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Investigating the effect of perioperative chlorzoxazone on acute postoperative pain after total hip and knee replacement surgery

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Abstract:

Background and aims Severe pre- and acute postoperative pain have been associated with development of chronic postoperative pain. Chlorzoxazone (a muscle relaxant) has been suggested to enhance acute postoperative pain recovery but the lack of larger randomized controlled trials have however questioned the continued use. Despite this, chlorzoxazone is still used for acute postoperative pain management following total knee or hip replacement (TKR or THR). The currentrandomized, double blinded, placebo-controlled, parallel group, clinical trial aimed to assess the effect of chlorzoxazone for postoperative pain management following TKR or THR.

Methods 393 patients scheduled for TKR or THR were included in the trial. Patients were assigned to 250mg chlorzoxazone three times daily for the first seven days postoperative or placebo. The primary outcome was pain after 5 meter walk assessed 24-hours postoperative. Secondary outcomes included, changes in preoperative pain at rest, worst pain in the last 24 hours, and Oxford Knee or Hip Score compared with 12 months follow-up. In addition, adverse events were assessed in the perioperative period.

Results No significant differences were found for any of the outcome parameters after TKR or THR. For neither TKR or THR no effects were demonstrated for pain after 5 meters walk 24-hours after surgery (P>0.313), or for any of the secondary outcomes (P>0.288) or adverse event (P>0.112) in the group receiving chlorzoxazone compared with placebo.

Conclusions The current study demonstrated no analgesic effects of postoperative chlorzoxazone administration compared with placebo on acute or chronic postoperative pain 12 months following TKR and THR.

Key words Total Knee Replacement, Total Hip Replacement, Chlorzoxazone, Muscel Relaxants, Postoperative Pain Management.

1 Introduction

Pain and reduced physical function are the main symptoms of osteoarthritis (OA). Total Knee Replacement (TKR) and Total Hip Replacement (THR) is the final treatment of the end-stage OA. The treatment is effective and produces long-lasting improvements of physical function and reduces pain for most patients.[1,2] Despite this, up to 20% of TKR-patients, and up to 10% of THR-patients suffer from chronic postoperative pain after otherwise technically successful surgeries.[3–5]

Despite the high number of surgeries performed[6], and the expected increase in the future[7], there is no consensus in the analgesic protocols after TKR and THR surgery.[8–11]

Treatment of acute postoperative pain is a multimodal analgesic strategy that involves optimizing perioperative analgesia, reducing opioid-related adverse events and in general limiting the causes of chronic postoperative pain.[8–10,12–14] Ideally, sufficient analgesia should be achieved using a synergistic effect of different drugs thus lowering the overall incidence of adverse effects.

Severe pain in the acute postoperative phase has been associated with chronic postoperative pain[15].

Chlorzoxazone is a muscle relaxant that has been suggested to enhance acute postoperative pain recovery[16], which thereby may reduce postoperative pain.

Chlorzoxazone inhibits mono- and polysynaptic reflexes in the CNS,[17,18] but the specific mechanism of action is not clear. A study by Van Tulder et al., 2003 suggested that chlorzoxazone may partly be associated with sedative effects due to the benzodiazepine derivative structure of chlorzoxazone.[16,17] Placebo-designed clinical studies of chlorzoxazone's beneficial effect on heterogeneous groups of patients with spasticity, motor neuron syndromes, as well as muscle pain and spasm of peripheral musculoskeletal diseases have not been able to demonstrate any significant analgesic effect.[17] Chlorzoxazone has also failed to show pain-relieving effect in the treatment of back pain.[17,19] Further, chlorzoxazone has also been used in spine surgery, however limited effect in

a large randomized controlled trial questioned the continued use.[20] Despite this, chlorzoxazone is still routinely used for acute postoperative pain management following TKR and THR.

The aim of this randomized, double blinded, placebo-controlled, parallel group, clinical trial was to investigate the effect of peri- and postoperative administration of chlorzoxazone on acute and chronic postoperative pain in patients scheduled for TKR and THR.

2 Methods

2.1 Study design and patients

The study was approved by the Danish Medicines Agency, the regional ethics committee N-20150024, and the Danish Data Protection Agency and was registered at EudraCT (2015-001214-10) and www.clinicaltrials.gov (NCT02405104, April 1, 2015). It was conducted in accordance with Good Clinical Practice guidelines and the Helsinki Declarations, and was monitored by the Good Clinical Practice Monitoring Unit of Aalborg and Aarhus University Hospitals.

Oral and written informed consent was obtained from all patients before participating in this single-center, prospective, randomized, double blind, parallel-arm, placebo-controlled clinical study. Patients scheduled to undergo elective, unilateral primary TKR or THR were assessed for eligibility (by surgeons and project nurses) and recruited at a prescheduled (study independent) hospital visit for clinical examination preceding admission for surgery, at Aalborg University Hospital, Farsø, Denmark, between September 2015 and September 2016. Patients were excluded based on the following criteria age below 18, preoperative use of gabapentinoids, systemic glucocorticoids, opioids, anxiolytics, antiepileptics or antidepressants (within 4 weeks), history of bipolar affective disorder, alcohol or drug abuse, malignant condition, liver disease, body mass index >40 kg/m2, diseases affecting central or peripheral nerve function, history of dementia or other cognitive dysfunction, allergies towards the medicine to be tested, lack of ability to walk 5 meters, and

pregnant or breastfeeding women. Further patients were excluded if there were perioperative complications, and any need of pain treatment apart from the standard.

2.2 Randomization, blinding and study drug intervention

Randomization, blinding procedures and study drug preparations were handled by a state-registered and certificated pharmacy, The Northern Denmark Regional Pharmacy, not otherwise involved in the trial. The patients were randomized in blocks of 10 (20 blocks) without the use of stratification variables.

The study drug, chlorzoxazone 250mg (Klorzoxazon®; Takeda Pharma, Taastrup, Denmark), and placebo were prepared by the pharmacy as tablets identical in appearance. The dosage of the study drug was chosen by recommendation by the Danish Pharmaceutical Information and Takeda Pharma.

The medication was self-administered, three times a day for 7 days, starting 2 hours preoperative, and thereafter at 8 AM, 4 PM and 10 PM on postoperative days 1 to 7. To facilitate drug compliance, the patients had to fill out a questionnaire twice a day. After study completion, any remaining drugs were collected as control of compliance.

2.3 Outcome measures and assessments

The primary outcome was pain 24 hours after post surgery, measured as Pain after walking 5 meters with a walking aid. This was chosen because previous studies have argued that pain on movement exerts the most direct adverse impact on postoperative functional recovery.[21] Twenty-four hours was chosen because almost all patients would be able to be mobilized at this time.[22] The secondary outcomes were the patients functional level determined by Oxford Knee and Hip Score 7 days postoperative, and changes in pain at rest, and worst pain in the last 24 hours, comparing preoperative and 12 months postoperative scores.

Baseline patient characteristics including preoperative pain were assessed at a hospital visit for general clinical examination preceding admission for TKR or THR.

During admission, patients were asked to rate their VAS score with a VAS ruler by a project nurse at 4, 6, 24, 28, 32 and 48 hours after surgery. After discharge patients placed a cross on the VAS line printed in the diary at day 2 to day 7, day 14 and at 12 months follow-up. A 10 cm Visual Analog Scale (VAS) was used (0 = no pain and 10 = worst pain imaginable).

Oxford Knee Score (OKS) or Oxford Hip Score (OHS) was assessed as baseline measure, and at day 2, 4, 7, 14 and at 12 months follow-up. The OKS and OHS are 12-item questionnaires assessing pain and function of the patient's knee or hip.

OKS answers were sub grouped into a functional component and a pain component. The patient scored each question (item) from 0 to 4, with 0 being the worst outcome and 4 being the best outcome. The functional component consists of item 2, 3, 7, 11 and 12. The pain component consists of item 1, 4, 5, 6, 8, 9 and 10. The summed scores of each subscale were then standardized to a range from 0 (worst) to 100 (best).[23,24]

Likewise, each question in OHS was scored by the patient from 0 to 4, with 0 being the worst outcome and 4 being the best outcome. This gave an overall score from 0 to 48, with 48 being the best outcome.[23]

Other outcomes assessed during admission were opioid consumption, postoperative fatigue, dizziness, nausea and vomiting. Opioid consumption was measured in milligrams per day. If different kinds of opioids were used, the dose were converted to morphine milliequivalents.

Postoperative fatigue was assessed at 6, 24, 32, and 48 hours after surgery. The 11-point numeric rating scale (NRS) was used (0 = no fatigue and 10 = worst fatigue imaginable; subjective rating by patients).[25] Vomiting was assessed at 6, 24, 32, and 48 hours and registered as number of events since last recording. Dizziness and nausea were assessed at 6, 24, 32, and 48 hours and in the diary

from days 2 to 6 each evening (before going to bed). The 4-point verbal rating scale was used (0 = no, 1 = mild, 2 = moderate and 3 = severe; subjective rating by patients).

2.4 Anesthesia, surgery, and analgesia

Surgery was performed under lumbar spinal anesthesia with bupivacaine 0.5%, 7.5mg (1.5ml) and optional supplemental propofol (1-5mg/kg/hour). Total knee replacement was performed using a midline skin incision and medial parapatellar arthrotomy. Total hip replacement was performed using the posterolateral approach. Both types of surgery were performed without application of surgical drains. TKR patients had Local Infiltration Anesthesia (LIA) with 100 mL 2% Ropivacain® during surgery, were as THR patients had no LIA.

A basic analgesic regime was used consisting of slow release oral acetaminophen and celecoxib. 2 hours preoperative, acetaminophen 2 g and celecoxib 400 mg were administered (together with the study drug); thereafter acetaminophen 2 g and celecoxib 200 mg were administered regularly at 8 AM and 10 PM up to and including postoperative day 6. Study drug as described previously. Rescue analgesics (administered on demand as required if VAS >50 mm at rest) consisted of intravenous sufentanil 5mg (patients above 70 years) and 10 mg (patients below 70 years) in the post anesthesia care unit (PACU) and subsequently of oral morphine 10mg (patients above 70 years) and 20 mg (patients below 70 years) at the ward and after discharge, up to a maximum of 4 doses per 24 hours. In very few cases, other opioids (ketobemidone, oxycodone), and intravenous morphine were used due to resistant pain (administered on demand if VAS >50 mm at rest, for one hour after last opioid administration). During admission, nausea and vomiting were treated with ondansetron 4 mg.

Patients followed a well-defined fast-track rehabilitation regime and were discharged to their homes according to routine functional discharge criteria.[22]

2.5 Sample size calculation

Estimated sample size for the primary outcome was calculated based on the results from Andersen et al. 2009 who assessed pain upon ambulation the first day after TKR and found a mean of 54 (SD: 25) on a VAS (0-100).[14] Thus, 50 patients in each group would allow the detection of a clinically relevant 30% difference in VAS pain after 5 meters walk 24 hours after surgery between Chlorzoxazone and placebo groups, at a 2-sided 5% significance level, and with a power of 90%. As to the secondary outcome, a 20% difference in OKS/OHS from preoperative to day 7 postoperative was wanted, also at a 2-sided 5% significance level, and with a power of 90%. This requires 90 patients in each group. Therefore, we decided to include 400 patients (100 in each group), which allow for dropouts, which is common problem in these longitudinal studies on osteoarthritis.[26–28]

2.6 Statistical analysis

Statistical analyses were performed in IBM SPSS Statistics (ver. 25, IBM Corporation, New York, USA), and we analyzed the outcome with the accessible measurements.

Normal distribution was assessed using the Kolmogorov-Smirnov test. Normal distribution was accepted for baseline characteristics, and not accepted for primary and secondary outcomes, as well for the rest of the other outcomes. Between group differences were evaluated with independent sample t-test or the nonparametric Mann-Whitney U-test. Data are presented as mean and 95% confidence interval (95% CI), median (range) or frequencies, as relevant. $P<0.05$ was considered significant. All outcomes were Bonferroni corrected to account for multiple comparisons.

3 Results

From September 2015 to September 2016 a total of 944 patients had a TKR or THR in our hospital. 551 of these did not meet the inclusion criteria for this study. The remaining 393 patients were screened and invited to participate in the study and were randomized into 4 groups.

After randomization 198 were scheduled for TKR and 195 were scheduled for THR. In TKR group, 100 patients were randomized to Chlorzoxazone group, and 98 patients to Placebo group. In THR group, 97 patients were randomized to Chlorzoxazone group, and 98 patients to Placebo group. 19 patients were excluded after randomization, 13 scheduled for TKR, and 6 scheduled for THR (Figure 1).

Baseline patient characteristics and preoperative data are presented in Table 1. The Placebo group demonstrated significantly better preoperative function in Oxford Knee Score (OKS) compared to the Chlorzoxazone group (P = 0.034), and the Chlorzoxazone group demonstrated significantly better preoperative in Oxford Hip Score (OHS) compare to the Placebo group (P=0.042). No other significant preoperative differences were found. Likewise, perioperative data and adherence to protocol were no significantly different between the groups.

3.1 Pain after 5 meters walk

No significant effect was found for primary outcome pain after 5 meters walk 24 hours postoperative for TKR (Bonferroni: P = 1.0) and THR (Bonferroni: P=1.0). However, a significance in pain after 5 m walk was found at 48 hours postoperative, favoring Placebo for TKA (Bonferroni: P= 0.048) (Table 2).

3.2 Pain at rest and Worst pain for the last 24 hours

No significant effect was found for the secondary outcome pain at rest and worst pain for the last 24 hours (Table 3).

3.3 Oxford Knee/Hip Score

No significant effect was observed for Oxford Knee and Hip Scores within the first seven postoperative days (Bonferroni: P>0.12), nor at 12 months follow-up (Figure 2).

3.4 Opioid consumption

No significant difference in opioid consumption the first 7 days postoperatively was found, neither for Oral vs IV analgesia (Table 4).

3.5 Other outcomes

Also, no intervention effect was observed for any of the other outcomes measured during admission: postoperative fatigue (Bonferroni: P>0.24), dizziness (Bonferroni: P=1), nausea (Bonferroni: P>0.11), and vomiting (Bonferroni: P>0.21) (Table 1).

4 Discussion

The current randomized, placebo-controlled, parallel group clinical trial administered chlorzoxazone preoperatively and for the first 7 postoperative days after THR and TKR surgery, and demonstrated no significant reduction in pain during mobilization, pain at rest or in worst pain in the last 24 hours or any adverse events when compared with placebo. In addition, no effect was demonstrated in Oxford Knee or Hip Score within the first seven postoperative days when comparing chlorzoxazone to placebo. Finally, chlorzoxazone did not improve chronic postoperative pain at 12 months follow-up compared with placebo.

4.1 Chlorzoxazone for postoperative pain management

The effect of muscle relaxants on acute postoperative pain must be considered as uncertain, but may in some cases be indicated, most often as an adjunct to other forms of therapy, for example analgesics, anti-inflammatory agents, physiotherapy and training.[17,18]

A systematic search of the literature revealed only one placebo-controlled trial of postoperative analgesic effect of chlorzoxazone. Nielsen et al.[20] demonstrated no reduction in acute postoperative pain after a single 500 mg administration of chlorzoxazone after spine surgery for patients with moderate-to-severe pain, which is in line with present study. Furthermore a study by Kumar et al.[29] investigated the efficacy of the combination of thiocolchicoside and aceclofenac versus

chlorzoxazone, aceclofenac and paracetamol in patients with acute lower backache associated with muscle spasm, and found the combination with chlorzoxazone inferior.

No studies found, have investigated the analgesic effect of chlorzoxazone after knee or hip surgery. A placebo-controlled study by Gong et al.[30] investigated the combined effect of administering Eperisone (a muscle relaxant) and celecoxib (COX-2 selective inhibitor) the first 2 postoperative weeks and found that the combination was superior to celecoxib alone and placebo on pain at rest, pain in ambulation and opioid use in the first 14 days postoperative. However, the reduction in pain is questionable for clinically relevance (a reduction on 0.74 in VAS), and furthermore, no long-term follow-up was available for comparison.

Adverse reactions to chlorzoxazone are relatively few. The most frequently related adverse events are fatigue and dizziness (about 1-10% of patients).[16] Adverse reactions are to some extent overlapping with the side effects that are related to the perioperative opioid treatment.[16] It is therefore possible that the frequency of adverse events overall is reduced if chlorzoxazone is found to be analgesic (and opioid-sparing).

The recommendations for postoperative pain management for both TKR and THR are: COX-2 selective inhibitors or conventional NSAIDs in combination with acetaminophen, supplemented with weak or strong opioids.[9,10,31]

However, present study demonstrated no reduction in adverse reactions, opioid consumption, or postoperative fatigue in the intervention group and can therefore not recommend perioperative administration of chlorzoxazone as treatment of acute postoperative pain following TKR and THR.

Present study demonstrated a significant difference in Pain after 5m Walk after TKR measured among the patients still hospitalized 48 hours postoperative favorizing the Placebo group. However, no difference in baseline characteristic, nor any other difference in any other available measures are present including 1-year follow-up, beside that they were hospitalized more than 48 hours

postoperatively. However, this finding is limited by missing data at 48 hours postoperatively, since approx. 70% of patients were discharged, which was not expected when this study was initiated. The strength of present study is that it is the first randomized, double blind placebo-controlled clinical trial investigating the analgesic effect of chlorzoxazone after TKR and THR.

5 Conclusion

The current clinical trial demonstrated no beneficial effects of chlorzoxazone giving perioperative and three times daily for 7 days postoperative on pain in the acute postoperative period or development of chronic posteoperative pain assessed after 12 months. Furthermore no effects were found on function. Based on these findings, it is thereby our recommendation not to use chlorzoxazone routinely for acute postoperative pain management following TKR and THR. However, a large sample multi-center study is recommended for confirmation of the findings of present study.

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Figure 1 CONSORT: Flow of patients through the phases of the trail. TKR, Total Knee Replacement; THR, Total Hip Replacement.

Figure 2 Development of Oxford Knee Score (OKS), function and pain, and Oxford Hip Score (OHS) from preoperative measurement to 12 months follow-up.

Table 1 Pre- and perioperative demographics and baseline patient characteristics for the four groups and comparisons between them. * indicate significant difference favorizing Placebo. ** indicate significant difference favorizing Chlorzoxazone.

(Data are expressed as count (percentage)[#], mean (95% CI)[†] or median (range)[¥]. Different kinds of opioids is converted to morphine milliequivalents. BMI, Body Mass Index. ASA score, American Society of Anesthesiologists Score. OKS, Oxford Knee Score. OHS, Oxford Hip Score. PACU, Post Anesthesia Care Unit.)

Table 2 Mean (95%CI) VAS pain scores after 5 meters walk. VAS 4-48hours postoperative were assessed during admission. 12 months were assessed from the patient's diary. * indicate significant difference in pain, favorizing Placebo.

Table 3 VAS pain scores at rest, and VAS worst pain score for the last 24 hours. VAS 4-48 hours postoperative were assessed during admission. The rest were assessed from the patient's diary.

(Data are expressed as mean (95% CI).)

Table 4 Consumption of opioids the first 7 days postoperatively. 1. and 2. postoperative day was assessed during admission. Morphine day 2 to 7 was assessed from the patient's diary. Different kinds of opioids are converted to morphine milliequivalents.

(Data are expressed as mean (95% CI). Mg, milligram. IV, Intravenous.)

*Table 1 Pre- and perioperative demographics and baseline patient characteristics for the four groups and comparisons between them. * indicate significant difference favorizing Placebo. ** indicate significant difference favorizing Chlorzoxazone.*

Characteristic	TKR, Chlorzoxazone (n=94)	TKR, Placebo (n=91)	P-value	THR, Chlorzoxazone (n=95)	THR, Placebo (n=94)	P-value
Age[†]	69.2 (67.5-70.9)	70.5 (68.6-72.3)	0.130	68.1 (65.0-71.2)	65.7 (63.3-68.1)	0.617
Male, n[#]	40 (42.6%)	42 (46.2%)	0.624	59 (62.2%)	61 (63.5%)	0.692
Female, n[#]	54 (57.4%)	49 (53.8%)		36 (37.9%)	33 (36.5%)	
Weight, kg[†]	88.4 (84.7-92.0)	84.2 (80.9-87.5)	0.113	81.8 (78.4-85.1)	84.16 (81.1-87.2)	0.379
Height, cm[†]	171.1 (169.2-173.0)	170.2 (168.3-172.2)	0.736	171.8 (168.9-174.7)	172.8 (171.2-174.4)	0.917
BMI, kg/m^2 [†]	30.1 (29.0-31.2)	29.0 (28.0-29.9)	0.178	27.8 (26.7-28.9)	28.1 (27.2-29.0)	0.634
Operation side: Right/Left[#]	48/46	54/37	0.260	51/44	48/46	0.720
ASA score, I/II/III[#]	23/60/8	14/62/6	0.401	30/50/8	35/47/9	0.679
Pain after 5m walk[†]	4.30 (3.7-4.9)	4.08 (3.5-4.6)	0.730	3.73 (3.2-4.3)	3.82 (3.3-4.3)	0.833
Pain at rest[†]	3.58 (3.1-4.1)	3.50 (3.0-4.0)	0.806	3.27 (2.8-3.7)	3.52 (3.0-4.0)	0.516
Worst pain the last 24 hours[†]	6.44 (6.0-6.9)	6.22 (5.7-6.7)	0.499	6.03 (5.6-6.5)	6.54 (6.0-7.0)	0.082
OKS, function[†]	55 (51-58)	59 (56-63)	0.034*	-	-	
OKS, pain[†]	44 (41-47)	44 (41-48)	0.978	-	-	
OHS[†]	-	-		25.19 (6.3)	22.73 (7.4)	0.042**
Duration of surgery, min[¥]	60 (63)	60 (91)	0.551	60.5 (86)	60 (80)	0.592
Bleeding intraoperatively, ml[¥]	100 (1000)	100 (500)	0.695	400 (900)	350 (1300)	0.997
PACU stay, min[¥]	80 (215)	85 (150)	0.982	67.5 (150)	60 (270)	0.668
Sedation (0-10)						
6 hours postoperative[¥]	0 (5)	0 (5)	0.240	0 (8)	0 (6)	1.0
24 hours postoperative[¥]	0 (4)	0 (4)	0.344	0 (8)	0 (6)	1.0
32 hours postoperative[¥]	0 (10)	0 (10)	1.0	0 (4)	0 (4)	1.0
48 hours postoperative[¥]	0 (2)	0 (6)	1.0	0 (2)	0 (1)	1.0
Dizziness (0-3)						
6 hours postoperative[¥]	0 (3)	0 (3)	1.0	0 (3)	0 (3)	1.0
24 hours postoperative[¥]	0 (2)	0 (3)	1.0	0 (3)	0 (3)	1.0

32 hours postoperative[¥]	0 (1)	0 (3)	1.0	0 (3)	0 (3)	1.0
48 hours postoperative[¥]	0 (1)	0 (2)	1.0	0 (3)	0 (2)	1.0
Nausea (0-3)						
6 hours postoperative[¥]	0 (2)	0 (2)	1.0	0 (2)	0 (2)	1.0
24 hours postoperative[¥]	0 (1)	0 (3)	1.0	0 (3)	0 (2)	1.0
32 hours postoperative[¥]	0 (1)	0 (1)	0.112	0 (1)	0 (3)	1.0
48 hours postoperative[¥]	0 (1)	0 (1)	1.0	0 (1)	0 (3)	1.0
Vomiting, n						
No of patients vomiting 0-6h[#]	3	0	0.510	1	7	0.21
No of patients vomiting 6-24h[#]	4	5	1.0	10	8	1.0
No of patients vomiting 24-48h[#]	3	8	1.0	7	6	1.0

Data are expressed as count (percentage)[#], mean (95% CI)[†] or median (range)[¥]. Different kinds of opioids is converted to morphine milliequivalents. BMI, Body Mass Index. ASA score, American Society of Anesthesiologists Score. OKS, Oxford Knee Score. OHS, Oxford Hip Score. PACU, Post Anesthesia Care Unit.

*Table 2 Mean (95%CI) VAS pain scores after 5 meters walk. VAS 4-48hours postoperative were assessed during admission. 12 months were assessed from the patient's diary. * indicate significant difference in pain, favorizing Placebo.*

Treatment group	**TKR, Chlorzoxazone**	**N**	**TKR, Placebo**	**N**	**P-value**	**THR, Chlorzoxazone**	**N**	**THR, Placebo**	**N**	**P-value**
Inclusion	4.30 (3.7-4.9)	76	4.08 (3.5-4.6)	76	1.0	3.73 (3.2-4.3)	82	3.82 (3.3-4.3)	82	1.0
4 hours postoperative	3.33 (2.6-4.1)	42	2.86 (2.2-3.5)	38	1.0	3.70 (2.9-4.6)	28	3.18 (2.4-3.9)	20	1.0
6 hours postoperative	4.09 (3.6-4.6)	73	3.62 (3.2-4.0)	68	1.0	3.94 (3.5-4.3)	63	4.10 (3.7-4.5)	63	1.0
24 hours postoperative	3.83 (3.5-4.2)	93	3.73 (3.4-4.1)	90	0.940	3.32 (3.0-3.7)	94	3.03 (2.7-3.3)	89	0.313
28 hours postoperative	3.57 (3.2-3.9)	93	3.54 (3.2-3.9	91	1.0	2.65 (2.4-2.9)	94	2.43 (2.2-2.7)	90	1.0
32 hours postoperative	3.97 (3.4-4.5)	33	3.58 (3-1-4.1)	42	1.0	2.78 (2.3-3.2)	30	2.68 (2.1-3.2)	28	1.0
48 hours postoperative	3.59 (3.0-4.1)	29	2.53 (2.1-3.0)	34	0.048*	2.38 (1.8-3.0)	24	2.37 (1.7-3.0)	27	1.0
12 months follow-up	1.09 (0.7-1.5)	86	1.20 (0.8-1.6)	83	1.0	0.65 (0.4-0.9)	90	0.66 (0.4-0.9)	88	1.0

Table 3 VAS pain scores at rest, and VAS worst pain score for the last 24 hours. VAS 4-48 hours postoperative were assessed during admission. The rest were assessed from the patient's diary.

Pain at rest	**TKR, Chlorzoxazone**	**N**	**TRK, Placebo**	**N**	**P-value**	**THR, Chlorzoxazone**	**N**	**THR, Placebo**	**N**	**P-value**
Preoperative examination	3.58 (3.1-4.1)	94	3.50 (3.0-4.0)	87	1.0	3.27 (2.8-3.7)	94	3.52 (3.0-4.0)	90	1.0
4 hours postoperative	2.72 (2.2-3.3)	94	2.25 (1.8-2.7)	91	1.0	3.06 (2.6-3.5)	94	3.21 (2.7-3.7)	94	1.0
6 hours postoperative	3.16 (2.7-3.6)	93	2.53 (2.2-2.9)	91	1.0	3.19 (2.8-3.6)	95	3.07 (2.7-3.5)	94	1.0
24 hours postoperative	2.13 (1.8-2.5)	94	1.80 (1.5-2.1)	90	1.0	1.72 (1.4-2.0)	95	1.49 (1.2-1.8)	94	1.0
28 hours postoperative	1.72 (1.4-2.1)	94	1.62 (1.3-1.9)	91	1.0	0.92 (0.7-1.1)	95	0.92 (0.7-1.2)	93	1.0
32 hours postoperative	1.91 (1.4-2.5)	36	1.65 (1.2-2.1)	44	1.0	0.95 (0.5-1.4)	31	1.13 (0.7-1.6)	32	1.0
48 hours postoperative	1.47 (0.8-2.1)	30	0.77 (0.4-1.1)	37	1.0	0.60 (0.2-1.0)	26	0.57 (0.2-0.9)	28	1.0
Day 2	2.44 (2.0-2.9)	88	2.08 (1.7-2.4)	88	1.0	1.39 (1.0-1.7)	92	1.43 (1.2-1.7)	93	1.0
Day 3	2.18 (1.8-2.6)	88	1.68 (1.4-2.0)	87	1.0	1.27 (1.0-1.6)	93	1.31 (1.1-1.6)	93	1.0
Day 4	2.13 (1.8-2.5)	88	1.77 (1.4-2.1)	85	1.0	1.34 (1.1-1.6)	92	1.35 (1.1-1.6)	93	1.0
Day 5	2.26 (1.9-2.7)	87	1.64 (1.4-1.9)	84	0.93	1.32 (1.0-1.6)	92	1.25 (1.0-1.5)	92	1.0
Day 6	2.28 (1.9-2.7)	87	1.84 (1.5-2.2)	83	1.0	1.20 (0.9-1.5)	91	1.13 (0.9-1.3)	92	1.0
Day 7	2.01 (1.7-2.4)	94	1.88 (1.5-2.2)	82	1.0	1.12 (0.9-1.4)	90	1.12 (0.9-1.3)	90	1.0
Day 14	1.99 (1.5-2.4)	77	1.57 (1.2-1.9)	77	1.0	0.95 (0.7-1.2)	81	0.99 (0.8-1.2)	84	1.0
12 months follow-up	0.91 (0.5-1.3)	88	1.05 (0.7-1.4)	85	1.0	0.53 (0.3-0.7)	90	0.48 (0.3-0.6)	88	1.0
Worst pain last 24h	**TKR, Chlorzoxazone**	**N**	**TKR, Placebo**	**N**	**P-value**	**THR, Chlorzoxazone**	**N**	**THR, Placebo**	**N**	**P-value**
Preoperative examination	6.44 (6.0-6.9)	94	6.22 (5.7-6.7)	88	1.0	6.03 (5.6-6.5)	93	6.54 (6.0-7.0)	90	1.0
Day 2	4.32 (3.8-4.8)	58	4.39 (3.7-5.1)	60	1.0	3.20 (2.6-3.8)	66	3.04 (2.5-3.6)	69	1.0
Day 3	3.95 (3.3-4.6)	58	3.42 (2.8-4.1)	59	1.0	3.00 (2.4-3.6)	65	2.89 (2.4-3.4)	69	1.0
Day 4	3.70 (3.1-4.4)	55	3.73 (3.1-4.4)	57	1.0	2.69 (2.2-3.2)	66	2.81 (2.3-3.3)	66	1.0
Day 5	4.10 (3.5-4.7)	57	3.36 (2.7-4.0)	57	1.0	2.62 (2.1-3.1)	65	2.43 (2.0-2.9)	69	1.0
Day 6	4.18 (3.5-4.9)	58	4.15 (2.6-5.7)	57	1.0	2.64 (2.1-3.2)	65	2.54 (2.0-3.1)	69	1.0
Day 7	4.22 (3.7-4.8)	80	3.27 (2.8-3.8)	81	0.29	2.68 (2.2-3.2)	89	2.30 (1.9-2.7)	89	1.0
Day 14	4.14 (3.5-4.8)	77	3.38 (2.8-4.0)	77	1.0	2.28 (1.8-2.8)	80	1.87 (1.5-2.3)	84	1.0
12 months follow-up	1.46 (1.0-1.9)	87	1.60 (1.1-2.1)	83	1.0	0.93 (0.6-1.2)	89	0.68 (0.4-0.9)	87	1.0

Data are expressed as mean (95% CI).

Table 4 Consumption of opioids the first 7 days postoperatively. 1. and 2. postoperative day was assessed during admission. Morphine day 2 to 7 was assessed from the patient's diary. Different kinds of opioids are converted to morphine milliequivalents.

Opioid consumption	**TKR, Chlorzoxazone**	**TKR, Placebo**	**THR, Chlorzoxazone**	**THR, Placebo**
1. postoperative day, total mg morphine/day	55.6 (50.4-60.9)	57.7 (51.2-94.1)	59.9 (54.3-65.5)	54.3 (49.3-59.2)
Oral vs IV mg morphine	51.5/3.5	56.5/2.1	56.6/3.3	52.0/2.3
2. postoperative day, total mg morphine/day	24.8 (19.1-30.4)	28.1 (19.6-36.7)	12.0 (8.5-15.5)	12.9 (9.1-16.7)
Oral vs IV morphine	24.7/0.1	28.0/0.1	12.0/0.0	12.9/0.0
Morphine day 2	14.8 (11.7-18.0)	14.4 (11.5-17.3)	8.2 (5.6-10.8)	5.9 (3.3-8.5)
Morphine day 3	11.1 (8.4-13.9)	10.1 (7.3-13.1)	6.3 (4.0-8.6)	4.2 (2.3-6.1)
Morphine day 4	10.7 (7.9-13.5)	10.1 (7.2-12.9)	5.8 (3.8-7.8)	4.6 (2.6-6.7)
Morphine day 5	12.3 (9.3-15.3)	10.1 (7.4-12.8)	5.2 (3.1-7.2)	4.2 (2.3-6.0)
Morphine day 6	11.7 (8.8-14.5)	9.8 (7.2-12.3)	5.4 (3.6-7.2)	3.2 (1.4-4.9)
Morphine day 7	5.9 (3.9-7.9)	6.2 (4.0-8.3)	2.4 (1.2-6.7)	2.9 (1.5-4.3)

Data are expressed as mean (95% CI). Mg, milligram. IV, Intravenous.

Figure 1 CONSORT: Flow of patients through the phases of the trail. TKR, Total Knee Replacement; THR, Total Hip Replacement.

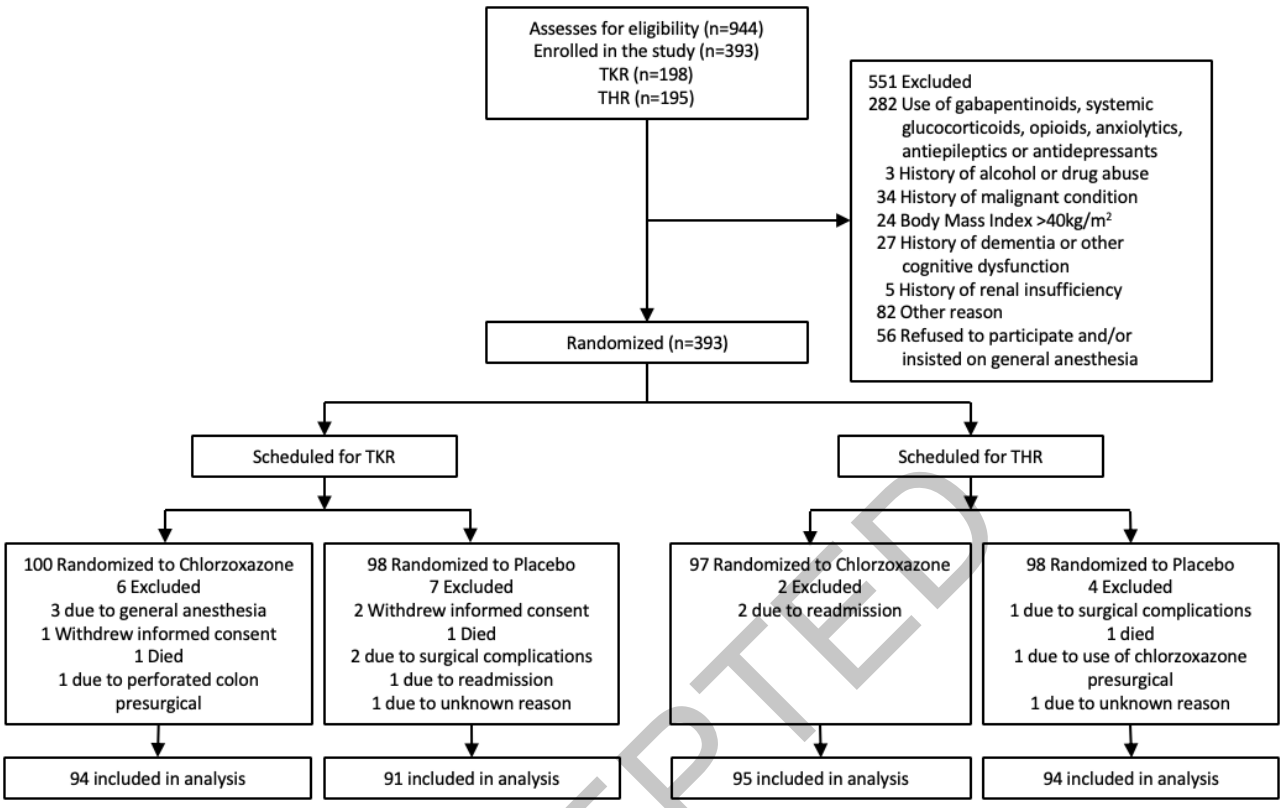

Figure 2 Development of Oxford Knee Score (OKS), function and pain, and Oxford Hip Score (OHS) from preoperative measurement to 12 months follow-up.