Investigating the Effect of Perioperative Chlorzoxazone on Acute Postoperative Pain After Total Hip and Knee Replacement Surgery

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Background and Aims: Severe preoperative and acute postoperative pain have been associated with the 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 has, however, questioned the continued use. Despite this, chlorzoxazone is still used for acute postoperative pain management following total knee replacement (TKR) or total hip replacement (THR). The current randomized, double-blinded, placebo-controlled, parallel-group, clinical trial aimed to assess the effect of chlorzoxazone for postoperative pain management following TKR or THR.

Methods: A total of 393 patients scheduled for TKR or THR were included in the trial. Patients were assigned to 250 mg chlorzoxazone 3 times daily for the first 7 days postoperatively or to placebo. The primary outcome was pain after 5 m walk assessed 24 hours postoperatively. 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. As regards TKR or THR, no effects were demonstrated for pain after 5 m walk 24 hours after surgery ($P>0.313$), or for any of the secondary outcomes ($P>0.288$) or adverse events ($P>0.112$) in the group receiving chlorzoxazone compared with placebo.

Conclusion: 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, muscle relaxants, postoperative pain management

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Pain and reduced physical function are the main symptoms of osteoarthritis (OA). Total knee replacement (TKR) and total hip replacement (THR) are the final treatments of end-stage OA. The treatments are effective and produces long-lasting improvements in 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 report 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 (AEs), 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 AEs.

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 monosynaptic and polysynaptic reflexes in the central nervous system,[17,18] but the specific mechanism of action is not clear. A study by Van Tulder et al,[16] suggested that chlorzoxazone may partly be associated with sedative effects due to the benzodiazepine derivative structure of chlorzoxazone.[17] Placebo-designed clinical studies of chlorzoxazone's beneficial effect on heterogeneous groups of patients with spasticity, motor neuron syndromes, and muscle pain and spasm of peripheral musculoskeletal diseases has 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] Furthermore, 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 perioperative and postoperative administration of chlorzoxazone on acute and chronic postoperative pain in patients scheduled for TKR and THR.

METHODS

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 on the basis of the following criteria: age below 18 years; preoperative use of gabapentinoids, systemic glucocorticoids, opioids, anxiolytics, antiepileptics, or antidepressants (within 4 wk); history of bipolar affective disorder; alcohol or drug abuse; malignant condition; liver disease; body mass index $>40\ kg/m^2$; diseases affecting central or peripheral nerve function; history of dementia or other cognitive dysfunction; allergies toward the medicine to be tested; lack of ability to walk 5 m; and pregnant or breastfeeding women. Furthermore, patients were excluded if there were perioperative complications, and any need for pain treatment apart from the standard.

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 250 mg (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, 3 times a day for 7 days, starting 2 hours preoperatively, 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.

Outcome Measures and Assessments

The primary outcome was pain 24 hours after surgery, measured as pain after walking 5 m 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 Score (OKS) and Oxford Hip Score (OHS) 7 days postoperatively, 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 Visual Analog Scale (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 days 2 to 7, 14, and at 12 months' follow-up. A 10 cm VAS was used (0 = no pain and 10 = worst pain imaginable).

OKS or OHS was assessed as a baseline measure and at days 2, 4, 7, and 14, and at 12 months' follow-up. The OKS

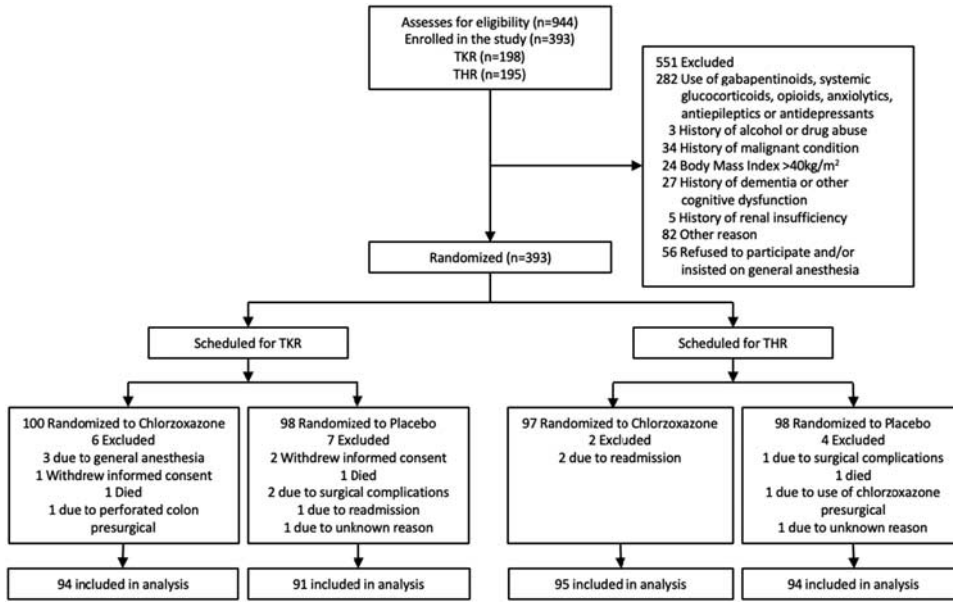

FIGURE 1. CONSORT: Flow of patients through the phases of the trial. THR indicates total hip replacement; TKR, total knee replacement.

and OHS are 12-item questionnaires assessing pain and function of the patient's knee or hip.

OKS answers were subgrouped 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 items 2, 3, 7, 11, and 12. The pain component consists of items 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 was 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 the number of events since the 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).

TABLE 1. Preoperative and Perioperative Demographics and Baseline Patient Characteristics for the 4 Groups and Comparisons Between Them

Characteristics	TKR, Chlorzoxazone (N = 94)	TKR, Placebo (N = 91)	*P*	THR, Chlorzoxazone (N = 95)	THR, Placebo (N = 94)	*P*
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‡	40 (42.6)	42 (46.2)	0.624	59 (62.2)	61 (63.5)	0.692
Female‡	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 5 m 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 h§	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 h postoperatively‖	0 (5)	0 (5)	0.240	0 (8)	0 (6)	1.0
24 h postoperatively‖	0 (4)	0 (4)	0.344	0 (8)	0 (6)	1.0
32 h postoperatively‖	0 (10)	0 (10)	1.0	0 (4)	0 (4)	1.0
48 h postoperatively‖	0 (2)	0 (6)	1.0	0 (2)	0 (1)	1.0
Dizziness (0-3)						
6 h postoperatively‖	0 (3)	0 (3)	1.0	0 (3)	0 (3)	1.0
24 h postoperative‖	0 (2)	0 (3)	1.0	0 (3)	0 (3)	1.0
32 h postoperatively‖	0 (1)	0 (3)	1.0	0 (3)	0 (3)	1.0
48 h postoperatively‖	0 (1)	0 (2)	1.0	0 (3)	0 (2)	1.0
Nausea (0-3)						
6 h postoperatively‖	0 (2)	0 (2)	1.0	0 (2)	0 (2)	1.0
24 h postoperatively‖	0 (1)	0 (3)	1.0	0 (3)	0 (2)	1.0
32 h postoperatively‖	0 (1)	0 (1)	0.112	0 (1)	0 (3)	1.0
48 h postoperatively‖	0 (1)	0 (1)	1.0	0 (1)	0 (3)	1.0
Vomiting, n						
No. patients vomiting (0-6 h)‡	3	0	0.510	1	7	0.21
No. patients vomiting (6-24 h)‡	4	5	1.0	10	8	1.0
No. patients vomiting (24-48 h)‡	3	8	1.0	7	6	1.0

Different kinds of opioids are converted to morphine milliequivalents.
*Significant difference favorizing placebo.
†Significant differences in favorizing chlorzoxazone.
Data are expressed as count (percentage)‡, mean (95% CI)§ or median (range)‖.
ASA indicates the American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; OHS, Oxford Hip Score; OKS, Oxford Knee Score; PACU, postanesthesia care unit; THR, total hip replacement; TKR, total knee replacement.

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TABLE 2. Mean (95% CI) VAS Pain Scores After 5 m Walk

Treatment Group	TKR, Chlorzoxazone	N	TKR, Placebo	N	*P*	THR, Chlorzoxazone	N	THR, Placebo	N	*P*
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 h postoperatively	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 h postoperatively	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 h postoperatively	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 h postoperatively	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 h postoperatively	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 h postoperatively	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 mo 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

VAS 4 to 48 hours postoperatively was assessed during admission.
Twelve months were assessed from the patient's diary.
*Significant difference in pain, favorizing placebo.
CI indicates confidence interval; THR, total hip replacement; TKR, total knee replacement; VAS, Visual Analog Scale.

Anesthesia, Surgery, and Analgesia

Surgery was performed under lumbar spinal anesthesia with bupivacaine 0.5%, 7.5 mg (1.5 mL) and optional supplemental propofol (1 to 5 mg/kg/h). TKR was performed using a midline skin incision and medial parapatellar arthrotomy. THR was performed using the posterolateral approach. Both types of surgery were performed without the application of surgical drains. TKR patients had Local Infiltration Anesthesia with 100 mL 2% Ropivacaine during surgery, whereas THR patients had no Local Infiltration Anesthesia.

A basic analgesic regime was used consisting of slow-release oral acetaminophen and celecoxib. Two hours preoperatively, 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. Further, study drug was administered as descriebed previously. Rescue analgesics (administered on-demand as required if VAS > 50 mm at rest) consisted of intravenous sufentanil 5 mg (patients above 70 y) and 10 mg (patients below 70 y) in the postanesthesia care unit and subsequently of oral morphine 10 mg (patients above 70 y) and 20 mg (patients below 70 y) 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 1 h after last opioid administration). During admission, nausea and vomiting were treated with ondansetron 4 mg.

TABLE 3. VAS Pain Scores at Rest, and VAS Worst Pain Score for the Last 24 Hours

Pain at Rest	TKR, Chlorzoxazone	N	TRK, Placebo	N	*P*	THR, Chlorzoxazone	N	THR, Placebo	N	*P*
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 h postoperatively	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 h postoperatively	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 h postoperatively	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 h postoperatively	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 h postoperatively	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 h postoperatively	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 mo 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 24 h										
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 mo 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).
VAS 4 to 48 hours postoperatively was assessed during admission.
The rest were assessed from the patient's diary.
CI indicates confidence interval; THR, total hip replacement; TKR, total knee replacement; VAS, Visual Analog Scale.

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

Sample Size Calculation

The estimated sample size for the primary outcome was calculated on the basis of results from Andersen et al[14] who assessed pain upon ambulation the first day after TKR and found a mean of 54 (SD: 25) on a VAS (0 to 100). Thus, 50 patients in each group would allow the detection of a clinically relevant 30% difference in VAS pain after 5 m 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 preoperatively to day 7 postoperative was needed, 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 allowed for dropouts, which is a common problem in these longitudinal studies on OA.[26–28]

Statistical Analysis

Statistical analyses were performed in IBM SPSS Statistics (version 25; IBM Corporation, Armonk, NY), 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 the independent sample t test or the nonparametric Mann-Whitney U test. Data are presented as mean and 95% confidence interval, and median (range) or frequencies, as relevant. P-value <0.05 was considered significant. All outcomes were Bonferroni corrected to account for multiple comparisons.

RESULTS

From September 2015 to September 2016, a total of 944 patients had a TKR or THR in our hospital. A total of 551 of these patients 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 the TKR group, 100 patients were randomized to the chlorzoxazone group, and 98 patients to the placebo group. In the THR group, 97 patients were randomized to the chlorzoxazone group, and 98 patients to the placebo group. A total of 19 patients were excluded after randomization, 13 scheduled for TKR, and 6 scheduled for THR (Fig. 1).

Baseline patient characteristics and preoperative data are presented in Table 1. The placebo group demonstrated significantly better preoperative function in OKS compared with the chlorzoxazone group ($P=0.034$), and the chlorzoxazone group demonstrated significantly better preoperative function in the OHS compared with the placebo group ($P=0.042$). No other significant preoperative differences were found. Likewise, perioperative data and adherence to the protocol were not significantly different between the groups.

Pain After 5 m Walk

No significant effect was found for primary outcome pain after 5 m walk 24 hours postoperatively 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 postoperatively, favorizing placebo for TKA (Bonferroni: $P=0.048$) (Table 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 the worst pain for the last 24 hours (Table 3).

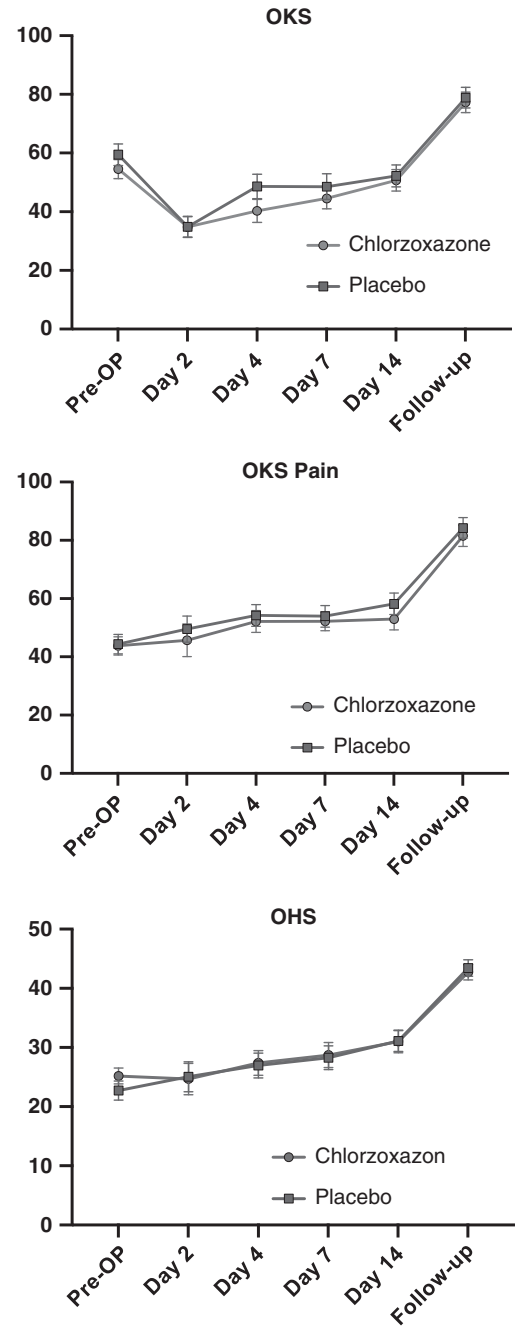

FIGURE 2. Development of Oxford Knee Score (OKS), function and pain, and Oxford Hip Score (OHS) from preoperative measurement to 12 months' follow-up.

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TABLE 4. Consumption of Opioids the First 7 Days Postoperatively

Opioid Consumption	TKR, Chlorzoxazone	TKR, Placebo	THR, Chlorzoxazone	THR, Placebo
1. Postoperative day, total mg morphine/d	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/d	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).
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.
CI indicates confidence interval; IV, intravenous; THR, total hip replacement; TKR, total knee replacement.

OKS/OHS

No significant effect was observed for OKS and OHS within the first 7 postoperative days (Bonferroni: $P > 0.12$) or at 12 months' follow-up (Fig. 2).

Opioid Consumption

No significant difference in opioid consumption the first 7 days postoperatively was found, nor for oral versus IV analgesia (Table 4).

Other Outcomes

Furthermore, 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).

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 it demonstrated no significant reduction in pain during mobilization, pain at rest, or in the worst pain in the last 24 hours or any AEs when compared with placebo. In addition, no effect was demonstrated in OKS or OHS within the first 7 postoperative days when comparing chlorzoxazone with placebo. Finally, chlorzoxazone did not improve chronic postoperative pain at 12 months' follow-up compared with the placebo.

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, and physiotherapy.[17,18]

A systematic search of the literature revealed only 1 placebo-controlled trial of the 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 the present study. Furthermore, a study by Rani 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) in the first 2 postoperative weeks and found that the effect of the combination was superior to the effect of 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 clinical relevance (a reduction of 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 AEs are fatigue and dizziness (about 1% to 10% of patients).[16] Adverse reactions are to some extent overlapping with the side effects that are related to perioperative opioid treatment.[16] It is, therefore, possible that the frequency of AEs 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 as follows: COX-2 selective inhibitors or conventional NSAIDs in combination with acetaminophen supplemented with weak or strong opioids.[9,10,31]

However, the 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.

The present study demonstrated a significant difference in pain after 5 m walk after TKR measured among the patients still hospitalized 48 hours postoperatively, favorizing the placebo group. However, no difference in baseline characteristics or any other differences in any other available measures were present, including a 1-year follow-up, besides that they were hospitalized for >48 hours postoperatively. However, this finding is limited by missing data at 48 hours postoperatively, as ~70% of patients were discharged, which was not expected when this study was initiated.

The strength of the 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.

CONCLUSIONS

The current clinical trial demonstrated no beneficial effects of chlorzoxazone given perioperatively and 3 times daily for 7 days postoperatively on pain in the acute postoperative period or on the development of chronic postoperative pain assessed after 12 months. Furthermore, no effects were found on function. On the basis of 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 multicenter study is recommended for confirmation of the findings of the present study.

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