Possible Neuropathic Pain in Patients With Osteoarthritis of the Knee Before and After Total Knee Arthroplasty

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Research article

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Abstract

**Background:** Although osteoarthritis (OA) is traditionally considered to be nociceptive, our objective was to examine neuropathic pain in the knees of OA patients using the pain DETECT questionnaire (PDQ).

**Methods:** A total of 180 knees in 158 consecutive patients who underwent total knee arthroplasty (TKA) were enrolled. The prevalence of neuropathic pain, unclear pain and nociceptive pain was determined before and after TKA. Knee pain was evaluated using a numerical rating scale (NRS). All patients were evaluated preoperatively and 6 months postoperatively. Neuropathic pain and unclear pain were grouped together as possible neuropathic pain. The relationship between possible neuropathic pain and pain intensity was evaluated.

**Results:** Before TKA, neuropathic pain and unclear pain were found in 10 and 30 knees, respectively. The remaining 140 knees were categorized as nociceptive pain. After TKA, the numbers of knees with neuropathic and unclear pain decreased to one and five, respectively. The prevalence of possible neuropathic pain decreased significantly from 22.2% to 3.3% (p < 0.001) after surgery. Among the six knees with possible neuropathic pain postoperatively, four had possible neuropathic pain preoperatively as well, while the remaining two patients had been classified as nociceptive pain preoperatively (p = 0.021). Knees with postoperative possible neuropathic pain had higher postoperative NRS scores than those with nociceptive pain (p = 0.011).

**Conclusions:** The prevalence of possible neuropathic pain decreased significantly after TKA, however, preoperative possible neuropathic pain might affect the presence of persistent postoperative pain.

**Background**

Pain is a major symptom of patients with osteoarthritis (OA), and persistent pain is a frequent and often disabling complication following total knee arthroplasty (TKA) for OA. The proportion of patients with persistent pain outcomes after TKA ranges from 8% to 27% [1]. Chronic pain is classified as nociceptive pain and neuropathic pain. But, this classification for pain is not the only way. We found many patients with unclear pain. Nociceptive pain is caused by stimulation of nociceptors through chronic inflammation [2], while neuropathic pain is defined as “pain caused by a primary lesion or dysfunction of the nervous system” by the International Association for the Study of Pain (IASP) [3]. Neuropathic pain has repeatedly been proposed as a major cause of persistent pain after TKA. Although OA pain is traditionally considered to be nociceptive in nature, some patients describe aspects of their pain as burning or shooting. Such characteristics suggest common mechanisms as neuropathic pain [4,5]. To determine whether the pain after TKA is nociceptive pain or neuropathic pain, the painDETECT questionnaire (PDQ) can be used [6-8]. This questionnaire was validated in a multicenter study with either neuropathic or nociceptive pain, as well as a population of patients with low back pain. The tool correctly classified 83% of patients to their diagnostic group with a sensitivity of 85% and a specificity of 80% [9]. However, evidence of PDQ for OA patients is lacking. In the previous study of Hasegawa et al. [8], no neuropathic
pain using PDQ was not found with 222 knees after TKA (mean 4.7 years) in the patients with OA. However, unclear pain (including nociceptive and neuropathic pain) was found in 9% of the knees. Postoperative moderate-to-severe pain was associated with unclear pain [8].

Our objective was to examine the occurrence of neuropathic pain in the knees of OA patients using the PDQ. We evaluated the prevalence of preoperative and postoperative neuropathic pain, and evaluated the relationship between neuropathic pain, pain intensity and stage of OA using the Kellgren-Lawrence (KL) system [10].

Patients And Methods

Patients

We enrolled 158 consecutive patients with OA (180 knees; female, n = 129 [145 knees] male, n = 29 [35 knees]; mean age, 74 [54-87] years; mean body mass index [BMI], 26.1 [17.8-44.1] kg/m²) who underwent TKA from 2016 to 2017. All the procedures were performed under general anesthesia by a single surgeon using the mid-vastus approach to TKA. Posterior-stabilized types were used in all knees. All knees were fixed bearing and all tibial, femoral, and patellar components were cemented. Patients with knee OA who had severe spinal cord-related pain preoperatively were not indicated for TKA.

Pain phenotype

Knee pain was evaluated using a numerical rating scale (NRS) ranging from 0 (none) to 10 (severe). Pain phenotype was assessed using the self-reporting PDQ, which includes nine questions regarding the intensity and quality of pain (Table 1) [6,7]. The scores related to the nature and presence of radiating pain (maximum score of 3) and the nature of pain (maximum score of 35) were summed up to obtain a maximum PDQ end score of 38. Neuropathic pain was considered unlikely (nociceptive pain group) when PDQ scores ranged between 0 and 12, whereas scores of 19 to 38 indicated neuropathic pain. Scores of 13 to 18 indicated unclear pain (including nociceptive and neuropathic components).

The prevalence of neuropathic pain, unclear pain and nociceptive pain before and after TKA were determined. All patients were evaluated preoperatively and 6 months postoperatively. Neuropathic pain and unclear pain were grouped together as possible neuropathic pain, and NRS scores were compared between the possible neuropathic pain and nociceptive pain groups before and after TKA. We also evaluated the relationship between preoperative pain group and the severity of OA using the KL system [10]. Our institutional review board approved this study, and all patients provided written, informed consent to participate.

Statistical analyses

Preoperative NRS scores, age, BMI and flexion angle were compared between knees with preoperative possible neuropathic pain and nociceptive pain using Mann-Whitney U tests. Sex and KL grade were
compared using Chi-squared tests. The prevalence of possible neuropathic pain and nociceptive pain before and after TKA was compared using Chi-squared tests. Postoperative NRS scores were compared between knees with postoperative possible neuropathic pain and nociceptive pain using Mann-Whitney U tests. Correlations between NRS and PDQ scores before and after TKA were determined using the Spearman correlation test. Changes in pain type before and after TKA were evaluated using Fisher's test. Previous study demonstrated possible neuropathic pain was up to 50% [11]. And the sample size was needed 35 knees (\(\alpha = 0.05, \text{power} = 0.8\)). Statistical significance was set at \(p < 0.05\). Data were statistically analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

Before TKA, neuropathic pain and unclear pain were found in 10 and 30 knees, respectively. The remaining 140 knees were categorized as nociceptive pain. After TKA, the numbers of knees with neuropathic and unclear pain decreased to one and five, respectively. Nociceptive pain was found in 174 knees after TKA (Table 2). The prevalence of possible neuropathic pain decreased significantly from 22.2% to 3.3% \((p < 0.001)\). Preoperative and postoperative NRS scores demonstrated no difference between the preoperative possible neuropathic pain group and nociceptive pain group. There were no differences in preoperative pain in relation to sex, age, BMI, KL grade, and preoperative flexion angle (Table 3). Preoperative NRS and PDQ scores showed positive correlation \((r = 0.385, p < 0.001)\). Similarly, postoperative NRS and PDQ scores showed positive correlation \((r = 0.365, p < 0.001)\). Knees with postoperative possible neuropathic pain had higher postoperative NRS scores than those with nociceptive pain \((p = 0.011)\). Among the six knees with possible neuropathic pain postoperatively, four had possible neuropathic pain preoperatively as well, while the remaining two patients had been classified as nociceptive pain preoperatively \((p = 0.021)\).

Discussion

A growing amount of evidence suggests that OA pain has a neuropathic component in some patients. Deeper understanding of the likely multiple mechanisms of OA pain has led to the use of centrally acting drugs to alleviate osteoarthritic pain [12].

Several animal studies supported the hypothesis that neuropathic pain would be part of OA pathogenesis [13,14]. Histologic assessment of the morphology of nerves in knee OA animal model by sodium monoiodoacetate (MIA) injection showed changes to nerves suggestive of neuropathic pain. Such changes include reduced nerve fiber density, expression of activation transcription factor-3 (ATF-3; a marker of nerve damage) in the spinal cord [13]. The presence of lysophosphatidic acid (LPA) in joint synovium has been found to correlate with myelin thickness and ATF-3 in OA model by MIA injection [14]. However, these hypotheses have not been proved in the patients of OA.

Previous studies demonstrated that neuropathic pain localized to the knees, assessed using the PDQ, affected 5% to 32% of patients [4,11,15-18]. Possible neuropathic pain has been variously reported in 21%
to 50% of cases (Table 4) [4,11,15-18]. The present study reported 6% and 22 % with neuropathic pain and possible neuropathic pain, respectively. This prevalence was lower than many studies; however, it was similar to Japanese report by Ohtori et al. [15]. Although, previous studies did not evaluate the outcomes after TKA in patients with neuropathic pain, the present study demonstrated the key role of preoperative possible neuropathic pain on postoperative pain. Using the Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) scale, Fitzsimmons et al. [19] reported that suspected neuropathic pain was present in 35.5% of pre-TKA patients, and in 23.6% of OA patients at 6 months post-TKA. Patients scoring 12 or greater on the scale were defined as having suspected neuropathic pain [19]. If surgeons recognize the presence of possible neuropathic pain before TKA, careful evaluation, including of spinal disease, is needed to avoid chronic postoperative knee pain. A recent study demonstrated that possible neuropathic pain with end-stage hip and knee OA was more strongly associated with pain at rest than pain on activity [20]. This indicates that the clinical presentation of pain at rest may warrant more thorough evaluation for potential neuropathic pain. Using S-LANSS, Razmjou et al. [21] showed that the prevalence of neuropathic pain was 14% at an average of 5 years after TKA. They also showed that patients with neuropathic pain (S-LANSS score of 12 or greater) remained more disabled, and with a higher level of depression and less satisfaction. Moreton et al. [4] evaluated PDQ and S-LANSS to determine agreement between the two assessment methods. PDQ assesses pain quality associated with augmented central pain processing in patients with OA. Although developed as a screening questionnaire, the PDQ may also function as a measure of characteristics that indicate augmented central pain processing. They found that agreement between PDQ and S-LANSS for pain classification was low, and it is currently unknown which tool may best predict treatment outcome. One of the important problems of PDQ is that when the patient has no pain, the patient is classified as nociceptive pain group. Nociceptive pain includes no pain.

Neuropathic pain is uncommon after TKA surgery. While approximately 20% of patients with advanced degenerative knee disease have elements of pain that test positive with a specific neuropathic pain, less than 3% of the patients assessed in this study continued to have similar pain symptoms noted after their surgery. The overlap of pain symptoms between osteoarthritis patients and this specific battery (PDQ), suggests that the inventory may not be a selective tool to assess for neuropathic pain. New onset neuropathic pain is uncommon after TKA, and may only impact 1-2% of patients. While the severity of pain may significantly impact these patients, it is not a likely explanation for up to 20% of patients who have reported dissatisfaction with TKA in a number of reported studies [22-24]. One of the reasons might be transformation of PDQ scores to category variable from continuous variable. When we used PDQ scores as continuous variable, postoperative NRS and PDQ scores showed positive correlation. We showed a nearly 9-fold decrease in the proportion of patients with neuropathic pain after TKA. However, knees with postoperative possible neuropathic pain had higher postoperative NRS scores than those with nociceptive pain. In addition, higher PDQ scores were associated with severe pain and might be resulted in worse outcome and less satisfaction after TKA.

Buvanendran et al. [25] reported that perioperative pregabalin administration reduces postoperative neuropathic pain. However, this remains controversial as two studies have generated conflicting results
Although the causes and factors associated with neuropathic pain warrant further investigation, preoperative assessment, including by the PDQ, may be useful to reduce the prevalence of postoperative chronic knee pain.

Limitations of this study include the absence of evaluations of spinal disease and only a 6 month follow-up period.

**Conclusion**

In conclusions, preoperative PDQ scores classified 22.2% of OA knee pain as possible neuropathic pain. Although it is important to consider neuropathic pain in the treatment of osteoarthritic knee pain, the prevalence of possible neuropathic pain decreased to 3.3% after TKA. However, the presence of possible neuropathic pain preoperatively might affect the occurrence of chronic postoperative pain.

**Abbreviations**

OA: osteoarthritis; PDQ: painDETECT questionnaire; TKA: total knee arthroplasty, NRS: numerical rating scale; IASP: International Association for the Study of Pain, KL: Kellgren-Lawrence; BMI: body mass index; NRS: numerical rating scale; MIA: monooiodoacetate; ATF-3: activation transcription factor-3; LPA: lysophosphatidic acid; S-LANSS: Self-administered Leeds Assessment of Neuropathic Symptoms and Signs

**Declarations**

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**Authors’ contributions**

MH was the main investigator and wrote the manuscript. ST and YN helped with data analysis. AS helped with the interpretation of the data and results. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data related to this case report are contained within the manuscript.

**Ethical approval and consent to participate**
The study was approved by the ethical committees, and all participants provided written informed consent.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Tables**

Due to technical limitations, tables xlsx are only available as a download in the Supplemental Files section.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Table1PDQJOSR.xlsx
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- Table3possibleneuropathicpainJOSR.xlsx
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