Beyond the joint

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Abstract

Residual pain is a major factor in patient dissatisfaction following total hip arthroplasty or total knee arthroplasty (THA/TKA). The proportion of patients with unfavourable long-term residual pain is high, ranging from 7 to 34%. There are studies indicating that a preoperative degree of central sensitization (CS) is associated with poorer postoperative outcomes and residual pain. It is thus hypothesised that preoperative treatment of CS could enhance postoperative outcomes. Duloxetine has shown to be effective for several chronic pain syndromes, including knee OA, in which CS is likely one of the underlying pain mechanisms. This study aims to evaluate the postoperative effects of preoperative screening and targeted duloxetine treatment of CS on residual pain compared to care-as-usual.

This multicenter, pragmatic, prospective, open-label, randomised controlled trial includes idiopathic hip/knee OA patients who are on a waiting list for primary THA/TKA. Patients, at risk for CS, will be randomly allocated to the preoperative duloxetine treatment program group or the care-as-usual control group. Primary endpoint is the degree of postoperative pain 6 months after THA/TKA. Secondary endpoints at multiple time points up to 12 months postoperatively are: pain, neuropathic pain like symptoms, (pain)sensitization, pain catastrophizing, joint associated problems, physical activity, health-related quality of life, depressive and anxiety symptoms, and perceived improvement. Data will be analysed on an intention-to-treat basis.

The study is approved by the local Medical Ethics Committee (METc 2014/087) and will be conducted according to the principles of the Declaration of Helsinki (64th, 2013) and the Good Clinical Practice standard (GCP), and in compliance with the Medical Research Involving Human Subjects Act (WMO).

The trial (protocol V.4.0, 07/2015) is registered in the Dutch Trial Registry with number NTR 4744 and in the EudraCT database with number 2013-004313-41.

Chapter 4

The Duloxetine in OsteoArthritis study (DOA study); effect of a preoperative pain treatment with duloxetine on postoperative outcome after total hip or knee arthroplasty: design of a pragmatic open-label randomised controlled trial

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Background and rationale

Total joint replacement (TJR) is considered to be a safe, successful and cost-effective procedure for the treatment of advanced osteoarthritis (OA)(1-3). Despite its success the overall incidence of dissatisfaction is high, as 7% of total hip arthroplasty (THA) patients and 20% of total knee arthroplasty (TKA) patients are dissatisfied one year after arthroplasty(4,5). Main factors associated with patient-perceived level of dissatisfaction after TJR are level of residual pain, functional outcome and accomplished level of preoperative expectations(4-7). Of all factors, residual pain seems to be the most prominent cause of dissatisfaction(4,5,7,8). The proportion of patients with unfavourable long-term residual pain is high, ranging from 7 to 23% after THA and 10 to 34% after TKA(9).

Over the past decades it has become clear that OA pain varies among patients with OA; from intermittent- to constant pain and from nociceptive- to neuropathic pain like symptoms(10). These variations may be explained by OA-induced changes in the biochemical environment around peripheral joint nociceptors and joint structures(11). It is thought that these changes could lead to hyper-excitability of the peripheral (peripheral sensitisation) and ultimately the central nervous system (central sensitization)(11-13). Central sensitisation (CS) can be defined as an "increased responsiveness of nociceptive neurons in the central nervous system", "this may include increased responsiveness due to dysfunction of endogenous pain control systems". In a subset of patients, it is hypothesized that CS combined with peripheral articular nerve disruption is accountable for, or at least associated with, joint-related neuropathic pain like symptoms such as allodynia and hyperalgesia, and other characteristics like spontaneous pain, widespread pain, referred pain and temporal summation(12-14).

There are indications that preoperative signs/symptoms suggesting CS are associated with poorer postoperative outcomes and residual pain after TJR(15-17). Lundblad et al. found less favourable pain relief 18 months after TKA in patients with preoperative features of possible CS such as low pain thresholds at remote sites (secondary hyperalgesia) and high preoperative VAS scores for pain at rest (spontaneous pain)(16). Wylde et al. further showed that CS associated features like multiple-site pain and preoperative pain sensitization at remote sites (secondary hyperalgesia) are independent determinants of residual pain 12 and 18 months after TKA(15,17). Hence, it is hypothesised that preoperative targeted treatment of CS could be beneficial towards decreasing the level of residual postoperative pain.

There is pre-clinical(18,19) and clinical evidence that duloxetine, a centrally-acting antidepressant, is efficacious in the treatment of chronic pain conditions in which CS is likely one of the prominent underlying pain mechanisms, such as diabetic peripheral neuropathic pain(20,21), fibromyalgia(22) and chronic low back pain(23). The mechanism of pain inhibition is thought to be related to the

amelioration of serotonin and norepinephrine activity in the central nervous system(24). There is also preclinical(25) and clinical evidence that duloxetine is beneficial for lowering chronic knee OA pain compared to a placebo(26-31). The observed knee OA pain relief was due to a direct analgesic effect and not due to mood improvement.

Based on the observed relationship between preoperative signs/symptoms indicating CS and negative postoperative outcomes; this study aims to evaluate the postoperative effects of preoperative targeted duloxetine treatment of CS on residual pain after THA/TKA compared to care-as-usual. The primary objective is therefore to determine the effect of preoperative targeted duloxetine treatment on residual pain 6 months after THA/TKA. Secondary objectives are to determine the effect at different pre- and postoperative follow-up time points (see Table 1) on: pain, neuropathic pain like symptoms, (pain)sensitization, pain catastrophizing, joint associated problems, physical activity, health-related quality of life, depressive and anxiety symptoms, perceived improvement and arthroplasty-related expectations.

Methods and design

This study is a multicenter (University Medical Center Groningen (UMCG)), Martini Hospital Groningen (MH) and Medical Center Leeuwarden (MCL)), pragmatic, open-label randomised controlled trial. After signing informed consent, eligible patients will be randomly allocated by means of a web-based system (ALEA®, FormsVision, Abcoude, the Netherlands) to an intervention or a control group (Figure 1). The intervention will consist of 10 weeks of preoperative duloxetine treatment (7 weeks on target dosage). This treatment period was chosen based on two large placebo controlled RCTs among knee OA patients which showed that the main pain-relieving effect of duloxetine reached a plateau after 7 weeks on target dosage(27,28). To reduce the risk of developing side effects(32), the first week of treatment will be initiated with half of the target dose (30mg/d). In the second week there will be up titration to the target dosage of 60mg/d (2x 30mg/d capsule). The last two treatment weeks (weeks 9 and 10) are a drug tapering phase: duloxetine dosage will be lowered to 30mg/d to reduce the risk of developing discontinuation symptoms(33). In the control group subjects will receive no specific intervention and solely receive standard preoperative care-as-usual. However, in all study subjects, usage of agents to address specifically neuropathic pain (in the peri- and early postoperative period), like gabapentenoids will be discouraged (by communicating this with the anesthesiologist) since this could potentially interfere with the study outcome(s). As the current waiting period for surgery is around 2-3 months, no significant treatment delay is expected. For each subject, the duration of the clinical trial will be around 15 months, including baseline visit, a ±11-week preoperative period and a one-year postoperative follow-up period (Table 1, Figure 1). The local Medical Ethics Committee of UMCG has approved the trial (METc 2014/087), which is registered in the Dutch Trial registry

(NTR 4744) and in the EudraCT database (2013-004313-41).

Patient selection and study population

When placed on the waiting list for THA/TKA, patients will be asked to fill in a questionnaire about neuropathic pain like symptoms (the modified-painDETECT questionnaire (mPD-Q)(34). The mPD-Q is derived from the original painDETECT questionnaire(49) and is composed of seven items evaluating pain quality, one item evaluating pain pattern, and one item evaluating pain radiation. The score result is an aggregated score ranging from -1 to 38 points(49). Patients experiencing a possible or likely NP phenotype (mPD-Q score ≤12 points) and who are willing to consider participation will receive written information about the study. After about two weeks the researchers will call the patients to ask if they have any questions regarding the study; if patients are willing to participate, they will be checked for inclusion and exclusion criteria (TB, WR).

Inclusion criteria

To be eligible to participate in this study, a patient must be an adult (age>18 years) diagnosed with primary hip/knee OA (based on clinical and radiological ACR criteria) and having a possible or likely NP phenotype (mPD-Q-score >12) at time of screening. The latter criterion is included to identify patients who are likely more at risk for developing residual pain, as research showed that characteristics of CS are more prevalent in hip/knee OA patients with a possible or likely NP phenotype(50,51). Based on previous research, we anticipate that about 20-40% of the patients that will be screened experience a possible or likely NP phenotype(34,51-54).

Exclusion criteria

Candidates who meet any of the following criteria will be excluded from participation.

General exclusion criteria:

- Surgical hip or knee joint procedures performed in the last year*;
- Intra-articular knee/hip injection or knee/hip arthroscopy in the past three months*;
- Cognitive and/or neurological disorders that could interfere strongly with questionnaire surveys (e.g. dementia)†;
- An unstable and/or severely ill patient that is likely to be hospitalized during the course of the

* This factor likely interferes significantly with the baseline measure.
† This factor likely interferes significantly with participating adequately in a randomized controlled trail with multiple time points.

study or the illness compromises study participation significantly*;

- Planned or intended THA or TKA procedure within the study duration (current planned arthroplasty not included)†;
- A history of significant peripheral nerve injury‡;
- Previous exposure to duloxetine§;

Duloxetine-related exclusion criteria:

- Allergy to duloxetine capsule (or another SNRI);
- Usage of non-selective monoamine oxidase (MAO) inhibitors, TCA's, SSRIs or SNRIs in the last year;
- Usage of strong CYP1A2 inhibitors;
- History of peptic ulcer disease or bleeding disorder (or another substantial risk factor for bleeding, like usage of coumarin derivates);
- Impaired liver function (alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) >100 International Units per Liter (IU/L) or elevated PT (INR) > 1.5), or known liver cirrhosis or liver transplantation;
- Severe renal impairment (Creatinine clearance-eGFR <30 ml/min), previous renal transplantation or under renal dialysis;
- Psychiatric disorders, severe depression/major depressive disorder (based on HADS score >15 on depression subscale)¶;
- A history of alcohol or other substance abuse (excluding nicotine and caffeine) or dependence within the five years prior to enrollment;
- History of cardiac arrhythmias, cardiac failure, myocardial infarction, or irregular heartbeat at baseline (by checking radial pulse rhythm);

* This factor likely interferes significantly with participating adequately in a randomized controlled trail with multiple time points.
† This factor significantly influences multiple postoperative outcome measures.
‡ This factor will probably influence pain quality in the lower extremities.
§ This factor likely influences the patient's expectations of the duloxetine treatment.
¶ Major depressive disorder is an exclusion criterion, since it is associated with an increased risk of suicide in the early stages of depression treatment by duloxetine.55

- Hyponatraemia (<135 mmol/l) or a history of frequent hyponatremias;
- History of uncontrolled hypertension, blood pressure >180 mmHg systolic or >110 mmHg diastolic at baseline;
- History of glaucoma (or increased intraocular pressure), uncontrolled thyroid disease or history of uncontrolled seizures;
- Currently pregnant or lactating, or planning to become pregnant within the study period (self-assessed), unwillingness to comply with reproductive precautions; women who could become pregnant must be willing to comply with approved birth control measures.

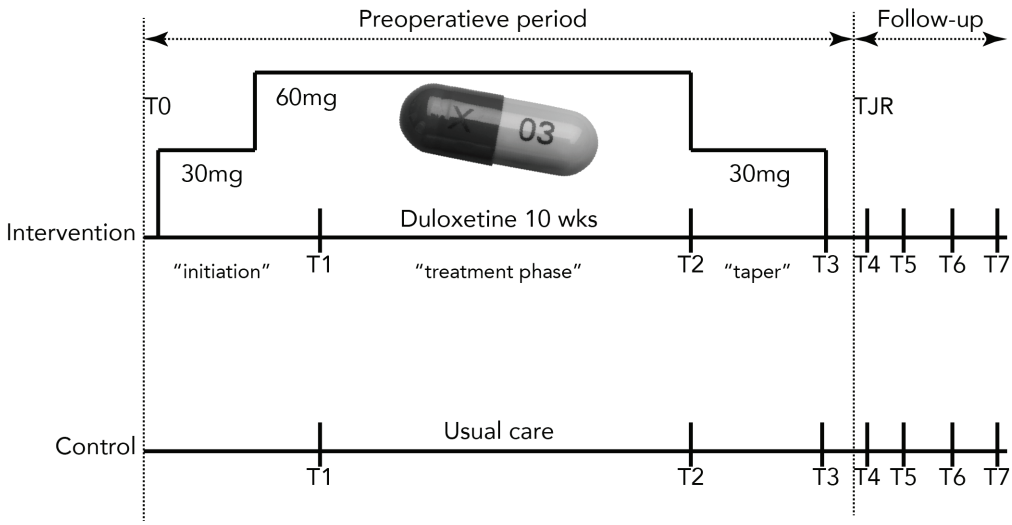

Figure 1. Schematic Scheme; Preoperative period: ±11-week including 10 weeks of duloxetine and a preoperative duloxetine free period; follow-up period: postoperative up to 1 year; "initiation": 2 week period, first week: 30mg p/d duloxetine; second week: 60mg p/d duloxetine; "treatment phase": 6 week period, 60mg p/d duloxetine; "taper": 2 week period, 30mg p/d duloxetine. TJR: total joint replacement (arthroplasty).

Study Procedures

Preoperative period

Baseline (T0)

Patients will visit the researcher of the outpatient clinic of their own hospital to screen for the following exclusion criteria: severe depression (based on HADS score >15 on the depression subscale), uncontrolled hypertension, hyponatraemia, impaired liver or renal function and pregnancy (applicable to women with child-bearing potential; hCG-urine dipstick and when screened positive hCG will be obtained in serum). If all of the inclusion criteria and none of the exclusion criteria are fulfilled, informed consent will be obtained and randomisation will follow. Randomisation in the web-based system will be executed by the local researcher (3 site specific researchers). A stratification factor will be the type of arthroplasty (hip/knee). After randomisation there is a baseline assessment, including patient characteristics and baseline values for outcome measures (see Table 1). This is thus a pragmatic trial, so no restrictions will be imposed on usage of escape (pain) medication or other medication. However, usage of agents to address specifically neuropathic pain symptoms (not including the study drug during the preoperative treatment period), like gabapentenoids should be avoided since this could potentially interfere with the study outcome(s). Therefore local care-as-usual will be slightly modified for study patients in the MZ and MCL, since these two hospitals use gabapentenoids in the peri- and early postoperative period (in a subset of patients).

Intervention Group: "Duloxetine"

Time point T0: Medication Period 1 – "initiation"

For safety reasons and to improve adherence, medication release takes place at three different time points. Since the risk of side effects is higher at the beginning of the treatment, the first study period is relatively short (2 weeks). Prior to medication release, the subject will be informed and warned about possible side effects. The patient will also receive a chart to record usage and side effects. This chart will be collected at every subsequent preoperative visit.

Time point T1: Medication Period 2 – "treatment phase"

This time point follows after two weeks of usage. Subjects will visit the outpatient clinic of their hospital and will receive a limited set of pain-related questionnaires (Table 1), which they have to fill in prior to the visit. The visit will further consist of sensitization measurements (QST) followed by duloxetine treatment evaluation. Drug accountability will be reported and any unused medication will be collected, registered and destructed following local protocol. Subsequently, duloxetine

		Enrolment & Allocation		Preoperative				Follow-up (postoperative)			General
Timepoint		T-1	T0	T1	T2	T3		T4	T5	T6-7	T^x
ENROLMENT											
Eligibility screen		x									
Informed consent		x									
Allocation		x									
INTERVENTIONS											
Duloxetine intervention			x	x	x	x					
ASSESSMENT											
Blood test[a]		x		x							
QST			x^b	x^b	x^b	x^b					
QUESTIONNAIRES	**Outcomes**										
mPD-Q	neuropathic pain like symptoms and pain (NRS: an aspect of the mPD-Q)(34)		x	x	x	x		x	x	x	
HOOS/KOOS	joint-associated problems and health-related QOL(35,36)		x	x	x	x		x	x	x	
VAS	pain intensity(37)		x	x	x	x		x	x	x	
PCS	pain catastrophizing(38-41)		x			x				x	
PGI-I	perceived improvements(42)				x	x				x	
IPAQ	physical activity(43,44)		x			x				x	
RAND-36	health-related quality of life(45)		x			x				x	
HADS	depressive and anxiety symptoms(46)		x			x				x	
HSSKR/HSSHR	arthroplasty-related expectations(47,48)		x			x					
Adverse events											x

ARTHROPLASTY

Table 1. Schematic time line

[a] blood test at T1 is only applicable to the duloxetine intervention group; [b] only applicable to the duloxetine intervention group; [x] no specific time point; -T1: screening, T0: baseline; T1: day 14-17; T2: day 56-60; T3: 0-2 days preoperative; T4: day 2-3 postoperative; T5: weeks 5-7 postoperative; T6-7: 6 and 12 months postoperative ± 2 weeks.
Abbreviations: QOL: Quality of Life; QST: Quantitative sensory testing. mPD-Q: Modified-painDETECT questionnaire; HOOS/KOOS: The Hip disability/ Knee injury and Osteoarthritis Outcome Score; VAS: Visual Analogue Scale-pain; PCS: Pain Catastrophizing Scale; PGI-I: Patient Global Impression of Improvement; IPAQ: International Physical Activity Questionnaire; RAND 36: RAND 36-item Health Survey; HADS: Hospital Anxiety and Depression Scale; HSSKR/HSSHR: Hospital for Special Surgery Knee/Hip Replacement Expectations survey.

(60mg/d) for the following 6 weeks will be handed over. Serum sodium level will be obtained once more to monitor for duloxetine-induced hyponatraemia, a complication that can occur early on after duloxetine initiation(56, 57).

Time point T2: Medication Period 3 – "taper phase"

This time point is defined as eight weeks after duloxetine initiation and marks the beginning of the drug-tapering phase. This visit is identically structured as the previous mentioned time point T1. Medication (duloxetine 30mg/d) for the final two treatment weeks will be handed over. Explicit warning will be given about discontinuation symptoms.

Time point T3: preoperative status

Subjects will receive the full set of questionnaires by mail (see Table 1), which they have to fill in the day before surgery. The questionnaires will be collected on the day of admission to the hospital. At the moment of collection, sensitization measurements (QST) will be performed (see Table 1). Since concomitant usage of NSAIDs and SNRIs is associated with diminished platelet function and therefore with perioperative bleeding(58), surgery will be performed minimal 4 days after last duloxetine usage (arthroplasty window, day 5-8).

Control Group: "Care-as-usual"

Time points T1, T2, T3

Time points T1 and T2 are defined as two weeks and eight weeks after baseline (T0) respectively. Subjects will receive a set of questionnaires at both time points (see Table 1) by mail, which they have to fill in. After completion they are asked to send them back by mail. Time point T3 is identical to the time point T3 of the intervention group.

Follow-up

Follow-up procedures will be identical for both study groups (see Figure 1). Time points T4 and T5, two days and six weeks postoperatively, consist of limited sets of pain-related questionnaires (see Table 1). At T4, questionnaires will be collected at the ward and at T5 at the outpatient clinic during the regular appointment with their orthopaedic surgeon. When collection at the hospital is not possible, the subject will receive the set of questionnaires by mail, to be filled in and sent back. Time points T6 and T7, 6 and 12 months postoperatively, will consist of the full set of questionnaires (see Table 1), which participants will receive by mail and have to send back.

Criteria for withdrawal

Subjects have the right to withdraw at any point during treatment without prejudice. The investigator or regulatory authority can discontinue a subject's participation in the trial at any time if medically or otherwise necessary. It is not advisable to discontinue duloxetine treatment abruptly, especially when taking 60mg/d. A subject who wishes to discontinue must contact the investigator to obtain discontinuation advice.

Adverse events (AEs) and data safety monitoring

All adverse events reported spontaneously by the subject or observed by the investiga¬tors or staff will be recorded. In case of a serious adverse event (SAE), the sponsor will report the SAE to the accredited medical ethics committee. Since every subject will undergo elective total hip or knee arthroplasty (THA/TKA), this potential SAE will not be seen as an SAE and this procedure and the related hospitalisation will not be reported as SAE. However, prolonged hospitalisation (>14 days) will be reported as SAE. Re-hospitalisation (for any reason) will also be reported and handled as a SAE. Suspected unexpected serious adverse reactions (SUSARs) will be reported to the medical ethics committee and. All AEs will be followed until they are gone, or until a stable situation has been achieved. The sponsor decided (approved by the medical ethics committee), based on the standards set by national regulations (NFU standards)(59) that no Data Safety Monitoring Board (DSMB) will be installed, as the risk profile of duloxetine is well-known and duloxetine is already registered as an analgesic agent in the US by the Food and Drug Administration (FDA) for use within OA patients(55). However, if more than one SUSAR is observed, contact will be sought with the medical ethics committee to re-evaluate the study. No additional subjects will be included during the re-evaluation period. The conduct and management will be monitored by an independent trained and educated monitor. Based on the negligible risk profile, minimal monitoring is required (according to the NFU standards)(59): one site visit per year).

Outcome measures

The following characteristics will be retrieved from patient questionnaires, physical examination, hospital information system or medical records.

Patient characteristics

Gender, age, patient-reported height (cm) and weight (kg), family status, highest reached level of education, duration of osteoarthritis pain symptoms, American Society of Anesthesiologists classification, Kellgren-Lawrence grade, previous joint procedures or injury, number of painful joint/body regions, comorbidities, smoking and alcohol consumption, and pain medication consumption.

Arthroplasty related characteristics

Method of anaesthesia, type of arthroplasty, surgical approach, postoperative analgesic consumption and arthroplasty-related complications.

Safety parameters

(Severe) adverse events, vital signs (blood pressure, pulse), and clinical laboratory testing.

Primary outcome

Primary outcome is the amount of residual pain 6 months after THA/TKA. The amount of (residual) pain will be measured with the pain subscale of the Hip disability and Osteoarthritis Outcome Score (HOOS) or the Knee injury and Osteoarthritis Outcome Score (KOOS). These Dutch questionnaires are proven to be valid and reliable(35,36). The key postoperative time-point 6 months was chosen as this is in practice considered as the first possible time-point to evaluate the "success" of the arthroplasty.

Secondary outcomes

Secondary objectives are to determine the effect at different pre- and postoperative follow-up time points (see Table 1) on pain, neuropathic pain like symptoms, pain catastrophizing, joint associated problems, physical activity, health-related quality of life, depressive and anxiety symptoms, perceived improvement and arthroplasty-related expectations. These outcomes will be assessed by means of several questionnaires at multiple follow-up time points (see Table 1). In addition to questionnaires, Quantitative Sensory Testing (QST) will be performed at several preoperative time points to asses pain and sensitization. Two QST modalities will be used: mechanical temporal summation (MTS) and blunt pressure pain thresholds (PPTs). Assessment will be performed at two locations, one close to the affected hip/knee and one at a location remote from the affected

hip/knee (contralateral forearm)(60). These two QST modalities will be executed by the local researcher. The researcher follows a standard operating procedure (SOP), based on the DFNS-QST protocol(61). Multiple OA-studies made use of segments of this protocol (or nearly identical procedures)(50,51,62,63).

1) Mechanical Temporal Summation (MTS):

MTS, a wind-up like pain to repetitive non-invasive mechanical stimulation, is a clinical manifestation of central integration and is believed to be a sensitive measure of central sensitization(63,64). The perceived intensity of a single pinprick stimulus (Optihair2 von frey filament 256mN, Marstock Nervtest, Germany) will be compared with that of a series of 10 repetitive stimuli at the same physical intensity (1/s applied within an area of 1 cm^2). The entire procedure will be repeated three times. The wind-up ratio is calculated as the ratio: mean rating of the three series divided by the mean rating of the three single stimuli.

2) Blunt Pressure Pain Thresholds (PPT))

An algometer (Force Ten TM FDX 25 Digital force gage, Wagner, instruments, Greenwich, CT, USA; 1cm^2 flat rubber tip) will be used to quantify the pain threshold. PPTs are proven to be highly reliable at painful, non-painful and remote body sites(62,65,66). PPTs are considered to be a reflection of peripheral sensitization/nociceptive processes at the site of the joint(60). At a remote site it is considered to reflect systemic altered pain processing/central sensitization(60). The PPTs at each site will be assessed three times and the average of those measurements will be noted.

Handling and storage of data and documents

Personal data will be handled confidentially. Every subject will receive a unique code, this code contains the number of the hospital (UMCG/MH/MCL) followed by a sequence number. Data of each subject will be collected under this unique code. A unique subject identification list will be used to link the data to the subject. The key to the code is safeguarded by the principal investigator. All source documents will be entered in an electronic CRF (OpenClinica). The retention period of the data and documents is 20 years.

Sample size

Sample-size calculation is performed with HOOS/KOOS pain as primary outcome measure. Based on a previous OA study, the common standard deviations for the pain subscale scores of the HOOS and KOOS are 17.7 and 17.2 respectively(67). As the smallest change score for the KOOS to be considered clinically relevant is 10 points (on a 0-100 scale)(68), power calculation is based on this difference. To detect this difference with 80% power (two-sided significance level

of 0.05), a total of 47 subjects is needed per group. Taking into account the possibility of 20% protocol violators and/or dropouts, inclusion of 59 subjects per group is aimed for (total group: 118 subjects). It is anticipated that this sample could be obtained between October 2014 and the end of 2016.

Statistical considerations

All statistical analyses will be conducted by using IBM® Statistical Package for the Social Sciences® (SPSS, version 22). Descriptive statistics will be used to describe the demographic and baseline characteristics of the subjects. Continuous variables will be summarised using means and standard deviations. Discrete variables will be summarised by proportions and percentages.

For the primary endpoint a Student's t-test (or a non-parametric equivalent in case of a skewed distribution) will be used to determine possible differences in pain on the KOOS/HOOS at 6 months postoperatively between the two groups. Generalized Estimating Equation (GEE) analysis will be used to determine possible differences in pain between the two groups over time, adjusted for relevant covariates. For the secondary endpoints Student's t-tests (or a non-parametric equivalent in case of a skewed distribution) will be used to determine possible differences in secondary outcome variables at multiple follow-up time points (see Table 1) between the two groups. GEE analyses will be used to determine possible differences in secondary outcome variables between the two groups over time, adjusted for relevant covariates. All data analyses will be done on an intention-to-treat basis. A P-value of < 0.05 is considered statistically significant.

Ethics and Dissemination

This study is approved by the local Medical Ethics Committee (METc 2014/087) and will be conducted according to the principles of the latest Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO) and the Good Clinical Practice standard (GCP). The study is investigator-initiated. No arrangements are made between the subsidising party and the investigator concerning publication of the research data. Independently of the outcome, the results of the study will be published in international peer-reviewed scientific journals. Patient data will be presented anonymously in any publication or scientific journal. All substantial amendments (modification to the protocol that is likely to affect the safety or the scientific value of the trial) will be notified to the local METc and to the competent authority (CCMO).

Discussion

The Duloxetine in Osteoarthritis study (DOA study) is, as far as we know, the first pragmatic randomized controlled clinical trial assessing the preoperative as well as the early and late

postoperative effects of a substantial preoperative targeted duloxetine regimen. To date, only one study has assessed the early and late postoperative effects of a single- or dual-dose perioperative duloxetine regimen in a TKA patient group(69). In this study no significant differences on pain scores were observed up to 6 months postoperatively between two perioperative 60mg doses of duloxetine and placebo. Our study differs significantly from this and other studies that focus on diminishing the risk of residual pain. Firstly, in this study only patients will be included that are probably at a higher risk for developing residual pain, based on having a higher chance of experiencing preoperative CS. This entails a more tailored approach, as we think not all preoperative OA patients are centrally sensitized (CS) and could benefit from atargeted preoperative treatment package. Secondly, in general, previous studies on residual postoperative pain are based on the theory(70,71) that surgery-induced tissue injury and acute postsurgical pain probably results in CS and residual pain, whereas our study is based on the theory that the preoperative centrally sensitized (CS) status induced by long-lasting OA is key, and as a consequence should be addressed preoperative instead of peri/postoperative. Furthermore, we believe that our chosen pragmatic trial design has validity to assess the effects of the treatment regimen, as it mimics real-life status with a care-as-usual control group as much as possible. Moreover, the endpoints of this pragmatic RCT are focused on the relevancy to everyday life, like hip- and knee-specific pain, function and quality of life. For these reasons, pragmatic randomized trials are an increasingly popular design to test implementation interventions(72). Conversely, due to the design used it will not be possible to analyse the direct effect of the duloxetine substance but rather the effect of the total targeted treatment package. Hence this study is powered for the effect measured in the total group; only limited hip-/knee-specific conclusions can be drawn. No significant group differences are anticipated due to the shared underlying pain mechanism though. Knowledge gained from this study can potentially improve postoperative pain relief and rehabilitation after TJR. Moreover, due to an extensive preoperative treatment period, it could provide specific insight into the effectiveness of duloxetine in advanced hip and knee OA patients with possible NP/CS.

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