The natural history of pain and neuropathic pain after knee replacement

A PROSPECTIVE COHORT STUDY OF THE POINT PREVALENCE OF PAIN AND NEUROPATHIC PAIN TO A MINIMUM THREE-YEAR FOLLOW-UP

A small proportion of patients have persistent pain after total knee replacement (TKR). The primary aim of this study was to record the prevalence of pain after TKR at specific intervals post-operatively and to ascertain the impact of neuropathic pain. The secondary aim was to establish any predictive factors that could be used to identify patients who were likely to have high levels of pain or neuropathic pain after TKR.

A total of 96 patients were included in the study. Their mean age was 71 years (48 to 89); 54 (56%) were female. The mean follow-up was 46 months (39 to 51). Pre-operative demographic details were recorded including a Visual Analogue Score (VAS) for pain, the Hospital Anxiety and Depression score as well as the painDETECT score for neuropathic pain. Functional outcome was assessed using the Oxford Knee score.

The mean pre-operative VAS was 5.8 (1 to 10); and it improved significantly at all time periods post-operatively (p < 0.001): (from 4.5 at day three to five (1 to 10), 3.2 at six weeks (0 to 9), 2.4 at three months (0 to 7), 2.0 at six months (0 to 9), 1.7 at nine months (0 to 9), 1.5 at one year (0 to 8) and 2.0 at mean 46 months (0 to 10)). There was a high correlation (r > 0.7; p < 0.001) between the mean VAS scores for pain and the mean painDETECT scores at three months, one year and three years post-operatively. There was no correlation between the pre-operative scores and any post-operative scores at any time point.

We report the prevalence of pain and neuropathic pain at various intervals up to three years after TKR. Neuropathic pain is an underestimated problem in patients with pain after TKR. It peaks at between six weeks and three-months post-operatively. However, from these data we were unable to predict which patients are most likely to be affected.

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The incidence of chronic pain and disability after total knee replacement (TKR) is reported to be between 8% and 34%.1,2 National Joint Registry data have revealed rates of dissatisfaction one year after TKR of more than 18%.3,4 Many causes of chronic pain after TKR have been described.5 Efforts have been made to improve the outcome by technological developments such as the use of navigation and custom-made cutting blocks,6-9 as well as methodology, such as by using kinematic rather than mechanical alignment.10,11 However, there still appears to be a group of patients with a technically satisfactory TKR and without evidence of infection who remain dissatisfied. Dissatisfaction is clearly multifactorial but a contributing factor is pain.12 However, revision has been found to have limited success when performed for pain alone.13

Neuropathic pain has been described after TKR. Buvanendran et al14 identified a rate of neuropathic pain of 5% six months post-operatively in a prospective series of 120 patients after TKR. Wylde et al2 identified rates of neuropathic pain of 6% three to four years post-operatively in a retrospective study of 632 patients after TKR. Why rates of neuropathic pain are so high has not been explained.

Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”.15 Common findings in neuropathic pain are a sensory deficit or hypersensitivity in the painful area and a gradual increase in pain following repetitive stimulation, and paroxysms of pain.16 Patients with neuropathic pain report having pain of longer duration and have greater interference from pain and significantly poorer quality of life than those with nociceptive pain.17 Neuropathic pain does not usually respond to simple analgesics and specific management strategies are needed.18

There is a lack of evidence about the natural history of pain and, specifically, neuropathic pain following TKR. Most studies on
pain focus on the early post-operative period with few continuing beyond three months after TKR.\textsuperscript{19-21}

We therefore designed a prospective study involving a cohort of patients undergoing TKR for osteoarthritis evaluating pain and any neuropathic element to it, at regular intervals, for a minimum of three years post-operatively. The primary aim was to establish the prevalence of pain at specific intervals post-operatively, and to ascertain the impact of neuropathic pain. A secondary aim was to establish any predictive factors that could be used to identify which patients were likely to experience high levels of pain or neuropathic pain after TKR.

**Patients and Methods**

A total of 96 patients with primary osteoarthritis of the knee were recruited to the study between July 2009 and May 2010. These were consecutive patients seen in a physiotherapist-led pre-operative education class, of whom 54 (56\%) were female. Their mean age was 70.6 years (48 to 89) and all underwent primary TKR. Baseline details included demographics, co-morbidities and the use of medication including anti-depressants and anti-neuropathics were recorded.

Pain was assessed using a 0 to 10 Visual Analogue Scale (VAS); this is a well evaluated tool.\textsuperscript{22} The 11-point Likert scale uses zero to represent no pain and ten to represent the worst possible pain. Improvements of > 30\% (i.e. three points on the scale) are thought to be significant.\textsuperscript{23} The VAS has also been interpreted as either no pain (VAS = 0), mild (VAS = 1 to 3), moderate (VAS = 4 to 6) or severe (VAS = 7 to 10).\textsuperscript{24}

Neuropathic pain was self-assessed using the painDETECT questionnaire.\textsuperscript{25} This has also been evaluated in a mixed pain clinic population, and we felt that was a better tool than others such as the self-administered version of the Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS),\textsuperscript{26} as it allowed patients to grade the severity of their symptoms and a number could be recorded which could be correlated with a VAS pain score. A painDETECT score 0 to 12 implies neuropathic pain is unlikely, 13 to 18 implies neuropathic pain is unclear (possible) and 19 to 38 means neuropathic pain is likely to be present.

Pre-operative anxiety and depression was evaluated using the HADS assessment tool.\textsuperscript{27} This was performed using GraphPad Prism version 6.00 for Windows, (GraphPad Software, La Jolla, California). Paired results were compared using paired Wilcoxon tests (non-parametric data). Correlation was determined using the Spearman correlation test for non-parametric data. R > 0.7 is deemed to be highly correlated, and r = 0.5 to 0.7 moderately correlated. A p-value of < 0.05 was considered to be statistically significant.

**Results**

The mean follow-up was 46 months (39 to 51). The rate for completion of the documentation was high, with 89 patients (94\%; one patient had died) responding at 12 months, and 80 (92\%; seven patients had died) responding at final follow-up, at which time 19 patients (20\%) had undergone contralateral TKR.

Pre-operative scores are shown in Table I. Pain scores improved up to the time of final follow-up (p < 0.001 for all data points compared with the pre-operative VAS for pain; Wilcoxon matched-pairs signed rank test; Fig. 1). The prevalence of pain at all points is shown in Table II and Figure 2.

<table>
<thead>
<tr>
<th>Pre-operative score (n = 96)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS pain</td>
<td>5.8</td>
<td>1 to 10</td>
</tr>
<tr>
<td>painDETECT</td>
<td>4.9</td>
<td>0 to 20</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>3.8</td>
<td>0 to 17</td>
</tr>
<tr>
<td>HADS depression</td>
<td>5.4</td>
<td>1 to 14</td>
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<tr>
<td>Oxford Knee Score</td>
<td>20</td>
<td>7 to 45</td>
</tr>
</tbody>
</table>

**Statistical analysis.** This was performed using GraphPad Prism version 6.00 for Windows, (GraphPad Software, La Jolla, California). Paired results were compared using paired Wilcoxon tests (non-parametric data). Correlation was determined using the Spearman correlation test for non-parametric data. R > 0.7 is deemed to be highly correlated, and r = 0.5 to 0.7 moderately correlated. A p-value of < 0.05 was considered to be statistically significant.
Pre-operatively, the painDETECT scores revealed a prevalence of possible neuropathic pain in five patients (5%) and likely neuropathic pain in only one patient (Table III).

Neuropathic pain became most prevalent six weeks post-operatively with 23 of 85 respondents (27%) having possible neuropathic pain, and seven (8%) having likely neuropathic pain. Three months post-operatively, 16 of 82 respondents (17%) had possible and two (3%) had likely neuropathic pain. After peaking between six weeks and three months, the proportion of patients having neuropathic pain then reduced to eight of 87 respondents (9%) with possible and two (2%) with likely neuropathic pain. One year post-operatively, the proportion of patients having neuropathic pain was five of 79 respondents (7%) with possible and one (1%) with likely neuropathic pain. The changes in painDETECT scores are shown in Figures 3 and 4.

The intensity of neuropathic pain varied with time. Of the seven patients with likely neuropathic pain six weeks post-operatively, only one had likely neuropathic pain at final follow-up (with one lost to follow-up). Of the five patients at final follow-up with likely neuropathic pain, only one had this pre-operatively, two had it six-weeks post-operatively (with no data collected for one patient at this time) and one had it three months post-operatively.

Of the five patients with possible neuropathic pain pre-operatively, one had developed likely neuropathic pain one year post-operatively (one was lost to follow-up). At three years post-operatively one new patient had developed likely neuropathic pain, two were lost to follow up and the other patient with neuropathic pain had died.

The single patient with likely neuropathic pain pre-operatively had high scores suggestive of neuropathic pain at every stage and at 40 months post-operatively. Pre-operatively she had no anxiety or depression, her VAS for pain was 10/10 and she was already on treatment for neuropathic pain. She had high levels of pain post-operatively and was treated with opiate patches, pregabalin and amitryptiline. She underwent two manipulations under anaesthesia and at the latest follow-up at 40 months she had a VAS pain score of 8/10, an OKS score of 17 and a painDETECT score of 21. Despite this, she thought the outcome of her TKR was ‘fair’ and she had ‘mixed’ satisfaction levels.

Patients with high painDETECT scores at final follow-up underwent secondary review of their medical records and radiographs. This revealed no features of malalignment or incorrect sizing that could explain the symptoms.

**Patient satisfaction.** Satisfaction one year post-operatively and at final follow-up is shown in Figures 5 and 6. At final follow-up, 11 of 79 respondents (14%) had mixed feelings about their TKR or were dissatisfied. In all, ten of this group had VAS pain scores of >7 on walking. Two had possible neuropathic pain and three had likely neuropathic pain. Of the 11 dissatisfied patients, six had undergone further surgery and one is awaiting arthroscopy to debride...
patellofemoral scar tissue, causing crepitus. No significant factors were identified pre-operatively that predicted dissatisfaction at final assessment.

Of the five patients with likely neuropathic pain at final follow-up, two were not satisfied with their operation, one had mixed feelings and two were satisfied. Of the five patients with VAS pain scores of > 7 at final follow-up, two were not satisfied with their operation, one reported a mixed outcome and two were satisfied.

A total of ten patients had high anxiety or depression scores pre-operatively (HADS > 11); three had high scores for both anxiety and depression; four had high scores for depression alone and three for anxiety alone. One patient died and two others were lost to follow-up. Only one patient, with depression, developed likely neuropathic pain at final follow-up; all other patients had painDETECT scores of < 12, all had VAS pain scores of < 5, and all but one patient had better than ‘mixed’ satisfaction levels.

There was no correlation between the pre-operative VAS pain scores and post-operative painDETECT scores at any stage (r < 0.5). Similarly, there was no correlation between the pre-operative painDETECT scores and the post-operative VAS pain scores at any stage (r < 0.5). However, at other intervals there were either moderate or high correlations between the VAS pain scores and the painDETECT scores at the same times post-operatively. VAS pain and painDETECT scores correlated at three months (Spearman correlation r = 0.74, 95% confidence intervals (CI) 0.61 to 0.82), nine months (r = 0.76, 95% CI 0.65 to 0.84), 12 months (r = 0.72, 95% CI 0.59 to 0.81) and at final follow-up (r = 0.76, 95% CI 0.65 to 0.85). The painDETECT scores at six weeks and six months post-operatively correlated only moderately with VAS pain scores at final follow-up (r = 0.53 and r = 0.50).

At final follow-up, a high (negative) correlation was identified between the OKS and the VAS pain (r = -0.86, 95% CI -0.78 to -0.91), and painDETECT (r = -0.77, 95% CI -0.69 to -0.83).
CI -0.85 to -0.65) scores. There was no correlation between the pre-operative HADS scores and any other scores.

**Complications and further surgery.** A total of 11 patients (11%) had a complication or underwent further surgery. Two patients underwent revision surgery, one for instability and one for deep infection; three patients sustained traumatic extensor mechanism injuries (one open avulsion of the patellar tendon, one avulsion of the quadriceps tendon and one patellar fracture, treated non-operatively); three patients underwent manipulation under anaesthesia within four months post-operatively; two underwent arthroscopic arthrolysis for stiffness and one underwent secondary patellar resurfacing. The mean VAS pain score at final follow-up in these patients, two of whom were lost to follow-up was 4.3 (1.3 to 10). The mean painDETECT score was 11.7 (2 to 21) and two had scores of > 18. Six of the remaining ten patients reported a ‘fair’ or ‘poor’ outcome, and seven reported their satisfaction as being ‘mixed’ or ‘worse’.

**Discussion**

This study confirms that there is a significant decrease in pain after TKR. However, for some, pain persists at three years post-operatively; with 12 of 80 patients (15%) having moderate pain and six of 80 (7%) having severe pain at a mean of 46 months. This is consistent with the findings of Wylde et al. who retrospectively identified 632 patients who had undergone TKR and sent out questionnaires between three and four years post-operatively, achieving a 73% response rate. Using the Western Ontario and McMaster Universities Arthritis Index score, 17% had moderate persistent pain and 15% had severe persistent pain.

We found significant improvements of pain after TKR at all points (p < 0.001) and levels of satisfaction that are consistent with United Kingdom patient reported outcome measures (PRoMS). Previous studies by Wylde et al. and Buvendran et al. found levels of neuropathic pain to be 5% at six months.
and 6% between three and four years post-operatively. Using the painDETECT score, we found that the rate of neuropathic pain was at its highest six-weeks post-operatively, with 8% having likely, and 27% having possible neuropathic pain. This rate then decreased and 3% had likely and 17% had possible neuropathic pain six months post-operatively. At final follow-up, 6% had likely and 7% had possible neuropathic pain.

Neuropathic pain adversely affects the quality of life. We have demonstrated that potentially up to 35% of patients have symptoms of neuropathic pain six weeks after TKR. The question arises whether these patients should receive specific treatment for these symptoms. It is possible that many of the symptoms experienced in the early post-operative period may be neuropathic in origin as part of the normal, inflammatory process. Significant symptoms can be treated in accordance with the National Institute for Health and Clinical Excellence (NICE) guidelines for the pharmacological management of neuropathic pain in adults. Amitriptyline or pregabalin are recommended as first line treatment, but when symptoms cannot be controlled, early referral to a specialist pain service is suggested.

This study has identified a correlation between pain as assessed using a VAS and neuropathic pain as assessed using the painDETECT score. There was a high correlation ($r > 0.7$) between these two at three months, one year and a mean 46 months after operation.

Pre-operative screening with painDETECT scores is unlikely to be useful in the absence of a correlation between the pre-operative scores and those at a minimum of three years. However, a moderate correlation was identified between the painDETECT scores at six weeks and three months and those at final follow-up. Thus, early intervention in these patients might be helpful.

There was no correlation between any pre-operative scores (VAS, painDETECT or HADS), and the post-operative scores. Depression has been reported to affect the outcome after TKR, and Wylde et al recently identified a relationship between the number of painful sites elsewhere in the body and chronic pain. We did not find any significant influence of depression on post-operative outcome.

Only one patient had high levels of neuropathic pain pre-operatively and continued with high levels of neuropathic pain up to three years post-operatively. It is unclear whether such patients should have the neuropathic element treated before being considered for TKR.

More than 80% of the dissatisfied patients had high levels of pain, and 45% had possible neuropathic pain. The dissatisfied patients had a high rate of post-operative intervention. The challenge for surgeons is to identify remediable faults in those with persistent pain and dissatisfaction after TKR. The study involved patients listed for primary TKR by consultant surgeons, and seen in a pre-operative clinic run by a physiotherapist. The education and explanations received by these patients may have helped alleviate anxieties about pain, and the fact that they were included in a study investigating pain after TKR may have biased the reports of pain according to the ‘Hawthorne effect’. We found no correlation between pre-operative levels of pain, neuropathic pain, anxiety or depression with outcome at a minimum of three years post-operatively. We did, however, find a moderate correlation between pain (VAS) and painDETECT scores six weeks, three months and three years post-operatively.

Overall, TKR is a very successful operation. We have been able to demonstrate that by nine months, a third of patients had no pain and a half only had mild pain. At final follow-up at a mean 46 months, almost half (45%) had no pain at all and a third experienced only mild pain. However, patients should be informed as part of the consent process that at three years post-operatively some may still have moderate or severe pain, for which no mechanical cause can be found.

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References


