Beyond the joint

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DOI:
10.33612/diss.166905204

Summary

Introduction

The aim of this thesis was to investigate the measurement of signs of sensitization in patients with hip or knee osteoarthritis, and to investigate the long-term effects of targeted preoperative treatment of sensitization with duloxetine after total knee or hip arthroplasty (TKA/THA).

In **chapter 1**, a general introduction is given to various topics covered in this thesis. Osteoarthritis is one of the most common causes of pain, disability and loss of quality of life worldwide. Pain, the main symptom of osteoarthritis, is a complex and multifactorial construct involving both intra- and extra-articular factors. The severity of OA pain cannot be fully explained from a purely nociceptive approach. Changes in the neurological processing of the pain signals, leading to peripheral and central sensitization, appear to play an important role in the experience of pain in osteoarthritis. In the scientific literature, neuropathic-like symptoms suggestive of sensitization are reported by 19% of patients with hip OA and 19-37% of patients with knee OA. There is currently no gold standard for measuring sensitization, regardless of the underlying disease. Moreover, pain in osteoarthritis patients is probably not purely due to sensitization, but it also retains a nociceptive part. It is likely represented by a mixed pain profile given all the different mechanisms involved in osteoarthritis (including sensitization). The Pain DETECT Questionnaire (PDQ) is the only questionnaire adapted to specifically measure neuropathic-like symptoms indicative of sensitization in patients with knee OA.

Part one

Part one of this thesis aimed at obtaining a reliable and valid screening tool for neuropathic-like symptoms, specifically for hip or knee OA patients. In **chapter 2**, the English-language modified painDETECT Questionnaire (mPDQ) was translated and adapted for Dutch patients with hip or knee osteoarthritis. A reliability study was conducted in 278 patients with osteoarthritis of the hip or knee, including a responsiveness analysis in 123 patients. The Dutch mPDQ shows good internal consistency and a small relative measurement error. The absolute measurement error is acceptable. Based on this study, the Dutch mPDQ appears to be suitable as a screening tool to identify patients with knee or hip osteoarthritis with a neuropathic-like pain profile, indicative of sensitization.

Chapter 3 focuses on the validation of the Dutch mPDQ. Structural validity studies confirmed two main components. However, the item about the pain pattern is unlikely to reflect the underlying construct. For the construct validity study, predefined hypotheses regarding the correlation between the mPDQ and several other questionnaires were formulated and then tested in a group of 168 patients. In a subgroup of 46 patients, the correlation with pain pressure threshold measurements (PPT) was additionally determined. Eighty percent of the hypotheses regarding

the correlation between the mPDQ and the other questionnaires were confirmed. Fifty percent of the hypotheses regarding the PPT measurements were met, probably due to heterogeneity of the PPT measurements and the limited size of this subgroup. The mPDQ appears to be a valid measuring instrument to determine the neuropathic-like complaints of patients with hip or knee osteoarthritis.

Part two

In part two of this thesis, the effect of preoperative treatment of sensitization with duloxetine on the postoperative outcomes after TKA/THA was investigated, in particular chronic residual pain. Up to 23% of patients after THA and up to 34% after TKA experience chronic residual pain. Sensitization is one of the main risk factors for poor outcome after TKA/THA, especially for chronic residual pain. In **chapter 4** a multicentre, pragmatic, prospective, randomized clinical trial was conducted in patients with end-stage primary hip or knee OA with signs of sensitization who were waiting for a TKA/THA (the DOA study). Seven weeks preoperative treatment with 60 mg duloxetine has been compared to usual care. The primary outcome measures are the Pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Hip Disability and Osteoarthritis Outcome Score (HOOS).

The long-term effect of preoperative duloxetine treatment is described in **chapter 5**. One hundred and eleven participants were enrolled and the mean change in KOOS/HOOS pain sub-scale was 37 (SD 28.1) in the intervention group and 43 (SD 26.5) in the usual care group (on a scale of 0-100). There was no statistictically significant difference found in change in score six months after TKA/THA between both groups ($p = 0.280$). The additional longitudinal data analysis showed no significant postoperative differences up to one year after TKA/THA. For the evaluation of change in pain over time, as described in chapter 5, it is essential to know the responsiveness and interpretability of the measuring instruments used. Responsiveness is defined by COSMIN (COnsensus based Standards for the selection of health Measurement Instruments) as "the ability of an instrument to detect changes over time in the construct to be measured", and interpretability as "the degree to which a qualitative meaning can be attributing (in other words, clinical or commonly understood connotations) to the quantitative change scores of an instrument".

In **chapter 6**, responsiveness and interpretability of the pain subscales of the KOOS and HOOS in knee and hip osteoarthritis patients were investigated. Both criterion validity (comparison with a gold standard) and construct validity (testing hypotheses using correlations with other questionnaires) were investigated. The study used data from 93 patients from the DOA study. The mean change was 4.3 and 4.6 points after duloxetine treatment for patients with knee or hip osteoarthritis, respectively, and 31.7 and 48.8 points after TKA/THA, respectively. The Area

Under the Curve was 0.72 (95% CI 0.527-0.921) and 0.79 (95% CI 0.588-0.983) for patients with knee and hip osteoarthritis, respectively. Of the predefined hypotheses, 69% were confirmed for both subscales, endorsing the responsiveness of the KOOS and HOOS pain subscales in patients with knee or hip osteoarthritis and patients after TKA/THA.

For interpretability, the Minimally Important Change (MIC) ranged between 12.2 and 37.9 for the KOOS pain subscale and between 11.8 and 48.6 for the HOOS pain subscale, depending on whether the change was assessed after treatment with duloxetine, or six months after TKA/THA. This indicates a significant response shift after arthroplasty. This means that when assessing the effects of preoperative treatments on the development of postoperative pain after hip or knee replacement, it is important to realize that the effect of the procedure itself is likely to produce a change in the patients' internal measure of pain relief.

General Discussion

Chapter 7 contains a general discussion of the findings of both parts of this thesis, including clinical implications and recommendations for future studies. Based on the findings of part one of this thesis, there is a need for more specific measuring instruments for measuring signs of sensitization in patients with hip and knee OA, and a need to further investigate the difference in sensitization between patients with hip or knee OA.

Part two of this thesis shows the need for future research into the treatment of sensitization in patients with knee or hip osteoarthritis. Consideration may be given to investigating different treatment regimens with duloxetine, or other neuromodulating medications, to investigate whether such medications play a role in the treatment of chronic residual pain after TKA/THA. Future research and clinical practice could also focus on offering behavioural strategies to patients who appear prone to sensitization, not only to treat current symptoms, but also to fall back on should sensitization recur in the future as a result of another physical or mental catalyst, such as surgery.