The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study

V. Wylde*, S. Palmer‡, I.D. Learmonth†, P. Dieppe§

Musculoskeletal Research Unit, University of Bristol, Avon Orthopaedic Centre, Southmead Hospital, Bristol, UK
Faculty of Health & Life Sciences, University of the West of England, Bristol, UK
Peninsula Medical School, Universities of Exeter and Plymouth, UK

Summary

Objective: Chronic pain after total knee replacement (TKR) is a prevalent condition, affecting about 20% of patients. The aim of this study was to explore the relationship between pre-operative pain thresholds and chronic pain after TKR.

Design: Patients listed for a TKR because of osteoarthritis participated in a Quantitative Sensory Testing (QST) session prior to surgery. Pressure pain thresholds (PPTs) and hot pain thresholds were assessed at the osteoarthritic knee and the forearm. Patients were followed-up at 1-year after TKR, and the severity of pain in the replaced knee was assessed using the WOMAC Pain score. Pre-operative median QST thresholds were compared to thresholds from a normative database collected from 50 people with no knee pain. The relationship between pre-operative pain thresholds and pain severity post TKR were tested using correlations.

Results: Fifty-one patients participated in a pre-operative QST session and completed a 1-year WOMAC Pain score. Pre-operatively, patients demonstrated evidence of localised (knee) and widespread (forearm) pain sensitisation in response to pressure stimuli compared to healthy participants. Pre-operative PPTs at the forearm were found to be significantly correlated with 1-year WOMAC Pain scores ($r = 0.37, P = 0.008$).

Conclusions: This study provides preliminary evidence that pre-operative widespread pain sensitisation, measured using pressure algometry, may be associated with chronic pain after TKR. Further research is needed to explore the predictive value of an assessment of pre-operative widespread pain sensitisation in identifying who is likely to develop chronic pain after TKR.

Introduction

Total knee replacement (TKR) is primarily performed to provide relief from chronic knee pain, most commonly caused by osteoarthritis (OA). For many patients, TKR is an effective surgical intervention. However, approximately 20% of patients continue to experience severe chronic pain in their replaced knee. There is a need to develop an effective screening protocol that could be used in a clinical setting to identify these patients before they undergo surgery. Patients who are likely to gain less benefit from TKR could then be targeted with interventions to reduce their risk factors for developing chronic post-surgical pain prior to undergoing surgery or they could be offered alternative treatment. The identification of non-responders is a particular pertinent issue because of the moves towards rationing access to joint replacement in the current economic climate.

Recent research has found that some patients with OA have pain sensitisation, which has the potential to be a risk factor for chronic pain after TKR. Pain sensitisation involves amplification in neuronal activity that can occur at both a local and generalised level, leading to increased sensitivity to nociceptive input and reduced pain thresholds. Using Quantitative Sensory Testing (QST), this study aimed to explore the relationship between pre-operative pain thresholds and chronic pain after TKR.

Patients and methods

Patient recruitment

Ethical approval was obtained from the Local Research Ethics Committee and all participants provided informed, written consent. The procedures followed were in accordance with the ethical
standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All consecutive eligible patients at one large elective orthopaedic centre were posted information about the study and asked to return a reply slip if they were interested in participating. Exclusion and inclusion criteria were established via a self-report screening questionnaire. Inclusion criteria included being listed for a primary TKR because of OA and being pain-free in their right forearm (to allow testing of widespread pain sensitisation at a body site distant to the osteoarthritic knee). Because QST involves the full co-operation of participants, individuals who had cognitive impairment or dementia were excluded.

Assessment times

TKR patients completed a questionnaire and participated in a QST session pre-operatively, and then completed a questionnaire at 1-year post-operatively.

Questionnaire

To assess the pain severity in the index knee, patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale. This questionnaire assesses the severity of knee pain from ‘none’ to ‘extreme’ when performing five different activities to produce a total score of 0–20, which was transformed to a 0–100 scale (worst to best).

QST

Patients underwent QST testing at a median of 17 days (2–30 days) before surgery. Testing was conducted in a private office by a single investigator (VW) using the same protocol and standardised instructions on each occasion. QST was performed at two body sites: the volar surface of the right forearm and the medial side of the index knee. These body sites were chosen because they could provide evidence of localised pain sensitisation (index knee) and widespread pain sensitisation (forearm). Pressure and heat pain thresholds were tested because they have been shown to demonstrate short-term test-retest reliability when used in knee OA patients.

Pressure pain thresholds (PPTs)

PPTs were measured using a digital algometer (Somedic, Sweden). A 1 cm² probe was held perpendicular to the skin and force applied at a constant rate of 10 kPa/s. Patients were instructed to say ‘stop’ when the sensation of pressure became the very first sensation of pain. The PPT was recorded three times and calculated as the average from the last two readings, with the first reading being excluded to increase reliability.

Hot pain thresholds

Hot pain thresholds (HPTs) were assessed using a QST analyser (Thermotest Modular Sensory Analyzer, Somedic, Sweden). The same thermode (25 x 50 mm²) was used in all tests. The method of limits algorithm was used, and the thermode adaptation temperature of 32°C increased at a rate of 0.5°C/s. Patients were instructed to press a response button as soon as the heat became painful. Each stimulus was generated after a randomised 4–6 s interval, and the stimulus was delivered four times at each body site and a mean value from the last three readings was calculated.

Sample size

Because this was an exploratory study, no formal sample size calculation was conducted. Previous studies assessing pain thresholds of joint replacement patients have included between 14 and 69 patients, and therefore it was decided that a sample of approximately 50 TKR patients would be a sufficient sample size to perform exploratory data analysis on the results.

Normative pain threshold data

To determine whether TKR patients had evidence of pain sensitisation, it was necessary to compare patient’s pain thresholds to pain thresholds of people without knee pain (referred to as healthy participants). Pain threshold data from a normative database established at this research centre was used. This database consists of QST data on 50 healthy participants with no knee pain. These healthy participants were recruited through three methods: from friends/family of knee OA patients participating in QST studies; from upper limb, urology or skin pigmentation clinics; and from research colleagues. Exclusion and inclusion criteria were established via a self-report screening questionnaire. Inclusion criteria included having no pain in either knee, no previous TKR, and being pain-free in the forearm. Exclusion criteria included cognitive impairment or dementia. To facilitate age matching of the healthy participants to OA patients, only healthy participants over the age of 50 years were approached. The pain threshold data was collected using the same QST methodology as this study, and was therefore utilised as normative data.

Statistical analysis

A Kolmogorov–Smirnov test revealed that some of the pain thresholds were non-normally distributed, and therefore non-parametric tests were used. Body region and QST modality were analysed separately to identify any modality-specific or region-specific somatosensory abnormalities. Summary statistics are presented as medians (interquartile ranges) and percentages. Mann–Whitney U tests were used to compare continuous variables between independent samples and Wilcoxon signed-rank tests were used to compare continuous variables between paired samples. Correlations between continuous variables were tested using Spearman Rank correlation coefficients. All statistical analysis was performed with the use of SPSS (version 16.0; SPSS, Chicago, Illinois).

Results

Patient demographics

Of the 469 eligible patients who were invited to participate in the study, 57 patients agreed to participate and attended a pre-operative QST session, giving a response rate of 12%. The gender distribution of the participants and non-participants were similar (58% female vs 66% female respectively) but participants were significantly younger than non-participants (68 years vs 71 years, P = 0.012). Of the 57 patients recruited into the study, one patient withdrew from the study and five patients did not complete a post-operative WOMAC Pain score. Therefore 51 patients and 50 healthy participants were included in the data analysis.

The median (interquartile range) age of the TKR patients was 68 years (61–75 years), which was not significantly different from the median age of 69 years (62–73 years) of the healthy participants (P = 0.692). There were 29 females in the patient group, compared to 21 females in the healthy participant group. Patients had a median of 4 (2–5) painful joints, which was significantly more than the median of 1 (0–2) painful joint in healthy participants (P < 0.001).

Post-operative WOMAC scores were completed at a median of 13 months (12–13 months) after surgery. Median WOMAC Pain scores significantly improved over the study period, from a median of
of 40 (30–55) pre-operatively to 90 (75–100) at 1-year post-operative ($P < 0.001$). At 1-year post-operative, 15 patients (29%) had a WOMAC pain score of $\leq 75$.

**Pre-operative pain thresholds**

Patient’s median pre-operative knee and forearm PPTs were significantly lower than healthy participant’s PPTs ($P < 0.001$). There were no significant differences in HPTs between patients and healthy participants at either the knee or the forearm ($P = 0.354$ and $P = 0.268$, respectively). Further data can be found in the supplementary file.

**Pre-operative pain thresholds and chronic pain after TKR**

There was no correlation between pre-operative HPTs or knee PPTs and 1-year WOMAC Pain scores (Table I). However, pre-operative forearm PPTs demonstrated a small but statistically significant correlation with 1-year WOMAC Pain scores ($r = 0.37$, $P = 0.008$), suggesting that patients with lower pre-operative PPTs thresholds at the forearm (i.e., greater widespread pain sensitisation) reported more severe pain in the replaced knee at 1-year after surgery. When patients were divided into low and high pre-operative forearm PPTs (dichotomised by median value), patients in the low PPT group were found to report significantly worse 1-year WOMAC Pain scores (85 (65–95)) compared to patients in the high PPT group (95 (85–100)) ($P = 0.031$). A scatterplot of the relationship between pre-operative forearm PPTs and 1-year WOMAC Pain Scores in presented in Fig. 1.

**Discussion**

This study found novel preliminary evidence that pre-operative PPTs at the forearm may be associated with pain severity in the replaced knee at 1-year after surgery. Significant associations between pre-operative QST measurements and chronic post-surgical pain have been found across a range of different surgeries, including thoracic surgery,$^{10}$ shoulder subacromial decompression$^{11}$ and hernia repair.$^{12}$ In relation to TKR, one study found that pre-operative electrical pain thresholds at the hand were significant predictors of knee pain severity at 18-months after surgery.$^{4}$ Another finding of the current study was that patients with knee OA listed for a TKR demonstrated evidence of pre-operative localised and widespread pain sensitisation in response to pressure stimuli. This is now well-established, with a systematic review and meta-analysis finding that OA patients have lower PPTs at both the affected joint and remote sites compared to healthy participants.$^3$

It is important to acknowledge the limitations of the study when interpreting the results. Although relatively large for this type of study, the sample size was small and therefore limited statistics could be conducted on the data. Factors known to influence the experience and reporting of chronic pain, such as gender and psychosocial factors,$^{13}$ were not controlled for in this study. Therefore, larger studies are needed to provide greater statistical power and confirm these preliminary results. Many of the healthy participants were from the same family as the TKR participants, and therefore genetic factors may have confounded the data on pain perception and sensitisation. Healthy participants also had an average of one painful joint which may have affected QST results. The recruitment rate into the study was low at 12%, likely because of the high participant burden due to the need to attend the hospital for the QST session, which may have resulted in selection bias. However, if future studies focus on pressure algometry, then PPTs could be measured during routine clinic appointments, and therefore would not necessitate the need for participants to attend additional research appointments. Also there were demographic differences between the participants and non-participants which may affect the generalisability of the results. However, the study was exploratory in nature, with the aim of generating avenues for further investigation in larger studies.

In summary, this study provides some preliminary evidence that pre-operative widespread pain sensitisation, measured using pressure algometry, may be associated with chronic pain after TKR. These findings suggest that further investigation is warranted into the role of pre-operative pain sensitisation in predicting chronic post-surgical pain. Larger studies, in which other known risk factors are assessed and controlled for, are needed to establish the sensitivity and specificity of pre-operative measures of pain sensitisation in the prediction of chronic pain after TKR. Evidence suggests that both electrical and pressure pain testing may be useful prediction tools and therefore future QST studies may benefit from including a multi-modal assessment approach. Further research could then evaluate whether the addition of an assessment of pre-operative pain sensitisation into a predictive model increases its ability to accurately identify who is likely to experience chronic pain after TKR. This would enable high risk patients to be targeted with pre-surgical interventions to improve their likelihood of a good outcome, or provide them with the opportunity to make an informed decision not to undergo major surgery which is unlikely to improve their pain.

**Author contributions**

Vikki Wylde was involved in the conception and design of the study, collection of the data, analysis and interpretation of the data, drafting of the article and final approval of the article.
Shea Palmer was involved in the conception and design of the study, analysis and interpretation of the data, critical revision of the article for important intellectual content, and final approval of the article.

Ian Learmonth was involved in the conception and design of the study, critical revision of the article for important intellectual content, and final approval of the article.

Paul Dieppe was involved in the conception and design of the study, analysis and interpretation of the data, critical revision of the article for important intellectual content, and final approval of the article.

Competing interest
The authors have no competing interests to declare.

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Supplementary data
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