Prevalence of Neuropathic Pain Varies in Patients With Knee Osteoarthritis in Different Treatment Stages

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Abstract

Background: Pain is the main symptom of knee osteoarthritis (KOA) and can be classified as nociceptive pain and neuropathic pain (NP). However, the prevalence and risk factors of NP in patients with KOA at different treatment stages vary in countries and are still unclear in China.

Methods: Patients in this retrospective study were divided into three groups according to treatment stage, including outpatient stage, preoperative total knee arthroplasty (pre-TKA) stage and postoperative TKA stage (post-TKA). A numeric rating scale (NRS) and PainDETECT questionnaire were used to evaluate nociceptive pain and NP. Patient demographics, radiological assessments using Kellgren-Lawrence (K-L) grades, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were analyzed.

Results: Of the 921 patients, the prevalence of possible and likely NP was 17.5% (56/320) and 2.5% (8/320) in the pre-TKA group compared with 3.4% (8/233) and 0.4% (1/233) in the outpatient group and 1.4% (5/368) and 0.5% (2/368) in the post-TKA group, respectively. In the pre-TKA group, higher NRS (NRS>3; *OR*=10.65, 95% *CI:* 3.25-34.92, $p<0.001$) and WOMAC pain (WOMAC>10; *OR*=4.88, 95% *CI:* 2.38-10.01, $p<0.001$) scores conferred an increased risk of unclear pain. Age, gender, BMI and K-L grade showed no significant differences among the unlikely, possible and likely NP groups.

Discussion: Different prevalence of NP occur in KOA patients at different treatment stages. Due to the low prevalence of NP in the outpatient and post-TKA groups, we suggest not regularly screening for NP in these patients, while it may be essential to screen for NP in patients waiting for TKA. In the latter group, higher NRS and WOMAC pain scores are important risk factors of NP.

Background

Knee osteoarthritis (KOA) is the most common joint disease in older adults worldwide (1, 2). Pain is the major symptom and reason that urges patients with KOA to seek help from doctors. However, the efficiency of pain treatment is relatively limited (3, 4). Moreover, although total knee arthroplasty (TKA) is the most effective operation for patients with late-stage KOA and significantly reduces pain, persistent pain still affects a certain proportion of patients after TKA and leads to dissatisfaction (5, 6). One of the major causes is the unclear mechanisms underlying the pain.

Recently, neuropathic pain (NP) was found to play an important role and widely existed in patients with KOA and after TKA (7, 8). Several studies have reported the prevalence of NP in these patients; for example, the prevalence of NP varied from 5.4–28% (9–12) in KOA patients, while 0–15.3% of patients after TKA were estimated to have NP (13–16). However, the prevalence of NP in different treatment stages, including the outpatient stage and the stages of preoperative and postoperative TKA, has not been compared. The understanding of the prevalence of NP in different treatment stages can not only help clinicians be aware of NP based on the characteristics of the population but also lead to the treatment of pain in a personalized strategic manner. Moreover, risk factors of NP need to be identified to

help clinicians recognize patients with NP. Therefore, the aim of this study was to investigate the prevalence and risk factors of NP in patients at different treatment stages, including outpatient and preoperative and postoperative TKA stages in China.

Methods

The protocol of this retrospective study was approved by the ethics committees of the Second Affiliated Hospital of Wenzhou Medical University.

Patient selection

Patients diagnosed with primary KOA according the American College of Rheumatology criteria were investigated in the study (17). The exclusion criteria included the following: 1. inflammatory arthritis (i.e., rheumatoid arthritis (RA), spondylarthritis and gout); 2. autoimmune disease (i.e., connective tissue disorders); 3. previous trauma; 4. symptoms of spinal disease; 5. joint replacement operation in the other knee; 6. cognitive disorders; 7. fibromyalgia; and 8. septic arthritis.

In total, three groups in different treatment stages were analyzed in this study, including the outpatient stage (outpatient-KOA group) and preoperative TKA (pre-TKA group) and postoperative TKA (post-TKA group) stages. The outpatient-KOA group included the patients coming to our outpatient department and diagnosed with KOA according to the above criteria. The pre-TKA group included patients waiting for TKA due to KOA, while the post-TKA group contained postoperative TKA patients due to KOA from August 2016 to August 2018 in our department.

Patient characteristics

A questionnaire including patient demography, knee function and pain evaluation was answered by the recruited patients. Patient demographics were recorded, including age and gender, in all three groups. BMI was recorded in the pre-TKA group. The function of the knee was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score in the outpatient-KOA group and the pre-TKA group (18). The WOMAC score included 3 subscales related to pain, stiffness and function. The higher the WOMAC score, the worse the joint function. The radiological grade of KOA was evaluated by the authors according to the Kellgren-Lawrence (K-L) grading scale (0=none, 1=doubtful, 2=minimal, 3=moderate, 4=severe) in the outpatient-KOA group and pre-TKA group (19). For the post-TKA group, the K-L grade of the knee before the operation was also recorded.

Pain evaluation

NP was measured according to the PainDETECT questionnaire (20). This questionnaire is widely used in NP evaluation related to KOA and contains questions related to pain-affected sensory symptoms, including burning pain, paresthesia, mechanical allodynia, spontaneous pain attacks, thermal hyperalgesia, numbness, and pressure hyperalgesia. Each type of pain was classified across 5 grades from none (0), hardly noticed (1), slightly (2), moderately (3), strongly (4) and very strongly (5). This

questionnaire also includes questions about the frequency and radiation of pain to describe the features of pain. Patients with a total score from 19 to 38 were considered likely to have NP, whereas a total score between 13 and 18 indicated ambiguous pain. Patients with a total score range from 0 to 12 were considered unlikely to have NP. Nociceptive pain was evaluated using a numeric rating scale (NRS), while the WOMAC pain score was used to measure function-related pain.

Statistical analysis

Data analysis and statistics were processed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Normally distributed data were described as the mean and standard deviation. Nonnormally distributed data were reported as the mean and 95% confidence interval (CI). The comparison of values was examined by ANOVA with/without Bonferroni correction or Kruskal-Wallis test depending on the results of the normality test and Levene's test. A chi-square test was used to determine cross-table data and calculate the odds ratio (OR) value. Correlation coefficients were determined by Spearman's rank correlation test using two-tailed *P* values. $P < 0.05$ was set as indicating a significant difference.

Results

Patient characteristics in the three different groups

A total of 921 patients were investigated in this study, including 233, 320, and 368 in the outpatient-KOA, pre-TKA and post-TKA groups, respectively. Patient demographics, knee function based on the WOMAC scores and radiological assessments are illustrated in Table 1. It was not surprising that the age in the outpatient-KOA group was 6.75 and 7.92 years younger than that in the pre-TKA and post-TKA groups ($p<0.001$). No difference was found for gender (p=0.401). However, knee function based on WOMAC scores were significantly worse in the pre-TKA group than in the outpatient-KOA group ($p<0.001$). In addition, the proportion of patients with different K-L grades was significantly different between the groups ($p<0.001$). Moreover, in the outpatient-KOA group, most of the KOA patients were in K-L grade 2 (51.1%), while 66.9% and 81.3% of pre-TKA and post-TKA patients, respectively, were in K-L grade 4.

Table 1
Demographic and radiological assessment in the outpatient, pre-TKA and post-TKA groups

		Outpatient-KOA	Pre-TKA	Post-TKA
Age (year)		62.94±10.68	69.69±7.55	70.86±7.08
Male/Female		64/169	93/227	118/250
Follow up time (months)		/	/	20.54±3.87
WOMAC		20.67±15.72	37.95±13.23	/
K-L grade				
	1	62	0	0
	2	119	41	23
	3	38	64	46
	4	14	214	299

Notes:

Abbreviations: K-L grade: Kellgren-Lawrence grade; KOA: knee osteoarthritis; TKA: total knee arthroplasty; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Prevalence of neuropathic pain was significantly different in the outpatient, pre-TKA and post-TKA groups.

To evaluate the prevalence of NP in the different groups, all of the participating patients answered a survey that included the PainDETECT questionnaire and an NRS during the study. In total, we identified 11 patients likely having NP and 69 patients possibly having NP. The number of patients and the prevalence of NP in the different groups are illustrated in Table 2. In general, the three groups had significantly different NP scores ($p<0.001$). The highest NP score existed in the pre-TKA group and dramatically decreased after TKA. Correspondingly, the pre-TKA group had the highest proportion of patients with possibly having (17.5%) and likely having (2.5%) NP. However, the prevalence of possible and likely NP in the outpatient-KOA and post-TKA groups was relatively low. Furthermore, we hypothesized that NP may be an unclear pain factor and found that the proportion of patients with unclear pain was significantly different in the pre-TKA group compared with the outpatient-KOA and post-TKA groups ($p<0.001$). In the post-TKA group, there were 111/368 (30.2%) patients who still had persistent pain whose NRS scores ranged from 1 to 4. In patients with persistent pain (NRS≥1), the percentages of possible and likely NP patients were 4.50% (5/111) and 1.80% (2/111), respectively. In summary, NP existed in the patients with KOA, but the prevalence was significantly different across the treatment stages.

To further explore the relationship between the NP score and other pain measurements, NRS and WOMAC pain scores were compared among the three different groups using the Kruskal-Wallis test. As shown in figure 1, the highest NRS occurred in the pre-TKA group compared with the outpatient group but was dramatically lower in the post-TKA group. Moreover, the WOMAC pain scores were higher in the pre-TKA group than in the outpatient group. In addition, we found that the PainDETECT scores were highly correlated with the NRS scores (r=0.704, p<0.001) and WOMAC pain scores (r=0.504, p<0.001). In summary, the NRS and WOMAC pain scores showed similar trends as NP in different groups and had a significant association with the PainDETECT score.

Table 2
The prevalence of neuropathic pain in the outpatient, pre-TKA and post-TKA groups

	Op-OA	Pre-TKA	Post-TKA
NP Score (mean, 95% CI)	3.63 (3.15-4.10)	7.93 (7.43-8.42)	1.29 (1.01-1.56)
NP Score			
None (<12)	224	256	361
Possible (12-18)	8	56	5
Likely (>19)	1	8	2
Percentage of unlikely NP pain	96.2%	80.0%	98.1%
Percentage of possible NP pain	3.4%	17.5%	1.4%
Percentage of Likely NP pain	0.4%	2.5%	0.5%
Notes:			
Abbreviations: CI: confidence interval; NP: neuropathic pain; OA: osteoarthritis; TKA: total knee arthroplasty.			

Risk factors of neuropathic pain in the pre-TKA group

Due to the low prevalence of NP in the outpatient group and post-TKA group, we suggest that it may be not necessary to regularly screen for NP in these patients. However, in patients waiting for TKA, NP screening may be necessary, and giving anti-NP medication to these patients may be helpful for relieving the pain.

To identify the patients with differing potential for developing NP, the correlated risk factors in the pre-TKA group were analyzed using the Spearman test, and the OR was calculated using the chi-square test. The characteristics of the patients in the unlikely NP, possible NP and likely NP groups are shown in Table 3. We found no significant differences in age (p=0.308), gender (p=0.059), BMI (p=0.343) or K-L grade (p=0.476) among these groups. However, significantly different NRS (p<0.001) and WOMAC pain

(p<0.001) scores were found among the three groups. Moreover, knee function measured using the WOMAC score also showed significant differences among the groups (p<0.001). We hypothesized that the possible and likely NP groups were more representative of an unclear pain group than the unlikely NP group was. We found that compared with patients with lower NRS (NRS≤3), the OR value of NP was 10.65 (95% CI: 3.25-34.92, p<0.001) in patients with higher NRS (NRS>3). In addition, compared with the lower WOMAC pain score group (WOMAC pain score ≤10), the OR value of NP was 4.881 (95% CI: 2.38-10.01, p<0.001) in the higher WOMAC pain score group (WOMAC pain score >10). Furthermore, compared with patients with lower WOMAC scores (WOMAC score ≤45), the OR value of NP was 2.44 (95% CI: 1.37-4.33, p=0.002) in patients with higher WOMAC scores (WOMAC score>45). In summary, due to the relatively high proportion of NP in the pre-TKA group, we suggest evaluating NP in patients waiting for TKA, especially those with high NRS (NRS>3) and WOMAC pain (WOMAC pain score >10) scores, because giving anti-NP medication may be helpful for relieving their pain during the waiting stage.

Table 3
Patient characteristics based on different levels of potential neuropathic pain in the pre-TKA group.

	Unlikely (<12)	Possible (12-18)	Likely (>18)
Age (year)	70.09±7.26	68.27±8.44	66.88±9.28
Male/Female	81/175	9/47	3/5
BMI	25.83±3.22	26.73±3.81	25.77±3.96
WOMAC	36.42±12.45	43.20±15.10	50.25±8.07
NRS	4.34 (4.11-4.58)	6.50 (6.04-6.90)	6.75 (4.92-8.58)
WOMAC Pain	6.33 (5.99-6.67)	8.54 (7.59-9.48)	10.88 (8.71-13.04)
K-L grade			
1	0	0	0
2	28	12	1
3	54	9	1
4	173	35	6
Notes:			
Abbreviations: BMI: body mass index; K-L grade: Kellgren-Lawrence grade; NRS: numeric rating scale; TKA: total knee arthroplasty; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.			

Discussion

Our study suggests that there are differing prevalence rates of NP in the various treatment stages of KOA, including the outpatient stage and the preoperative and postoperative TKA stages. To our knowledge, this

is the first report to compare the prevalence of NP in different treatment stages of KOA. This may lead to personalized treatment strategies for different treatment stages of KOA. Our findings also add evidence to a growing body of literature that NP contributes to a portion of KOA pain.

The prevalence of NP in KOA patients in the outpatient department or community has been reported in several studies. The lowest prevalence (5.4%) was reported by Ohtori, while the highest prevalence (33.3%) was reported in Oteo-Alvaro's research (10, 21). A meta-analysis showed that 23% of KOA patients had symptoms of NP (12). The large range of prevalence shows the great heterogeneity encountered in KOA patients. Compared with this previous research, our research had the lowest prevalence of NP in outpatient KOA patients. Potential explanations for the different prevalence rates of NP between our research and other studies include the following: 1. differential recruitment practices (depending on the people investigated, outpatient or community setting (10, 11)); 2. differential inclusion and exclusion criteria (inclusion criteria such as knee pain patients or patients diagnosed as KOA; exclusion criteria such as whether to exclude patients with possibly related diseases, such as lumbar disease); and 3. ethnic and cultural differences between regions and countries (for example, the lowest prevalence of NP in previous reports occurred in an East Asian country (10)). In this context with varied prevalence rates of NP, we suggest that cross-domain and multinational research using unified standards should be conducted in the future. However, based on our results, we suggest that it is not necessary to use neuropathic tools to regularly screen patients with KOA in the outpatient department.

There are a limited number of studies focused on the prevalence of NP in patients during the preoperative-TKA period, and the reported prevalence has shown a wide range of differences. In one study, after investigating 96 patients during the preoperative TKA period, Phillips reported that only one in ninety-six patients had a PainDETECT score greater than 19 (14). In contrast, Kurien found that NP existed in 30% of patients before TKA (22). In our study, 2.5% of patients likely had NP, while 17.5% of patients possibly had NP in the pre-TKA group. This result is in the range of previous research (1.0%-30%) and showed a relatively low prevalence of NP. However, compared with the prevalence in the outpatient department patients, the prevalence of NP in patients during the pre-TKA period was dramatically higher. Because the waiting time for TKA varies from months to years across different hospitals, we suggest that screening for NP in patients waiting for TKA and providing anti-NP medication may be useful to relieve their pain during the waiting period.

This study confirms that although TKA is effective in relieving pain, a certain proportion of patients still endure persistent pain, and NP contributes to persistent pain after TKA. However, the prevalence of NP after TKA varied from 0-15% in different reports depending on the follow-up time and population investigated. For example, Albayrak reported that 15.3% of patients likely have NP, the prevalence increased up to 22.9% in the severe pain patients (NRS>3) (15), while Masahiro Hasegawa reported 9% of patients after TKA endure unclear pain, although no patients met the criteria for likely NP according to the PainDETECT questionnaire in Japan (16). A review estimated that the prevalence of NP ranges from 5.2% to 13% in the 6-month postoperative period (23). Compared with these results, our study demonstrated a relatively low prevalence of NP after TKA and similar rate as Masahiro Hasegawa's research. Despite the

fact that medications for anti-NP have been demonstrated to be useful for the treatment of persistent pain after TKA in several reports (24, 25), due to the low prevalence of NP after TKA, we suggest that it is not necessary to regularly screen for NP in these patients.

Numerous risk factors of NP have been identified in KOA patients. Hochman found the pain intensity, presence of referred back/hip pain, number of painful joints and one or more self-reported neurological conditions were risk factors of NP in KOA patients (11). Albayrak reported that being widowed, having a low education level, being a housewife, having employment that required physical effort, having presurgical pain at rest and having presurgical restricted walking distance were risk factors for NP after TKA (15). Moreover, pain intensity and PainDETECT scores have been strong correlated in several studies (10, 14, 26-28). In line with their results, we also found that the NRS and WOMAC pain scores had high correlations with NP, and the patients with high NRS and WOMAC pain scores had a higher risk of NP. Therefore, due to the strong correlation between pain intensity and NP, we suggest evaluating NP in patients with high NRS and WOMAC pain scores. In the future, more risk factors should be investigated to help clinicians identify these patients.

This study has some limitations. First, we did not investigate the length of time with knee pain, which limited further analyses with correlations of NP and time because central sensitization may depend on the duration of persistent pain. Therefore, the time issue should be considered in future research. Second, the changes in NP before and after TKA in the same patients were not recorded in this study. Whether NP existing before TKA affects the development of NP after TKA remains unclear. This should be clarified in future research.

Our study has implications for both clinical practice and future research. Compared with medications treating nociceptive pain, the treatment strategy for NP is different and includes antidepressant, antiepileptic, topical anesthetic, and opioid agents (29). However, because the prevalence of NP is different depending on the treatment stages of KOA, clinicians should consider NP features in different treatment stages and develop a personalized pain treatment strategy, especially in patients waiting for TKA with higher NRS and WOMAC pain scores. In addition, the mechanisms of NP should be further elucidated, which may help to treat NP in these patients.

Conclusion

Considering the coexistence of nociceptive pain and NP in KOA patients, we suggest treating the patients according to their features of pain. Moreover, different prevalence rates of NP occurs in patients in different treatment stages and may lead to personalized treatment strategies. NRS and WOMAC pain scores are important risk factors for NP.

Abbreviations

BMI Body mass index

CI Confidence interval

K-L grade Kellgren-Lawrence grading scale

KOA knee osteoarthritis

NP Neuropathic pain

NRS numeric rating scale

OR Odds ratio

RA Rheumatoid arthritis

TKA Total knee arthroplasty

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

Declarations

Ethics approval and consent to participate

The experimental protocol was approved by the Ethics Committees of the Second Affiliated Hospital of Wenzhou Medical University. Informed consent was obtained from all patients.

Consent for publication: Not applicable

Availability of data and material

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

Competing interests: The authors declare that they have no competing interests

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Author contributions

Study conception and design: LL, MD and PF. Collection and assembly of data: LL, ZHZ, HLZ, YYL, LHX, ZY, MD and PF. SPSS statistical analysis: LL, MD and PF. Analysis and interpretation of data: LL, MD and PF. Manuscript: LL, MD and PF. All authors approved the final version to be published.

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Figures

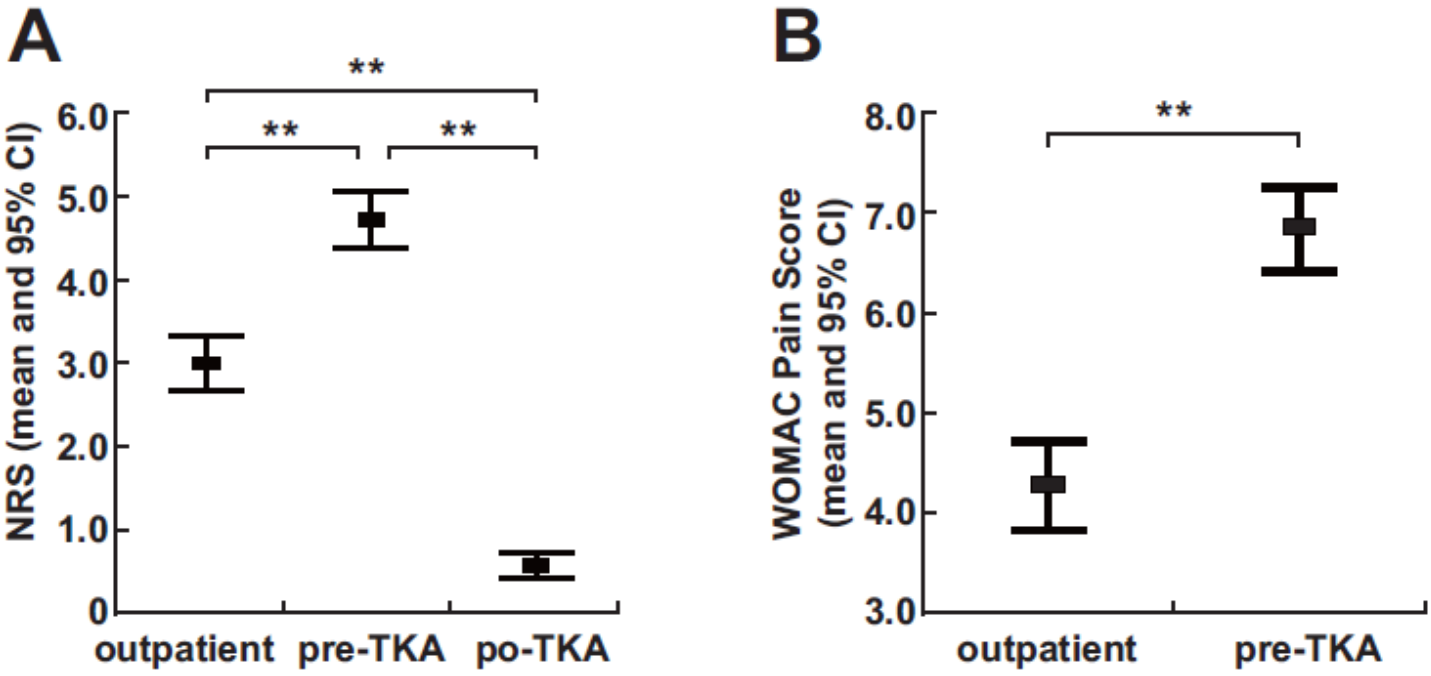

Figure 1

Comparison of NRS and WOMAC pain scores among the outpatient, pre-TKA and post-TKA groups. (A). Comparison of NRS scores among the outpatient, pre-TKA and post-TKA groups. (B). Comparison of WOMAC pain scores between the outpatient and pre-TKA groups. ** $p<0.01$, * $p<0.05$.