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Mediating role of pain sensitization in preoperative and postoperative pain in knee osteoarthritis patients

Tianjiao Shen¹, Ji Yuan¹, Di Wang², Xiaoqing Chai², Hai Gu¹, Lingsuo Kong^{1*} and Yinghong Wang^{3*}

Abstract

Objective This study aims to explore the relationship between preoperative and postoperative pain in patients with knee osteoarthritis (KOA) undergoing total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKR), and to assess the mediating roles of central and peripheral sensitization.

Methods This prospective cohort study enrolled a total of 105 eligible KOA patients. The Visual Analog Scale (VAS) was used to assess preoperative and postoperative pain levels. Multivariate linear regression analysis and Bootstrap mediation analysis were conducted to investigate the impact of preoperative pain intensity on postoperative pain.

Results This study revealed a significant positive correlation between preoperative VAS scores during movement and pain scores 3 days postoperatively (β =0.4018, p=0.0017), as well as a significant correlation with pain scores 6 months postoperatively (β =0.735, p=0.004). Central sensitization (β =0.0446, p<0.0001) and peripheral sensitization (β =0.0333, p=0.0015) exhibited significant mediation effects between preoperative and postoperative pain. Additionally, preoperative VAS scores (B=1.107, p=0.014, OR=3.027), age (B=0.207, p=0.036, OR=1.229), and duration of arthritis (B=0.190, p=0.013, OR=1.210) were significant predictors of postoperative analgesic demand.

Conclusion This study demonstrates that preoperative pain intensity is closely related to postoperative pain in KOA patients undergoing TKA and UKR, with central and peripheral sensitization playing significant mediating roles in this process. In particular, preoperative pain management is crucial for alleviating postoperative pain and improving patients' quality of life. Therefore, when formulating individualized pain management strategies, the central and peripheral sensitivity of patients should be comprehensively considered. Future research is necessary to develop and evaluate innovative pain control methods integrating central and peripheral mechanisms to optimize postoperative rehabilitation and long-term health outcomes.

Keywords Pain sensitization, Preoperative pain, Postoperative pain, Knee arthroplasty, Mediating effect, Pain management

*Correspondence: Lingsuo Kong konglingsuo3201@ustc.edu.cn Yinghong Wang wyh518@ustc.edu.cn Full list of author information is available at the end of the article



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Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis in adults, characterized by chronic pain and loss of mobility [1, 2]. It most commonly occurs after the age of 40, with prevalence rates rising sharply with age [1, 2]. OA can coexist with other chronic conditions and exert negative impacts. Globally, 595 million people were living with OA in 2020, equivalent to 7.6% (6.8-8.4%) of the global population, and it is projected that the number of knee OA cases will increase by 74.9% (59.4-89.9%) by 2050 compared to 2020 [1, 2]. Hip and knee osteoarthritis (KOA) are among the leading causes of disability worldwide, significantly affecting patients' quality of life and imposing a heavy socioeconomic burden [2-4]. The World Health Organization has designated 2021-2030 as the "Decade of Healthy Aging," emphasizing the need to address conditions like OA that severely impact functional ability and quality of life [1, 2].

For patients with severe symptoms of KOA, joint replacement surgery can effectively alleviate pain and improve joint function [5–7]. Total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKR) are two types of knee replacement surgeries [8]. However, the incidence of chronic post-surgical pain (CPSP) is high, and its formation is complex, potentially related to factors such as postoperative tissue damage, inflammatory responses, and the patient's physiological and psychological state [9]. Pain sensitization plays a crucial role in the onset and maintenance of chronic pain [10]. Central sensitization refers to an increase in the sensitivity of pain transmission pathways in the spinal cord and brain, leading to enhanced pain perception [10, 11]. Peripheral sensitization involves an increased response of peripheral nerve endings to painful stimuli, with these mechanisms acting collectively in the generation of chronic pain [10-12]. Studies have indicated that preoperative pain intensity is closely associated with the occurrence of CPSP. [10] High preoperative pain intensity may increase the risk of CPSP, a relationship that may be explained by mechanisms of pain sensitization [13]. The aim of this study is to explore the mediating role of pain sensitization in the association between preoperative pain and CPSP in patients with KOA. Through this research, we hope to uncover important mechanisms influencing CPSP.

Methods

General information

This is a prospective and observational study conducted at the First Affiliated Hospital of the University of Science and Technology of China(USTC). This study obtained approval from the Ethics Committee (Ethics Approval Number: 2021 KY Ethics Review No. 158). All participants signed informed consent forms before enrolling in the study. Inclusion criteria were as follows: patients with KOA aged between 45 and 75 years; diagnosed with KOA of Kellgren–Lawrence grade II or above confirmed by X-ray; scheduled to undergo TKA or UKR; and capable of completing questionnaires and follow-ups. Exclusion criteria were as follows: history of mental illness, substance abuse, severe neurological or cardiovascular diseases; previous knee surgery; coexistence with other chronic pain syndromes (e.g., fibromyalgia); use of medications affecting the central nervous system within the past 3 months; and pregnant or lactating women. Note: Patients with well-controlled hypertension were not excluded.

Research methods

This is a prospective cohort study conducted from November 2021 to December 2022. Patients with KOA who met the inclusion criteria were consecutively recruited. Sample size calculation was based on the requirements for mediation analysis, referring to the recommendations of Fritz and MacKinnon [14], using the bias-corrected Bootstrap method. With 80% power and a significance level of 0.05, the minimum required sample size was 71 cases. During the study, we recruited a total of 165 eligible patients. After several months of follow-up and data screening, 105 patients were ultimately included for analysis (Fig. 1).

Preoperative assessment

All patients completed the following assessments 1–2 weeks before surgery. 1. Collection of demographic information and medical history; 2. Pain assessment: The Visual Analog Scale (VAS) was used to evaluate patients' pain levels at rest and during activity. Patients marked their pain level on a 10-cm straight line, with the VAS score ranging from 0 to 10, where a higher score indicated greater pain intensity; 3. Pain sensitization assessment: Central sensitization: Pressure pain thresholds of the anterior wall muscles were measured using the Wagner FPXTM pressure algometer [15]; Peripheral sensitization: Pressure pain thresholds were measured at three standard tender points around the knee joint.

Surgery and perioperative management

Surgical type (TKA or UKR), surgical duration, anesthesia method, and medication use were recorded. All patients were treated according to a standardized perioperative management protocol, including preoperative antibiotic prophylaxis, intraoperative blood loss control, postoperative pain management, and early functional exercise.



Fig. 1 Flow diagram of the recruitment process

Postoperative assessment

Follow-up assessments were conducted 3 days and 6 months postoperatively, including pain assessment (using the VAS to evaluate pain at rest and during movement); complication recording, such as nausea and vomiting, blood transfusion needs, and length of hospital stay; and analgesic medication use.

Statistical analysis

In this study, we used SPSS 27.0 software for data analysis. For baseline characteristics, descriptive statistical methods were employed, with continuous variables presented as means and standard deviations, and categorical variables presented as frequencies and percentages. To assess the relationship between preoperative factors and postoperative pain, we used multiple linear regression analysis, controlling for confounding factors such as age, gender, BMI, surgical type, and hypertension. Additionally, mediation effect analysis was conducted using the Bootstrap method (5000 Bootstrap samples) and the Process plugin in SPSS (Model 4) to explore the mediation role of preoperative pain (independent variable: preoperative VAS score during movement) on postoperative pain at 3 days (dependent variable), with central sensitization (pressure pain threshold of the anterior wall muscles) and peripheral sensitization (pressure pain threshold of the knee joint) as mediator variables. The significance of the mediation effect was determined by a 95% confidence interval not containing zero (p < 0.05). Furthermore, binary logistic regression analysis was performed to investigate the factors influencing postoperative rescue analgesia needs, examining the predictive effects of preoperative VAS scores, age, and duration of arthritis, and analyzing the relationship between remifentanil usage and postoperative nausea.

Results

Baseline characteristics

A total of 105 patients with knee OA were included in this study, including 84 females (80.0%) and 21 males (20.0%). The mean age of the patients was 57.8 ± 3.2 years, and the mean BMI was 26.3 ± 2.5 kg/m². In terms of surgical types, 50 patients (47.6%) underwent TKA, and 55 patients (52.4%) underwent UKR. Detailed baseline characteristics of the patients are presented in Table 1.

Table 1 Patients baseline clinical feature	eatures analysis ($n = 105$)
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Characteristic	Mean±SD or Number		
	(%)		
Age (years)	57.8±3.2		
Gender (female proportion)	84 (80.0%)		
Body Mass Index (BMI, kg/m ²)	26.3 ± 2.5		
Anterior wall muscle tenderness value (N)	124.9 ± 9.1		
Knee joint tenderness value (N)	105.6±8.7		
Preoperative resting VAS score (cm)	1.6 ± 0.7		
Preoperative movement VAS score (cm)	3.6 ± 0.7		
Number of hypertensive patients (case)	18 (17.1%)		
Number of UKR patients (case)	55 (52.4%)		
Number of TKA patients (case)	50 (47.6%)		

The VAS score ranges from 0 to 10 cm. The tenderness value is measured in newtons $\left(N\right)$

Relationship between preoperative and postoperative pain

Multiple linear regression analysis showed that the preoperative pain level (VAS score during movement) was significantly positively correlated with the pain level 3 days after surgery (VAS score during movement) (β =0.4018, SE=0.1247, *p*=0.0017, 95% CI [0.1543, 0.6493]), and it was also significantly correlated with the pain level 6 months after surgery (β =0.735, *p*=0.004). The overall model was significant (F(7, 96)=2.142, *p*=0.046). This indicates that higher preoperative pain levels are associated with higher postoperative pain levels.

Mediation analysis

The mediation effects of central sensitization (indicated by anterior wall muscle tenderness value) and peripheral sensitization (indicated by knee joint tenderness value) on the relationship between preoperative movement pain (X) and postoperative movement pain 3 days after surgery (Y) were analyzed using the Bootstrap method (5000 samples) (Table 2). The analysis of central sensitization showed that preoperative movement pain had a significant effect on the anterior wall muscle tenderness value (β =2.9817, SE=1.2230, *p*=0.0166, 95% CI [0.5543, 5.4091]), and the anterior wall muscle tenderness value had a significant effect on postoperative movement pain 3 days after surgery (β =0.0446, SE=0.0094, *p*<0.0001, 95% CI [0.0260, 0.0632]). The indirect effect was 0.1329 (Bootstrap SE=0.0633, 95% CI [0.0310, 0.2772])(Fig. 2).

The analysis of peripheral sensitization showed that preoperative movement pain significantly affected the knee joint tenderness value (β =2.6132, SE=1.1891, p=0.0304, 95% CI [0.2530, 4.9733]), and the knee joint tenderness value also had a significant effect on postoperative movement pain 3 days after surgery (β =0.0333, SE=0.0102, p=0.0015, 95% CI [0.0131, 0.0534]). The indirect effect was 0.0870 (Bootstrap SE=0.0473, 95% Bootstrap CI [0.0079, 0.1931]). The results indicate that both central and peripheral sensitization play important mediation roles in the impact of preoperative pain on postoperative pain (Fig. 3).

The duration of arthritis had a significant effect on both the anterior wall muscle tenderness value and the knee joint tenderness value ($\beta = 0.7291$, SE = 0.2326, p = 0.0023, 95% CI [0.2674, 1.1907]), ($\beta = 0.4558$, SE = 0.2262, p = 0.0466, 95% CI [0.0069, 0.9047]), while factors such as age, gender, and BMI had no significant effects (p > 0.05).

Postoperative outcomes and influencing factors in KOA patients

We employed binary logistic regression analysis to identify factors associated with postoperative rescue analgesia requirements. The results indicated a significant correlation between preoperative VAS scores and the need for rescue analgesia (B=1.107, p=0.014, OR=3.027), suggesting that patients with higher preoperative pain scores are more likely to require postoperative rescue analgesia. Additionally, age (B=0.207, p=0.036, OR=1.229) and duration of arthritis (B=0.190, p=0.013, OR=1.210) were also identified as significant predictors. Gender,

 Table 2
 Analysis of the mediating effect of preoperative pain on postoperative pain

Type of mediating effects	Pathway	Effect	Standard FRROR (SF)	95% confidence	<i>p</i> -value
Central nervous system sensitization	Direct effect (preoperative pain \rightarrow M)	2 9817	1 2230	[0 5543 5 4091]	0.0166
	Direct effects ($M \rightarrow$ postoperative pain)	0.0446	0.0094	[0.0260, 0.0632]	< 0.0001
	Indirect effect	0.1329	0.0633	[0.0310, 0.2772]	-
Peripheral nerves sensitization	Direct effect (preoperative pain \rightarrow M)	2.6132	1.1891	[0.2530, 4.9733]	0.0304
	Direct effects (M \rightarrow postoperative pain)	0.0333	0.0102	[0.0131, 0.0534]	0.0015
	Indirect effect	0.0870	0.0473	[0.0079, 0.1931]	-

P-values for indirect effects are usually estimated indirectly by the Bootstrap method and are therefore not reported directly



Indirect effect (ab) = 0.1329, 95% CI [0.0310, 0.2772]

* *p* < 0.05, ** *p* < 0.01

Fig. 2 Sensitization model of the central nervous system



Indirect effect (ab) = 0.0870, 95% CI [0.0079, 0.1931]

* *p* < 0.05, ** *p* < 0.01

Fig. 3 Sensitization model of the peripheral nerves

surgical approach, BMI, and hypertension did not demonstrate significant associations. The predictive accuracy of the model was 84.8%. Furthermore, we explored the relationship between remifentanil usage and postoperative nausea. The results showed no significant correlation between remifentanil usage and postoperative nausea (B=0.008, p=0.107, OR=1.008). The overall predictive accuracy of this model was 90.5%. Among other postoperative outcomes, the average length of hospital stay was 3.095 days (SD=0.354), with 4.76% of patients requiring blood transfusions; 2 patients (1.9%) were admitted to the ICU, and 1 patient (0.95%) experienced hypothermia. These findings provide important insights for postoperative management in clinical practice and are detailed in Table 3.

Discussion

Based on the Global Burden of Disease (GBD) database [16, 17], the age-standardized years lived with disability (YLDs) rate for OA has been continuously rising [1]. Population growth, aging, and the lack of effective treatments are expected to significantly increase the number of cases [1, 2]. As a significant public health issue, the severity of KOA underscores the necessity of improving pain management after knee arthroplasty. This study reveals the relationship between preoperative and postoperative pain in KOA patients undergoing TKA and UKR, emphasizing the importance of preoperative pain management. The results show a significant positive correlation between preoperative pain intensity and postoperative pain, indicating that patients with higher preoperative pain levels may experience more severe postoperative pain symptoms. This finding is consistent with those of Hasegawa et al. [18] and Wylde [19]. Pua et al. [20] further pointed out that preoperative psychological status and physiological factors also affect postoperative pain manifestation.

In randomized, double-blind, placebo-controlled trials, although preoperative intra-articular injection of methylprednisolone acetate (MP) significantly reduced preoperative inflammatory markers such as IL-6, its impact on acute pain and sensitization after TKA was not significant. This suggests that managing peripheral inflammation alone may not be sufficient for comprehensive relief of postoperative pain [21]. Our study found that central and peripheral neural sensitization have significant mediating effects in the influence of preoperative pain on short-term chronic pain after surgery, aligning with existing literature [22–24] that observes the impact of preoperative pain on postoperative chronic pain. Kurien et al. [25] found that patients with neuropathic pain symptoms identified by the PainDETECT questionnaire are prone to developing chronic pain postoperatively. However, Høvik et al. [26] did not find an association between preoperative pain catastrophizing and long-term pain, but these results emphasize the importance of the sensitization process in early postoperative pain management. GBD data show that the burden of KOA is heaviest among individuals over 65 years old [1, 2], which aligns with the characteristics of our study population and supports the analysis results regarding the impact of age on the mediating effect of central neural sensitization.

Furthermore, through binary logistic regression analysis, we found that preoperative VAS scores, age, and duration of arthritis are important predictors of postoperative analgesic demand. This suggests that special attention should be given to these factors during preoperative assessment to develop individualized pain management strategies. Although there was no significant correlation between remifentanil usage and the occurrence of postoperative nausea, its overall prediction accuracy was 90.5%, demonstrating its potential clinical value.

This study is the first to explore the mediating role of central and peripheral nociceptive sensitization in TKA and UKR knee arthroplasty, providing a new perspective on understanding the impact of preoperative pain on short-term postoperative pain. However, the study's single-center design may limit the generality of the results. Future large-sample, multicenter studies are needed to validate our findings. Intervention strategies targeting nociceptive sensitization are a focus of future research.

Table 3	Analys	sis of Posto	perative (Dutcomes	and influ	uencing f	factors in	KOA patients
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Project	Outcome
Relationship between requirement for rescue analgesia and preoperative VAS score on movement	The regression coefficient (B) = 1.107, $p = 0.014$, odds ratio (OR) = 3.027
Number of patients requiring rescue analgesia (case,%)	13 (12.38%)
Mean dose of remifentanil(µg)	773.96±72.53
Correlation between nausea and vomiting and remifentanil dose	p>0.107
Mean length of hospital stay (days)	3.095 ± 0.354
Proportion of patients requiring blood transfusion (cases, %)	5 (4.76%)
Number of patients admitted to the intensive care unit (ICU) (case,%)	2 (1.90%)
Number of patients with hypothermia (example,%)	1 (0.95%)

The VAS score is a visual analog scale from 0 to 10. All percentages are proportions relative to the total sample size

Existing literature suggests that specific medications and physical therapies may help alleviate neural sensitization [27]. In clinical practice, the importance of preoperative nociceptive sensitization assessment cannot be overlooked, as it helps identify high-risk patients and develop individualized pain management strategies. Postoperative rehabilitation programs should also comprehensively consider nociceptive sensitization to optimize rehabilitation plans and reduce long-term pain and functional limitations.

Conclusion

This study provides an in-depth analysis of the relationship between preoperative and postoperative pain in KOA patients undergoing TKA and UKR, finding a significant positive correlation between preoperative pain intensity and postoperative pain. Central and peripheral neural sensitization play critical mediating roles in the influence of preoperative pain on postoperative pain, indicating the need to prioritize neural sensitization factors in preoperative assessment. Additionally, preoperative VAS scores, age, and duration of arthritis are important predictors of postoperative analgesic demand, suggesting the adoption of individualized strategies in pain management. This study provides clear guidance for clinical practice, emphasizing the importance of integrating multilevel analgesic strategies targeting both central and peripheral mechanisms.

Author contributions

Tianjiao Shen: Data collection and analysis; wrote the main manuscript text Di Wang, Xiaoqin Chai, Hai Gu: Propose research questions, design experiment scheme Ji Yuan: Data collection and analysis Lingsuo Kong; Yinghong Wang: revision of papers; Read and approve the final version of the submission.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Ethical Committee at the first Affiliated Hospital of USTC approved this prospective trial. Written informed consent was obtained from all patients recruited to the study, in accordance with the code of the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Pain, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, Anhui, China. ²Department of Anesthesiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, Anhui, China. ³Department of Pharmacy, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230031, Anhui, China.

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