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Study Protocol

Effects of zolpidem administration on postoperative pain in patients after total knee arthroplasty: Study protocol for a randomized controlled trial

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Abbreviations: TKA: Total knee arthroplasty; VAS: Visual analogue score; ROM: Range of Motion; RCT: Randomized controlled trial; PSG: Polysomnography; PCA: Patient-controlled analgesia; PONV: Postoperative nausea and vomiting

Abstract

Background: Postoperative patients commonly have sleep disturbances. Sleep quality is associated with pain intensity. Thus, a vicious cycle of poor sleep quality that increases pain and disrupts sleep quality occurs. However, little is known about the impact of postoperative sleep management on postoperative pain and functional recovery after total knee arthroplasty (TKA). Here, we designed a randomized controlled trial to investigate the effects of zolpidem on postoperative pain control and functional recovery after TKA. We hypothesized that zolpidem would decrease postoperative pain and simultaneously improve knee ROM and sleep quality.

Methods: This randomized, prospective, controlled trial will include 88 patients scheduled to undergo unilateral TKA. Patients will be randomized to one of the two groups, one of which will receive zolpidem postoperatively. The primary endpoint will be the visual analogue scale (VAS) pain score on postoperative day 2. Secondary outcomes are sleep quality (nocturnal arousal, frequency of body movements, and sleep effects), knee joint range of motion, opioid consumption, incidence of postoperative nausea and vomiting (PONV), and rescue analgesic consumption. Protocols were developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

Discussion: Sleep quality significantly affects pain intensity. Therefore, it is hypothesized that postoperative administration of hypnotics to improve sleep quality may reduce pain intensity. In this study, we hypothesized that zolpidem administration will decrease postoperative pain, which will simultaneously improve knee joint ROM and sleep quality. This randomized, controlled trial will provide insight into optimizing perioperative sleep management strategies by evaluating the effects of postoperative hypnotic administration in patients post-TKA. These results of the study may improve clinical practice in terms of perioperative sleep management and enhance patient recovery and satisfaction.

Name of the registry: Effects of Sleep Management on Postoperative Pain in patients after total knee arthroplasty. A randomized controlled study.

Trial Registration: UMIN000039116

Date of registration: 2020/Jan/15

URL of trial registry: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000044407

Background

Moderate to severe pain occurs after total knee joint replacement surgery [1-4]. Severe postoperative pain increases the need for analgesics, decreases motivation for physical activity, and decreases willingness to participate in rehabilitation. This results in a longer hospital stay and delayed return to society [1-4].

Postoperative pain interferes with sleep [5]. Deterioration in sleep quality also increases pain intensity [5]. Half of postoperative patients experience sleep disturbances during hospitalization [6,7]. Sleep quality and pain intensity are bidirectionally related [8,9]. The quality of sleep is related to the intensity of pain the next day, and pain during the day is related to the quality of sleep that night [8,9]. Poor sleep quality increases pain intensity, which further worsens the quality of sleep and creates a vicious cycle.

Postoperative sleep disruption causes postoperative pain and functional limitation in TKA patients [10]. This suggests that postoperative sleep improvement might lead to pain relief and functional recovery. However,

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patients are prescribed various medications to control pain but are rarely prescribed medications that target sleep difficulties as a part of postoperative interventions [10]. Although improved sleep quality has been highlighted as an important outcome across studies, there is a gap in the clinical guidelines for the management of acute postoperative pain [11], and little is known about the effect of postoperative sleep control on postoperative pain and functional recovery after TKA.

It is speculated that improving the quality of postoperative sleep can reduce pain and promote functional recovery. However, prescribing analgesics is considered in clinical practice, but prescribing sleeping pills for sleep disturbances is rarely done. Although the importance of improving sleep quality has been reported, there is a gap with its application in the actual clinical practice [10]. Sleep disturbances after TKA exacerbate postoperative pain and impair functional recovery [11], but the impact of sleep control on postoperative pain and functional recovery remains unelucidated.

Only two randomized controlled trials (RCTs) have investigated the effects of interventions for postoperative sleep on postoperative pain after TKA. Krenk et al. evaluated the effect of zolpidem on postoperative sleep following TKA [12] and concluded that zolpidem did not significantly improve sleep architecture, although there was a feeling of improvement in sleep quality and fatigue associated with fewer postoperative arousals.

Gong et al. investigated sleep quality in the early stages after TKA [5]. The results showed that the patients treated with zolpidem had improved sleep quality, decreased pain scores, and increased active range of motion (ROM).

In these studies, the length of hospital stay was very short, and only a few sleep assessments were conducted. therefore, the effect of the intervention on sleep was unclear. In addition, a drainage tube and bioelectrodes were installed, which may not allow for a true post-operative assessment because they could limit the behavior of patients post-operatively.

Here, we designed a randomized controlled trial to investigate the effects of zolpidem on postoperative pain control, ROM, and sleep quality after TKA. Measurements are to be performed for 7 consecutive days after surgery. No contraptions for drainage are to be used after surgery, and sleep quality will be monitored by a mattress-type actigraphy without direct sensors to allow for free movement [13]. We hypothesized that the administration of zolpidem would reduce postoperative pain scores and improve ROM and sleep quality.

Methods/Design

Study design

This open-label, single-center, prospective RCT focuses on postoperative sleep conditions, pain, and ROM during the 7-day period after TKA, and will be conducted at our university hospital. The protocol was prepared according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The study protocol has been peer-reviewed and was approved by the institutional review board of our hospital (Mito Kyodo General hospital Ethics Committee).

Participants

Patients with osteoarthritis or rheumatoid arthritis who are scheduled for unilateral primary TKA will be recruited. At least 20 years of age is required, as is the ability to comprehend and follow the study protocol, as well as the ability to provide written informed permission prior to enrollment. Those who are allergic to zolpidem or any of its components, as well as other drugs, have gastrointestinal hemorrhage or ulcers, or have a history of severe hepatic, renal, or cardiovascular failure will be excluded from the study. Those who have had therapy for a sleep issue in the past or who are currently undergoing treatment for a sleep disorder will be excluded as well (Figure 1).

Randomization

Randomization will be performed centrally using the University Hospital Medical Information Network (UMIN) Internet Data and Information System for Clinical and Epidemiological Research, Cloud version Center. A computer-generated scheme, matched by illness (osteoarthritis or rheumatoid arthritis), will be used to randomize patients (1:1 ratio). Within a 14-day period before surgery, the patients will be assigned to either the intervention or control group.

Interventions

Patients in the zolpidem group will receive 5 mg of zolpidem tartrate orally at 9 PM for 7 consecutive days after surgery. Patients in the control group will not receive any hypnotic medication during this period.

Perioperative analgesia

All surgeries are performed under general anesthesia with a single-dose sciatic nerve block and femoral nerve block using ultrasound guidance and an electrical nerve stimulator. A patient-controlled analgesia (PCA) pump with fentanyl is used immediately postoperatively, and the PCA is withdrawn at 9 am on the second postoperative day. The use of diclofenac suppositories for rescue analgesia is permitted. The amount of fentanyl consumed, and rescue used will be recorded. In addition, patients will be given 400 mg celecoxib 2 h after surgery and an additional 200 mg 6 h after that. Thereafter, 200 mg is administered twice daily until postoperative day 7 [13].

Surgical procedure

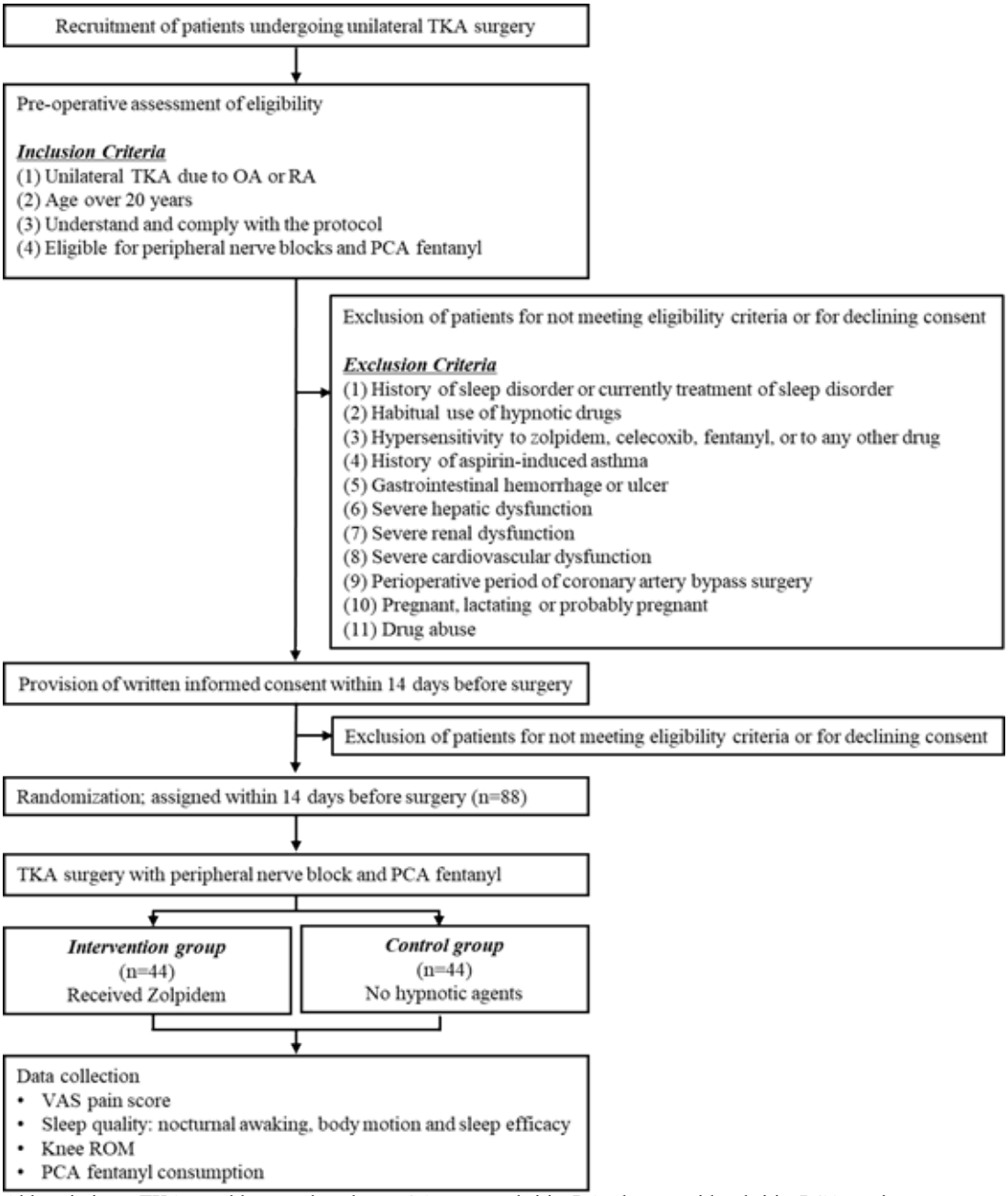
For all procedures, a pneumatic tourniquet will be employed. A medial parapatellar approach will be used to implant a cemented posterior-stabilized prosthesis (Triathlon Systems; Stryker Orthopedics, NJ). Drain will not be used to allow for unrestricted movement [13]. A clinically prescribed postoperative rehabilitation program will be followed. ROM training and walking practice will start the day after the surgery [13].

Primary outcome measure

Patient-reported VAS pain scores at 9 AM on postoperative day 2 will be considered the primary outcome measure in this study. Participants will be provided detailed instructions regarding the proper use of the VAS before the study. On the VAS, 0 and 100 represent no pain and the worst imaginable pain, respectively.

Secondary outcome measures

Measurement of sleep quality will be performed for 7 days after surgery using the SLEEPSCAN mattress-type actigraphy device (Tanita Corporation, Tokyo, Japan), which does not require bioelectrodes or other direct sensors to be attached to the human body. Sleep quality will be evaluated in terms of



Abbreviations: TKA, total knee arthroplasty; OA, osteoarthritis; RA, rheumatoid arthritis; PCA, patient-controlled analgesia

Figure 1. *Enrollment Flow diagram of the trial design.*

nocturnal awakening time, frequency of body movements, and sleep efficacy.

Active ROM of the knee joint will be measured on postoperative days 2 and 7. The VAS pain scale will be measured daily at 9:00 a.m. until postoperative day 7. Total fentanyl consumption by PCA will be assessed at 9:00 AM on postoperative day 2. The incidence of PONV, frequency of antiemetic use, and need for rescue analgesics will be recorded for the first 7 postoperative days.

Assessment of safety

Study drugs will be stopped immediately in participants showing significant deterioration caused by severe adverse events, as determined by common terminology. The criteria for adverse events (CTC-AE) ver. 4.0 will be reported to the principal investigator who will declare any unexpected serious adverse reaction to the institution.

Data collection

Data will be collected at each time point by a specific research assistant to reduce variability in patient descriptions of VAS pain scores, fentanyl consumption, PONV, and rescue analgesic use. To minimize procedure discrepancies, a specific physical therapist will measure active ROM using a digital goniometer. The physical therapist and research assistant will not be involved in the clinical management of the patient (Table 1).

Table 1. *Data collection schedule*

	Study period							
	enrollment	**allocation**	**Post-allocation**					**Discontinuance**
timepoint	**Before surgery**		**surgery**	**Post-surgical days**				
	14 days	**within 14 days**		**1**	**2**	**3-6**	**7**	
Enrollment								
Eligibility screen	●							
Informed consent	●							
Allocation		●						
Interventions								
Zolpidem group	←	←	←	←	↔	↔	↔	→
Control group	←	←	←	←	↔	↔	↔	→
Assessment								
VAS pain score		●		●	●	●	●	●
Sleep Quality		●*		●*	●*	●*	●*	●*
ROM		●			●		●	●
PCA Fentanyl consumption					●			●
PONV				●	●	●	●	●
Rescue consumption				●	●	●	●	●
Adverse events				●	●	●	●	●

* Overnight measurements

Abbreviations: VAS, visual analog scale; ROM, range of motion of the knee; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting

Right after each patient completes the study, the collected data will be transferred to the UMIN Internet Data and Information System for Clinical and Epidemiological Research, Cloud version Center.

Sample size calculation

Using a power analysis based on previously published data evaluating the efficacy of zolpidem on VAS pain scores following TKA, sample sizes are chosen to detect significant differences [5]. VAS pain scores were previously reported to be 35 ± 12 mm in the zolpidem group and 48 ± 17 mm in the control group h hours after TKA [5]. To detect a significant difference, we hypothesized that the VAS pain scores for the zolpidem and control groups would be 35 ± 20 mm and 48 ± 20 mm, respectively. Power and sample size calculations indicated that a sample size of 40 patients per group would provide 80% power (alpha ¼ 0.05, two-tailed) to detect a minimal difference of 10 mm between the two groups. Assuming a 10% dropout rate, we determined that a minimum of 88 patients would be required, which is 44 patients per group.

Statistical analysis

All patients undergoing randomization will be subjected to an intention-to-treat analysis. Comparisons between the zolpidem and control groups will be made using the Wilcoxon signed-rank test, which is a nonparametric test. All tests will be two-sided. The significance level will be set at $p<0.05$.

Discussion

This randomized controlled trial design was developed to address the hypothesis that administration of zolpidem after TKA would reduce postoperative pain score and improve ROM and sleep quality.

Sleep quality is closely related to pain intensity [8,9]. Postoperative sleep disturbances contribute to postoperative pain and functional limitations in TKA patients [13]. Patients are prescribed a variety of medications to control pain, but rarely are they prescribed medications that target sleep disturbances as part of a postoperative intervention. Therefore, we hypothesized that postoperative administration of hypnotic medications could improve sleep quality and ultimately lead to a reduction in pain intensity and persistent postoperative pain.

Poor sleep quality is commonly managed with hypnotics such as zolpidem, zopiclone, melatonin, and benzodiazepines. These medications may be prescribed postoperatively to improve sleep quality [9,14].

Zolpidem, a nonbenzodiazepine, is a drug commonly used in clinical practice to induce sleep [14]. It has a very short half-life of approximately 2 hours, which results in earlier onset of sleep and minimizes daytime residual effects at low doses. Administration of this drug does not increase the risk of cognitive impairment or falls [12]. It is considered safe and effective because patients undergoing TKA are usually elderly.

To date, only two RCTs have examined the effect of zolpidem

administered for postoperative sleep on postoperative pain after TKA [5,15]. Both studies used PSG for sleep assessment. Compared to subjective methods such as questionnaire testing, objective methods of measuring sleep quality, such as PSG and actigraphy, are considered more accurate [16]. PSG is often used to assess sleep stages but requires a directly implanted sensor. This limits freedom of movement, which may affect the results, and there are also problems related to sensor placement immediately after the procedure. In this study, a mattress-type actigraphy was employed to evaluate sleep quality. This technique uses bioelectrodes on the human body to allow free movement and is a reliable and simple method for monitoring sleep-wake rhythms without the use of direct sensors [13,17,18]. We believe that the findings of this study will reflect the reality of clinical practice.

A limitation of this study is that it will be open labelled. However, our data will come from patient-reported outcomes, and participants will not be influenced by any other information. Patient–reported outcomes will provide a better depiction of the clinical condition of patients. Therefore, we believe that this study will provide some insights into postoperative sleep control with multimodal analgesia, which could help improve perioperative clinical practice.

Clinical relevance and importance

This randomized controlled trial will provide insights into the optimization of perioperative sleep management strategies by evaluating the effects of postoperative administration of hypnotic medications in patients after TKA. These results could improve clinical practice for perioperative sleep management, as well as patient recovery and satisfaction.

Trial status

This study is ongoing and patient recruitment has not been completed at this time. Patients were recruited after obtaining approval from the ethics committee. The first participant was enrolled on June 6, 2020. The recruitment is scheduled to be completed on December 31, 2022.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Tsukuba University Hospital Mito Clinical Education and Training Center, Mito Kyodo General Hospital (No 19-32). All changes to the protocol should be maintained as a protocol supplement. Modification of the protocol and informed consent must be submitted to the ethics committee for review. Written informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

TM has received funding from Japan Society for the Promotion of Science (JSPS) KAKENHI (19K18486)..

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Authors' contributions

TM was the principal investigator of the manuscript. TM conceived the study, led the proposal and protocol development, and drafted and wrote this manuscript. NT contributed to the development of anesthetic protocols. EM contributed to the development of the statistical analysis plan. NT and EM contributed to the development of the study design and proposal. ST and YI contributed to the development of knee ROM measurements. All authors read and approved the final manuscript.

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