

Perioperative Music Therapy Enhances Pain Management and Sleep Quality in Patients Aged 50–70 Years Undergoing Total Knee Arthroplasty: A Randomized Controlled Trial

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Purpose: Music therapy (MT) has recently shown its value in alleviating pain in surgical patients. To explore its perioperative analgesic effects in patients undergoing total knee arthroplasty (TKA) under general anesthesia, we conducted a randomized single-blind clinical trial.

Patients and Methods: Eighty-six patients aged 50–70 years (ASA II–III) undergoing TKA at Honghui Hospital were randomly assigned to either a music group or a control group. The music group listened to music via headphones from 10 minutes before anesthesia induction until awakening after surgery. The control group wore headphones without music for the same period. All patients received standardized general anesthesia with BIS values maintained between 40 and 60. Postoperatively, a patient-controlled analgesia (PCA) pump was used. Outcome measures included Visual Analogue Scale (VAS) pain scores, analgesic dosage, PCA usage, Nausea VAS (NVAS), Pittsburgh Sleep Quality Index (PSQI), and satisfaction with analgesia at 1h, 2h, 3h, 12h, 24h, and 48h after surgery.

Results: The music group showed significantly fewer PCA presses at 1h and 3h post-operation ($p < 0.05$), with no significant differences at later time points. Sleep quality and analgesia satisfaction on the first postoperative night were also significantly better in the music group ($p < 0.05$). No significant differences were found in VAS, NVAS, or analgesic dosage at most time points.

Conclusion: Perioperative music therapy can effectively support PCA for a specific postoperative period, alleviating early postoperative pain, enhancing sleep, and improving patient satisfaction with analgesia in TKA patients.

Keywords: music therapy, self-controlled analgesia, total knee arthroplasty, pain manage

Introduction

Total knee arthroplasty (TKA) is currently the most effective treatment for end-stage knee osteoarthritis and rheumatoid arthritis, significantly reducing pain, improving joint mobility, and enhancing patients' quality of life.^{1,2} As a well-established surgical procedure, TKA is projected to have an annual surgical volume of 3.416 million cases in the United States by 2040, according to recent studies.³ However, postoperative pain remains an inevitable challenge of TKA and is a primary predictor of patient dissatisfaction following the procedure.⁴ Acute postoperative pain is more likely to result in poor sleep quality, impaired postoperative mobility, and even chronic pain development.⁵ Perioperative pain is not only a physical trauma for patients but also a significant psychological stressor.⁶

Patient-controlled analgesia (PCA) is a commonly used method for acute postoperative pain management; however, approximately 28% of patients still experience moderate to severe pain despite using PCA.⁷ According to pain



management theory, combining non-pharmacological strategies with analgesics is more effective than relying on medication alone.⁸ Studies have shown that non-pharmacological adjuncts to pain management can effectively reduce intraoperative sedative and analgesic requirements, enhance patient satisfaction, and mitigate postoperative pain.^{9–11}

Music therapy refers to a therapeutic approach that achieves healing effects through singing, listening to selected music, or playing musical instruments. It is an interdisciplinary product of medical psychology, music, and humanities.¹² Over the past two decades, the potential role of music therapy in perioperative interventions has gained increasing attention.^{13,14} Studies have shown that music can modulate neural oscillatory activity, notably increasing alpha rhythm (8–12 Hz) power in the cortex. This specific brainwave pattern is associated with a state of relaxed alertness and reduced physiological arousal. Furthermore, music engages the limbic system, particularly structures like the amygdala and hippocampus, and can stimulate the release of endogenous opioids (eg, beta-endorphins) within central nervous system pathways involved in pain modulation and reward.¹⁵ In addition, listening to music can activate the parasympathetic nervous system while suppressing the sympathetic nervous system.¹⁶ However, the outcomes of music interventions in clinical practice have shown inconsistency.¹⁴ To evaluate the efficacy of music therapy for acute postoperative pain relief in TKA patients, this study designs a single-blind randomized controlled trial to explore the impact of perioperative music therapy on postoperative PCA usage, pain intensity scores (VAS), sleep quality (PSQI), and patient satisfaction with analgesia.

Methods and Materials

Design

This study is a single-blind randomized controlled trial on music therapy and pain management following knee arthroplasty from January 2023 to January 2024 (Figure 1). It has been approved by the Medical Ethics Committee of our hospital (No. 201901008) and registered in the Chinese Clinical Trial Registry (ChiCTR2000032027). Informed consent was obtained from patients and their families before the experiment.

Sample Size Calculation

A two-sample *t*-test was used to estimate the required sample size. The significance level was set at $\alpha = 0.05$, and the power ($1-\beta$) at 90% ($\beta = 0.1$). Based on a standard deviation (S) of 0.91 and an expected between-group difference (δ) of 0.47, the following formula was applied: $n = \left\lceil \frac{(Z_{\alpha/2} + Z_{\beta}) * S}{\delta} \right\rceil$. Thus, the minimum sample size was calculated to be 39 patients per group. Considering a 10% dropout rate, the final sample size was increased by 4 participants, resulting in 43 patients per group.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Patients aged 50 to 70 years; (2) Classified as American Society of Anesthesiologists (ASA) physical status II–III; (3) Scheduled for elective total knee arthroplasty under general anesthesia; (4) No hearing impairments, language difficulties, or neurological disorders; (5) Able to understand and use the Patient Controlled Intravenous Analgesia (PCIA) pump, Visual Analogue Scale (VAS), and Nausea Visual Analogue Scale (NVAS);

Exclusion criteria: (1) History of chronic alcohol abuse or substance use disorder; (2) Long-term opioid use; (3) Morbid obesity, defined as BMI > 40 kg/m²; (4) Neurological conditions (eg, Parkinson's disease, stroke sequelae) that may affect pain perception or cognition; (5) Participation in other clinical trials that may interfere with the outcomes of this study.

The surgeries were conducted by the same group of doctors to avoid differences due to variations in surgical technique. Patients were randomly assigned to the music group and the control group using a random number table, with 43 patients in each group.

Anesthesia Method

Upon entering the operating room, patients were monitored for blood pressure (BP), heart rate (HR), oxygen saturation (SpO₂), electrocardiogram (ECG), and bispectral index (BIS). Combined intravenous and inhalation general anesthesia

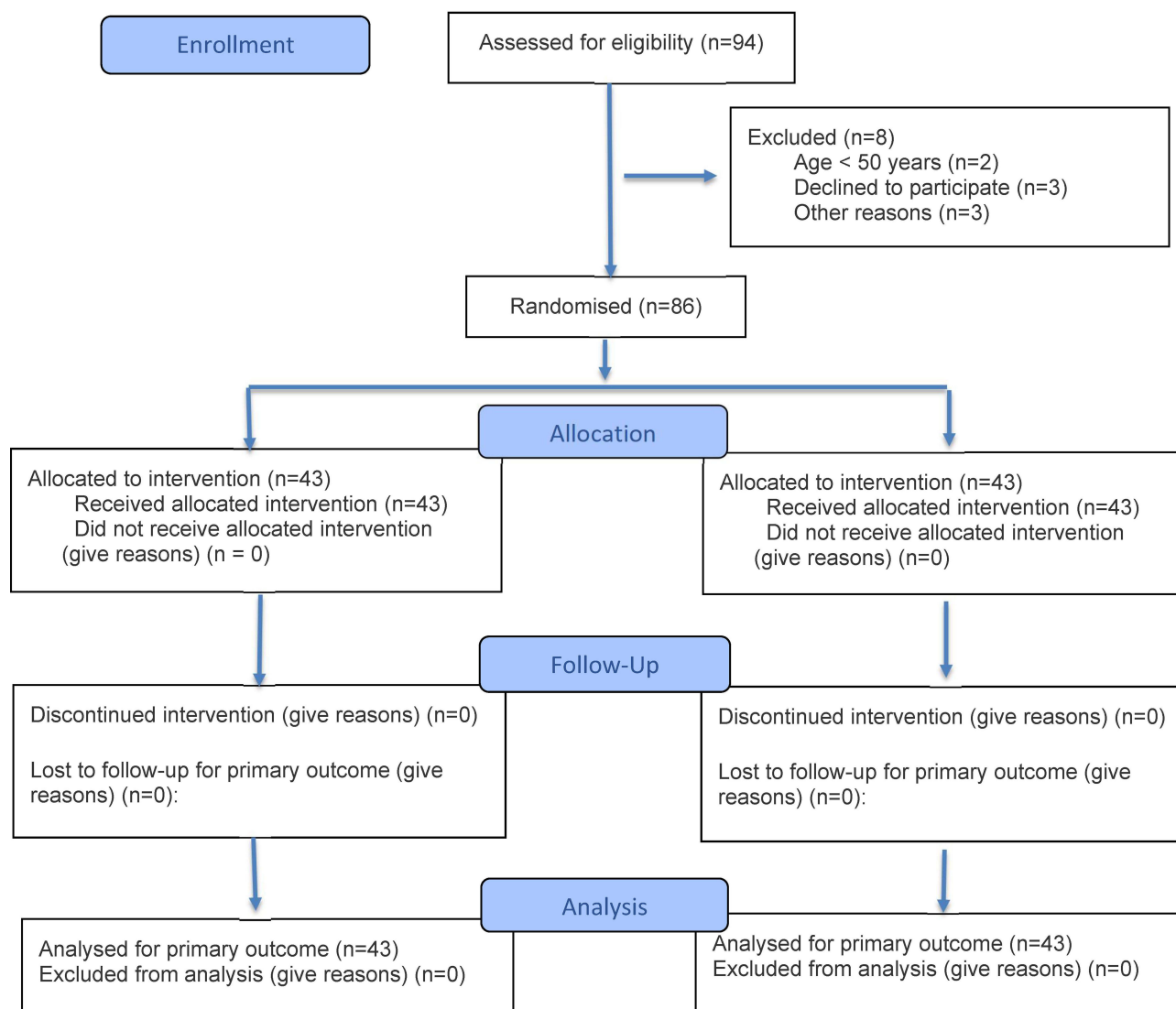


Figure 1 CONSORT flowchart.

was used. For anesthesia induction, midazolam 1 mg, sufentanil 0.3 $\mu\text{g}/\text{kg}$, etomidate 0.3 mg/kg, and rocuronium 0.6–0.8 mg/kg were administered, followed by mechanical ventilation after tracheal intubation. Anesthesia maintenance was achieved through continuous intravenous infusion of propofol at 4–12 mg/kg/h and remifentanyl at 0.1–0.3 $\mu\text{g}/\text{kg}/\text{min}$, maintaining the BIS value between 40 and 60.

Pain Management Method

After the surgery, once the patient was fully awake, they were connected to a Bater electronic analgesia pump. The PCA setup included 30 μg of dexmedetomidine (Yangtze River Pharmaceutical Group Co., Ltd., batch number: 17091321), 10 mg of tropisetron (Shandong Luoxin Pharmaceutical Group Co., Ltd., batch number: 517032241), diluted with 100 mL of 0.9% sodium chloride injection. PCA parameters were set as follows: loading dose of 2 mL, continuous infusion rate of 2.0 mL/h, patient-controlled dose of 1.5 mL per use, maximum dose of 15 mL, and lockout time of 10 minutes.

Music Therapy Method

The music group selected three preferred songs from a curated library of relaxing instrumental music provided during the pre-anesthesia visit one day before the surgery. This library consisted predominantly of Western classical music (eg, slow

movements from sonatas or concertos), Chinese traditional instrumental music (eg, Guzheng, Pipa solos), and nature sounds blended with soft harmonies. Each selected song had a duration ranging from 4 to 6 minutes, forming a personalized playlist of approximately 12–18 minutes total. Playlists were set to loop continuously. On the day of surgery, after entering the operating room, patients in the music group began wearing sound-isolating headphones (SONY WH-1000XM3, both with active noise cancellation enabled) 10 minutes before anesthesia induction and played their selected music at a pre-set comfortable volume level (60 dB maximum, adjusted once by the patient upon initiation if desired, within safe levels to prevent hearing damage). The control group patients also wore the same model of headphones 10 minutes before anesthesia induction, but they did not listen to music; the headphones were inactive. They were informed that the purpose of wearing headphones was to reduce ambient operating room noise (typically ranging between 50–65 dB(A) from equipment) and alleviate anxiety. Both groups maintained the aforementioned protocol throughout the entire perioperative period until the patient awakened post-surgery and was deemed responsive by the anesthesiologist, after which the tracheal tube was removed and the headphones were taken off before returning to the recovery room. The total music listening duration varied per patient based on surgery and anesthesia time, but encompassed the period from pre-induction (10 min prior) to emergence (typically 120–180 minutes later), ensuring continuous auditory stimulation during anesthesia administration and surgery.

Observation Indicators

Pain scores (VAS) were recorded for the patients at 0, 1, 2, 3, 12, 24, and 48 hours postoperatively while lying supine. A 10 cm horizontal line was drawn on paper, with one end marked as 0 (indicating no pain) and the other end as 10 (indicating severe pain); the middle section represented varying degrees of pain. Patients marked their level of pain along the line based on their self-assessment. The amount of analgesics used, the number of PCA pump activations, and the severity of NVAS were also recorded. The NVAS was represented on a 100mm ruler divided into 10 segments, with 0 on the far left indicating no nausea and 10 on the far right representing the most severe nausea imaginable. The sleep score on the night following surgery was assessed using the Pittsburgh Sleep Quality Index (PSQI), which measures sleep quality based on factors such as sleep disturbances, sleep duration, and sleep efficiency. Higher scores for sleep duration and efficiency and lower scores for sleep disturbances indicate better sleep quality for the patient. Pain satisfaction was evaluated using a four-point scale: very satisfied, somewhat satisfied, satisfied, and unsatisfied.

Statistical Analyses

Before conducting parametric tests, the normality of continuous variables was assessed using the Shapiro–Wilk test, and all data were found to comply with a normal distribution. Continuous data were expressed as mean \pm standard deviation, and comparisons between groups were analyzed using independent samples *t*-test. Repeated measures data were analyzed using repeated measures ANOVA. Categorical data were presented as frequencies (percentages), and comparisons between groups for categorical data were performed using χ^2 test. Statistical analyses were conducted using SPSS version 27.0, with a significance level set at $p < 0.05$ indicating statistical significance.

Results

General Information

From June to December 2019, 86 elderly patients scheduled for elective total knee arthroplasty were selected. They were classified as ASA (American Society of Anesthesiologists) II–III, with no hearing impairments, language difficulties, neurological imbalances, history of alcohol abuse, or drug addiction. There were no statistically significant differences ($p > 0.05$) in gender composition, age, weight, height, disease duration, comorbidities, smoking history and other general data between the two groups, indicating comparability (Table 1).

Comparison of VAS Scores at Postoperative Time Points

The VAS scores at various postoperative time points showed no statistically significant differences between the two groups ($p > 0.05$) (Table 2).

Table 1 General Information ($\bar{x} \pm s$)

Group	Gender (Male/Female)	Age	Weight (kg)	Height (cm)	Surgical Duration (h)	Disease Duration (months)	Comorbidities (n%)	Smoking History (n%)
Music group (n = 43)	27/16	59.6 ± 7.3	63.1 ± 4.1	163.3 ± 3.2	2.1 ± 0.6	3.27±0.5	5/11.6%	6/14.0%
Control group (n = 43)	25/18	61.1 ± 7.8	61.9 ± 4.6	162.7 ± 2.9	2.2 ± 0.7	3.41±0.2	6/14.0%	4/9.30%
<i>p</i>	0.659	0.360	0.205	0.365	0.479	0.531	0.326	0.291

Notes: Independent samples *t*-test for continuous variables; χ^2 -test for categorical variables.

Table 2 VAS Scores at Various Postoperative Time Points ($\bar{x} \pm s$)

Group	1h After Surgery	2h After Surgery	3h After Surgery	12h After Surgery	24h After Surgery	48h After Surgery
Music group (n = 43)	3.5 ± 1.2	2.1 ± 1.1	1.4 ± 0.6	1.4 ± 0.4	1.2 ± 0.4	1.1 ± 0.3
Control group (n = 43)	3.3 ± 1.1	1.9 ± 0.8	1.6 ± 0.6	1.3 ± 0.3	1.3 ± 0.5	1.1 ± 0.2
χ^2	5.192					
<i>p</i>	0.247					

Note: Repeated measures ANOVA was used to compare VAS scores between groups across time points.

Postoperative PCA Usage

Comparison of PCA activation times and drug usage between the two groups showed that the music group had significantly lower PCA activations at 1 hour and 3 hours postoperatively than the control group ($p < 0.05$). However, there were no statistically significant differences in analgesic drug usage at all time points between the groups ($p > 0.05$) (Table 3).

Comparison of Postoperative Adverse Reactions

There were no statistically significant differences in NVAS scores at various postoperative time points between the two groups ($p > 0.05$) (Table 4).

Table 3 Postoperative PCA Usage ($\bar{x} \pm s$)

Group	Usage Frequency						Analgesic Dosage (mL)					
	1 hour	2 hour	3 hour	12 hour	24 hour	48 hour	1 hour	2 hour	3 hour	12 hour	24 hour	48 hour
Music group (n = 43)	1.5 ± 1.3 ^a	3.3 ± 2.5	4.5 ± 3.2 ^a	9.2 ± 6.7	12.0 ± 10.7	15.7 ± 8.6	9.0 ± 5.0	15.2 ± 7.3	21.6 ± 7.7	35.6 ± 14.6	52.2 ± 21.1	67.0 ± 17.8
Control group (n = 43)	1.9 ± 1.6	5.0 ± 4.6	5.7 ± 5.5	10.7 ± 8.5	12.8 ± 7.5	16.0 ± 11.2	10.0 ± 5.0	16.5 ± 7.7	22.3 ± 9.2	31.7 ± 15.0	53.1 ± 16.2	62.7 ± 22.8

Notes: Repeated measures ANOVA was used to compare PCA usage frequency and analgesic dosage between groups over time. Compared with the control group, ^a $p < 0.05$.

Table 4 Comparison of Postoperative Nausea Visual Analog Scores ($\bar{x} \pm s$)

Group	1h After Surgery	2h After Surgery	3h After Surgery	12h After Surgery	24h After Surgery	48h After Surgery
Music group (n = 43)	3.5±1.2	2.1±1.1	1.4±0.6	1.4±0.4	1.1±0.3	1.5±0.3
Control group (n = 43)	3.3±1.1	1.9±0.8	1.6±0.6	1.3±0.2	1.0±0.1	1.7±0.4
χ^2	15.72					
<i>p</i>	0.217					

Notes: Repeated measures ANOVA was used to compare postoperative nausea VAS scores between groups across time points.

Table 5 Sleep Quality Index on the Night After Surgery ($\bar{x} \pm s$)

Group	Sleep Time	Sleep Efficiency	Sleep Disorders
Music group (n = 43)	8.14 ± 0.59	5.78 ± 0.24	11.42 ± 1.89 ^a
Control group (n = 43)	5.25 ± 1.20	3.16 ± 0.36	23.14 ± 2.18
<i>p</i>	< 0.001	< 0.001	< 0.001

Notes: Independent samples t-test was used to compare sleep quality parameters between groups.

^a *p* < 0.05.

Table 6 Comparison of Patient Satisfaction with Postoperative Analgesia

Group	Very Satisfied		Quite Satisfied		Satisfied		Dissatisfied	
	Number	Ratio (%)	Number	Ratio (%)	Number	Ratio (%)	Number	Ratio (%)
Music group	14	32.56	15	34.88	12	27.91	2	4.65
Control group	12	27.91	12	27.91	9	20.93	10	23.25
χ^2	6.198							
<i>p</i>	0.026 ^a							

Notes: χ^2 -test was used to compare patient satisfaction levels between groups. Compared with the control group, ^a*p* < 0.05.

Sleep Quality Index on the Night After Surgery

Patients in the music group had higher sleep duration and sleep efficiency scores and lower sleep disturbance scores compared to the control group, with statistically significant differences (*p* < 0.05) (Table 5).

Comparison of Postoperative Pain Satisfaction

The postoperative pain satisfaction rate in the music group (95.35%) was significantly higher than that in the control group (76.75%), with a statistically significant difference (*p* < 0.05) (Table 6).

Discussion

TKA is a highly invasive procedure often associated with moderate to severe, intermittent, or persistent pain postoperatively. Such pain hinders early joint function training, increases the risk of postoperative complications, and negatively impacts patient prognosis.¹⁷ Moreover, pain stimuli can easily trigger various cardiovascular events, exacerbate underlying diseases, and even lead to severe complication.¹⁸ Thus, selecting a scientific and effective postoperative analgesic method is critical for TKA patients. This study found that compared to the control group, the music therapy group exhibited significantly fewer PCA pump presses in the short-term postoperative period (1 hour and 3 hours after surgery). Additionally, the music therapy group demonstrated longer sleep duration and higher sleep efficiency compared to the control group, with lower sleep disturbance scores. Furthermore, the music therapy group showed significantly higher analgesic satisfaction levels compared to the control group. These findings suggest that music therapy can partially enhance the analgesic efficacy of PCA and improve postoperative sleep quality in TKA patients. However, no statistically significant differences were observed in VAS scores, analgesic consumption, or nausea scores at any postoperative time points. These results are inconsistent with those reported in previous studies,^{19,20} possibly due to the insufficient duration of music listening in the music therapy group in this study. The reduction in PCA button presses among the music group may reflect a decrease in the patient's perceived need for analgesia or anxiety-driven non-therapeutic demands induced by the music therapy, rather than a substantial reduction in underlying analgesic requirement, explaining the lack of difference in total drug consumption. Further investigation is needed to clarify the underlying reasons. The results of this study suggest that the main value of music therapy is to improve the subjective experience of pain, such as satisfaction and sleep, rather than directly enhancing the intensity of analgesia or accelerating functional recovery.

PCA provides effective and long-lasting analgesia, with broad clinical applications and indications, and is commonly used for postoperative pain relief.²¹ However, its analgesic mode is relatively singular, and its effectiveness is influenced by drug dosage. Insufficient dosage results in suboptimal pain control, while excessive dosage increases the risk of adverse effects such as nausea, vomiting, urinary retention, dizziness, and pruritus. These intolerable side effects often lead patients to discontinue its use, posing certain limitations in clinical practice.^{22,23} The modern gold standard for pain management after TKA is based on the Multimodal Analgesia (MMA) protocol. Its core is to achieve synergistic analgesia and significantly reduce opioid requirements and side effects by combining non-opioid techniques such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) /COX-2 inhibitors, regional nerve blocks (such as obturator nerve block or adductor canal block), local infiltration analgesia (LIA), and intravenous dexamethasone. In this context, the present study positioned music therapy as an adjunctive intervention for MMA rather than an independent analgesic method. Studies have shown that perioperative music therapy can provide postoperative analgesic effects and reduce the consumption of analgesic drugs, thereby decreasing the incidence of opioid-induced side effects such as nausea and vomiting, and improving patient satisfaction.^{24,25} This may be attributed to the relaxing and soothing nature of music, which serves as a positive stimulus to the brain, allowing patients to fully relax and enhancing their tolerance to pain.²⁶ Moreover, music therapy can provide pleasant auditory stimulation that inhibits central pain transmission, thereby exerting an analgesic effect.²⁷ Research by Baran et al²⁸ demonstrated that the use of music therapy during renal surgery significantly reduced patients' pain scores. Similarly, Ortega et al²⁹ found that perioperative music therapy during nasal fracture reduction surgery significantly lowered systolic blood pressure and pain levels. In the field of orthopedic surgery, a study by Schijven et al³⁰ also showed that listening to music significantly alleviated pain in awake patients undergoing surgery. Furthermore, they found that the use of video glasses and headphones to watch movies intraoperatively did not yield significantly better results than simply listening to music through headphones.

Unlike some other studies, this experiment employed music therapy during the anesthetic state of patients intraoperatively. It has been demonstrated that at sufficient anesthetic depth to meet surgical requirements, such as a BIS value between 40 and 60, the brain retains the ability to process auditory information via implicit memory mechanisms.³¹ This indicates that the brain can still process musical signals under certain levels of anesthesia. Similar to our findings, a multicenter randomized controlled trial by Nowak et al showed that using headphones to play background music and provide positive therapeutic suggestions during general anesthesia reduced opioid consumption and pain scores within the first 24 hours postoperatively.³² Kaydu et al³³ similarly found that music therapy during general anesthesia decreased postoperative pain levels and reduced analgesic consumption. For studies with higher levels of evidence, a meta-analysis integrating results from five clinical studies indicated that music intervention during general anesthesia significantly reduced postoperative pain in a statistically significant manner.³⁴

Although some studies used the same music for all participants to reduce heterogeneity. In our study, however, patients personally selected their preferred music for preoperative intervention. This approach was adopted because studies have shown that personal associations and emotional engagement with music have a greater impact on sedation and analgesic effects than the intrinsic characteristics of the music itself. Specifically, participants may choose different types of music, but they aim to achieve the same psychological goals, namely reducing pain.³⁵ A recent study by Markus et al demonstrated that in a Cold Pressor Test involving 548 healthy volunteers, the participants' preferred music, regardless of genre, significantly enhanced pain tolerance.³⁶ Can et al compared the effects of different music genres on pain in patients undergoing extracorporeal shock wave lithotripsy and found that patients experienced greater satisfaction when listening to their preferred music. Notably, most current studies employ patient-selected music as a method for perioperative pain management.³⁷⁻³⁹

This study partially validated the auxiliary role of music therapy in postoperative pain management after total knee arthroplasty and its potential benefits in improving postoperative sleep quality. However, this study has certain limitations: First, it did not fully account for individual differences in pain tolerance among participants, nor did it use standardized methods to assess each participant's pain tolerance threshold preoperatively. Objective tests, such as the Cold Pressor Test or other pain threshold measurements, could quantify individual pain tolerance, potentially mitigating the impact of inter-individual differences in pain sensitivity on study outcomes. Second, this study did not comprehensively evaluate objective physiological parameters, such as blood pressure and heart rate, nor did it assess anxiety

induced by postoperative pain, which might limit the interpretation of some results. Moreover, the lack of systematic observation of these variables might have overlooked the broader potential effects of music therapy. The central design and insufficient sample size may limit the generalizability of the findings. Furthermore, the study primarily relies on patient-reported outcome measures (eg, VAS, PSQI) to assess treatment effects, without incorporating objective physiological markers such as cortisol levels or long-term follow-up data to evaluate sustained recovery trajectories. Additionally, the study does not quantify the influence of music therapy on clinical decision-making, including opioid prescription practices. Therefore, future studies should incorporate these key physiological and psychological parameters into their design to more comprehensively evaluate the mechanisms and clinical significance of music therapy.

Conclusion

In conclusion, while this experiment did not convincingly demonstrate that music therapy can effectively alleviate postoperative pain, decrease analgesic usage, or reduce adverse effects such as nausea and vomiting, it can be definitively stated that perioperative music therapy, without increasing anesthetic risks, not only can effectively assist PCA for a certain duration postoperatively but also significantly enhances postoperative sleep and increases patient satisfaction with pain management. Currently, the research on the mechanisms of music therapy is still in its early stages, and standard implementation protocols for music therapy have yet to be established; these issues warrant further investigation and resolution.

Abbreviations

TKA, Total Knee Arthroplasty; MT, Music Therapy; PCA, Patient-Controlled Analgesia; PCIA, Patient-Controlled Intravenous Analgesia; VAS, Visual Analogue Scale; NVAS, Nausea Visual Analogue Scale; PSQI, Pittsburgh Sleep Quality Index; ASA, American Society of Anesthesiologists; BIS, Bispectral Index; BMI, Body Mass Index; BP, Blood Pressure; HR, Heart Rate; SpO₂, Oxygen Saturation; ECG, Electrocardiogram; RCT, Randomized Controlled Trial; ANOVA, Analysis of Variance.

Data Sharing Statement

The datasets used and analyzed during this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki. And this study was approved by the Medical Ethics Committee of Honghui Hospital (Approval No. 201901008) and registered in the Chinese Clinical Trial Registry (ChiCTR2000032027).

Consent for Publication

All authors have read and approved the final version of this manuscript and agree to its submission for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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