled group, improved perioperative sleep could significantly reduce the level of early-stage rest pain at 24 and 72 h, and the level of active pain at 72 h postoperatively, which confirmed our hypothesis. However, compared with the control group, significant reductions in VAS score were not found in active pain 24 h postoperatively in the sleep-improving group, which might be due to the reason that the intensity of active pain at 24 h postoperatively was too high to reduce.

The postoperative analgesic drugs varied among studies from opioids to NSAIDs, but the amount of analgesic consumption also had a significant reduction. This result indicated the medical cost may decline by the simple means of improved sleep.

PONV were the common complications when analgesics were applied. As shown in Fig. 7, the incidence of those

**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
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- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Fig. 7 Incidence of PONV. Significant heterogeneity was found, no significant difference was found in the postoperative PONV incidence between the sleep-improving group and the control group.

side effects showed no significant difference between the two groups. This result indicated that the usage of hypnotics or other means to improve sleep in patients undergoing TKA or THA would not increase the incidence of PONV. Many factors might be related to the result, such as the different methods of anesthesia or decrease of analgesic drugs use.

As far as we know, this systematic review and meta-analysis might be the first review on the effect of perioperative sleep management on early-stage postoperative pain and adverse effects after TKA or THA. All the literature included were RCTs, which are the highest level of evidence. However, due to the various study designs and the analytical approach, heterogeneity in those studies may occur.

There are several potential limitations to our meta-analysis. Since most of the included literature was conducted by anesthetists or physicians, some valuable information, such as operative approach, types of prosthesis, and methods of fixation, were not reported in detail. However, it is believed that this information is usually very important to orthopaedic surgeons, and perioperative sleep has the large effect on the degree of postoperative pain, so these factors need to be taken into account in future studies. Also, there were different ways of improving the sleep quality or quantity of the patients, some of them used drugs, others did not. The mechanism of drug action is not the same, which has a certain effect on the persuasion of the conclusion and points to a direction for future research. The usage of drugs to improve patients' sleep also had a potential risk to increase the occurrence of postoperative delirium and cognitive dysfunction; however, there was a study²⁷ comparing different kinds of postoperative delirium from sleeping drugs, but the sample size was small with few similar studies.

Conclusions

Prolonged sleep duration, rapid sleep deprivation, or reduced night awakenings can improve sleep quality or quantity to a certain extent. According to the meta-analysis results, our hypothesis was confirmed that improved perioperative sleep, regardless of quality or quantity, could significantly reduce the pain level at the early stage after TKA or THA. The total amount of analgesic drug consumption was decreased, without significant increase to the incidence of PONV. Therefore, according to the existing evidence, it is necessary to enhance perioperative sleep management for patients undergoing TKA or THA, regardless of the means, to improve the quality or quantity of sleep.

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Authors Contributions

Songpo Shen (SS), Yingjie Wang (YW), Qiang Zhang (QZ), Hua Qiang (HQ), Xisheng Weng (XW). Conceiving the review: SS, YW, QZ, HQ, and XW. Coordinating the review: SS. Undertaking manual searches: SS and YW. Screening search results: SS, YW, QZ, HQ, and XW. Organizing retrieval of papers: SS, YW, and QZ. Screening retrieved papers against inclusion criteria: SS, YW, QZ, HQ, and XW. Appraising quality of papers: SS, YW, and QZ. Abstracting data from papers: SS and YW. Writing to authors of papers for additional information: SS and YW. Providing additional data about papers: QZ. Obtaining and screening data on unpublished studies: SS and YW. Entering data into Review Manager 5 (RevMan 2014): SS and YW. RevMan statistical data: SS and

YW. Interpretation of data: SS and YW, QZ. Statistical inferences: SS and QZ. Writing the review: SS, YW, QZ, HQ, and XW. Guarantor for the review (one author): SS. Persons responsible for reading and checking review before submission: SS and QZ.

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