Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty


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Background. Optimal pain treatment with minimal side-effects is essential for early mobility and recovery in patients undergoing total hip arthroplasty. We investigated the analgesic effect of pregabalin and dexamethasone in this surgical procedure.

Methods. One hundred and twenty patients were randomly allocated to either Group A (placebo), Group B (pregabalin 300 mg), or Group C (pregabalin 300 mg + dexamethasone 8 mg). The medication and acetaminophen 1 g were given before operation. Spinal anaesthesia was performed. Postoperative pain treatment was with acetaminophen 1 g three times daily and patient-controlled i.v morphine, 2.5 mg bolus. Nausea was treated with ondansetron. Morphine consumption, pain intensity at rest and during mobilization, nausea and vomiting, sedation, dizziness, and consumption of ondansetron were recorded 2, 4, and 24 h after operation. P<0.05 was considered statistically significant.

Results. Twenty-four hour morphine consumption was significantly reduced in Groups B [mean (sd) 24 (14) mg] and C [25 (19) mg] compared with Group A [47 (28) mg]. Vomiting was reduced in Group C compared with Group B (P=0.03). Sedation was significantly increased in Group B compared with the other groups.

Conclusions. Pregabalin resulted in a 50% reduction in 24 h postoperative morphine requirements. This was not associated with a reduced incidence of nausea or vomiting. Pregabalin resulted in increased levels of sedation. Combining pregabalin and dexamethasone provided no additional effects on pain or opioid requirements.

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Total hip arthroplasty is associated with postoperative pain of moderate intensity in the early postoperative period. Patients are often elderly and may have significant comorbid conditions; therefore, opioid-related side-effects such as nausea and sedation are especially undesirable in this population. Consequently, optimal pain treatment with minimal side-effects is essential to allow early mobility, optimal functional recovery, and to reduce postoperative morbidity and mortality.

It has been suggested that postoperative pain treatment should be specific in relation to the surgical procedure and that a combination of different, preferably non-opioid, analgesics should be administered in order to provide additive or synergistic effects together with reduced, opioid-related side-effects.

Both gabapentinoids and glucocorticoids have demonstrated opioid-sparing effects in a number of clinical studies of postoperative pain, but procedure-specific data in relation to total hip arthroplasty of these medications, or their combination, are not available. Consequently, for our study, we have chosen a dose of pregabalin that demonstrated efficacy in the first published clinical study of pregabalin in acute pain, and a dose of dexamethasone that demonstrated opioid-sparing and pain-relieving effects in a study of laparoscopic cholecystectomy. The hypothesis of our study was that ‘protective’ administration of pregabalin would reduce opioid requirements, pain, and side-effects, and that the addition of dexamethasone would further improve analgesia and reduce side-effects after hip surgery. We expected that this combination of drugs...
administered before surgery would demonstrate additive and prolonged postoperative analgesia.

The aim of this prospective, double-blind, randomized, placebo-controlled study was therefore to investigate the effect of pregabalin, and of a combination of pregabalin and dexamethasone, on morphine consumption (primary end point), pain scores, and side-effects (secondary end points) in patients undergoing hip joint alloplastic surgery.

Methods

The study was carried out at Hoersholm Hospital, the Capital Region of Denmark. It was conducted in compliance with guidelines for Good Clinical Practice (GCP) and was monitored by Copenhagen University Hospital GCP Unit. The design and the description adhere to the Consolidated Standards of Reporting Clinical Trials statement (CONSORT). Approval was obtained from the Danish Medicines Agency, the local Regional Ethics Committee, and The Danish Data Protection Agency. The study was registered at www.ClinicalTrials.gov: NCT00235261.

Patients undergoing primary alloplastic hip joint replacement surgery, aged 55–75 yr, BMI between 18 and 35, ASA I–III, and having a planned spinal anaesthesia for the procedure, were eligible for the study. Patients were not admitted to the study if any of the following criteria were present: (i) inability to cooperate, (ii) allergy to any drugs in the study, (iii) treatment with antacids or anti-depressants, (iv) a history of diabetes or epilepsy, (v) known impaired kidney function, (vi) alcohol, drug abuse, or both, (vii) a daily intake of analgesics, except for non-steroidal anti-inflammatory drugs, COX-2 inhibitors, or acetaminophen, and (viii) treatment with systemic glucocorticoids within 4 weeks before surgery.

When referred to the Department of Orthopaedics, patients received written information regarding the trial and signed and dated informed consent was obtained from all patients.

All patients received acetaminophen and spinal anaesthesia. Oral acetaminophen 1 g was given as premedication 1 h before anaesthesia. Spinal anaesthesia was performed at the L3/4 (alternatively L2/3 or L4/5) using 3 ml plain bupivacaine 5 mg ml⁻¹. Hypotension was treated with isotonic sodium chloride, Voluven (hydroxyethyl starch, HES, 130/0.4), i.v. ephedrine 5–10 mg, or both, at the discretion of the anaesthetist. The same five orthopaedic specialists performed all surgical procedures using the lateral approach for the arthroplasty.

Postoperative pain treatment consisted of oral acetaminophen 1 g every 8 h, initiated 4 h after operation, and patient-controlled i.v. (PCA) morphine (CADD-Legacy PCA model 6300, Astra Tech, Taastrup, Denmark) 2.5 mg bolus, 10 min lockout time. Nausea of at least moderate level was treated with i.v. ondansetron, 4 mg starting dose and 1 mg supplemental doses. No other analgesic, anti-emetic, or sedative drugs were used during the 24 h study period.

The study was randomized, double-blind, and placebo-controlled. Study medication was prepared by the hospital pharmacy into identical capsules of either 300 mg pregabalin or placebo. A separate package containing either dexamethasone or isotonic sodium chloride was opened and prepared into a neutral syringe by a nurse, who was not a part of the study or any handling of the patient. All medications were given to the patient by one of the investigators. Study medication was marked with the name of the project, the investigator's name, and consecutive numbers according to a computer-generated block randomization schedule prepared by the hospital pharmacy. Each block contained nine numbers and the patients were assigned consecutively to their group according to their number. The investigators did all assessments. No person was aware of group assignment until all patients had been included and assessments were completed.

Patients were randomly allocated to one of the following three treatment groups: Group A: placebo+placebo; Group B: pregabalin (Lyrica®, Pfizer)+placebo; and Group C: pregabalin+dexamethasone (Fortecortin®, Merck). One hour before anaesthesia and according to their groups, patients received pregabalin 300 mg or placebo orally. Likewise, before the induction of anaesthesia, i.v. dexamethasone 8 mg or placebo was given.

The primary outcome measure was patient-controlled morphine consumption from 0 to 4 and 0 to 24 h after operation. Secondary outcome measures were postoperative pain score at rest and during mobilization, and side-effects: nausea, vomiting, sedation and dizziness.

Before operation, all patients were instructed in the use of the visual analogue scale (VAS) (0 mm, no pain; 100 mm, worst pain imaginable) and patient-controlled anaesthesia. Pain scores (before operation) at rest and during mobilization (from sitting to standing position) were assessed.

Patients were visited by the investigators 2, 4, and 24 h after operation. At each visit, outcomes were measured in the following order: morphine consumption, VAS pain score at rest and during mobilization, nausea, number of vomits, sedation, and dizziness.

Total PCA morphine consumption from 0 to 2, 0 to 4, and 0 to 24 h after operation were recorded. VAS pain scores were assessed by the patients at 2, 4, and 24 h after operation, both supine and during mobilization from the supine to the sitting position. Levels of nausea, sedation, and dizziness, at the time of visit by the investigator, were assessed by the patient using a four-point verbal scale (none, mild, moderate, and severe). Number of vomits in the postoperative periods 0–2, 2–4, and 4–24 h was assessed by the patients. Finally, total 24 h consumption of ondansetron was recorded.

On the basis of morphine usage in a retrospective sample of 30 patients in our department, who had total hip
alloplastic surgery, the anticipated morphine requirement was 30 (15) mg in 24 h. We considered a 40% reduction (12 mg) to be clinically relevant. With a type I error (α) of 5% and a power (1−β) of 80%, sample size calculations showed that 31 patients in each group were required.

Data are presented as median (IQR) or mean (sd) as appropriate. P<0.05 was considered statistically significant. To assess for normality, the Kolmogorov–Smirnov (K–S) test was performed on the data set. Assumption of normality was rejected for most data, and consequently data were compared using the non-parametric Kruskal–Wallis (K–W) test for independent samples. Significant Kruskal–Wallis values were Bonferroni corrected with a factor 3 for the three different time points investigated. If the Bonferroni corrected Kruskal–Wallis test value was significant, groupwise comparisons were performed at each time point using Mann–Whitney rank sum test for unpaired data. Significant Mann–Whitney values were again Bonferroni corrected with a factor 3 for the number of groups.

Categorical data were analysed with χ² test. For sedation and dizziness, the arithmetic ‘mean’ scores for each patient was calculated and compared by attributing numerical values to the scores from each patient: none, 0; slight, 1; moderate, 2; and severe, 3.

Calculations were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL, USA).

**Results**

From November 28, 2005 to June 18, 2007, we considered 514 consecutive patients aged 55–75 yr for inclusion in the study. One hundred and twenty-six patients were included and randomly assigned to their treatment group. However, six patients were later excluded from the study, resulting in data from 120 patients in the final analyses (Fig. 1).

There were no significant differences between the groups for patient characteristics and perioperative data, except for the weight (Group B vs C; P=0.01) (Table 1). The median numbers of days staying in hospital were 4, 5, and 4 for Groups A, B, and C, respectively (NS).

For the first 2 and 4 h after operation, there were no significant differences between the groups in morphine consumption (Fig. 2). The total 24 h morphine consumption was significantly reduced in Groups B [24 (14) mg] and C [25 (19) mg] compared with Group A [47 (28) mg] (P<0.003). Between Group B and Group C, there was no significant difference (P=0.90) (Fig. 2).

For VAS pain scores at rest, or during movement, there were no significant differences between the groups at any time points (Figs 3 and 4). For nausea scores, there were no significant differences between treatment groups at any time points. Nausea was of mild nature in most patients, with two patients in each group experiencing moderate nausea and one patient having severe nausea in Group A (Table 2). The incidence of vomiting was generally low with 32 (Group A), 30 (Group B), and 40 (Group C) patients not experiencing vomiting at all. Total 24 h number of vomits and number of patients vomiting were not significantly different between Group A and Group B. In Group C, total 24 h number of vomits was significantly lower than in Group B (P=0.03), but not different from that of Group A. Likewise, total 24 h number of patients vomiting was significantly lower in Group C vs Group B (P=0.03), but not different from that of Group A (Table 2). For the consumption of ondansetron, there were no significant differences between the groups (Table 2).

The mean 24 h sedation scores were significantly higher in Group B compared with Group A (P<0.003) and Group C (P=0.02). Sedation was most prominent at 2 and 4 h, whereas, at 24 h, there were no significant differences between the groups (Table 3). For mean 24 h dizziness scores, there were no significant differences between treatment groups (P=0.24).

**Discussion**

Preoperative administration of pregabalin 300 mg resulted in a nearly 50% reduction in 24 h postoperative morphine consumption (Fig. 2). The total 24 h morphine consumption was significantly reduced in Groups B [24 (14) mg] and C [25 (19) mg] compared with Group A [47 (28) mg] (P<0.003). Between Group B and Group C, there was no significant difference (P=0.90) (Fig. 2).

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requirements in patients undergoing total hip arthroplasty under spinal anaesthesia. This opioid-sparing effect was not associated with a reduced incidence of nausea or vomiting. Pregabalin 300 mg resulted in increased levels of sedation. The combination of pregabalin 300 mg and i.v. dexamethasone 8 mg reduced sedation and vomiting compared with pregabalin 300 mg alone, but provided no additional effects on pain or opioid requirements.

Gabapentin has demonstrated substantial opioid-sparing and pain-relieving abilities in a large number of clinical studies of postoperative pain. Glucocorticoids have both anti-inflammatory and anti-emetic properties and have demonstrated prolonged postoperative analgesic effects in several procedures. Dexamethasone has been shown to reduce postoperative analgesic requirements in both dental (8 and 16 mg), laparoscopic (8 mg), and breast (8 and 16 mg) surgery. The main results of our study could not confirm our hypothesis that pregabalin and dexamethasone would demonstrate prolonged and additive analgesic effects. We observed reduced morphine requirements in the groups receiving pregabalin, but no additional opioid-sparing or clinically significant prolonged pain-relieving effects of adding dexamethasone to pregabalin. We only have data on accumulated morphine requirements at 2, 4, and 24 h after operation, and our results cannot document if the opioid-

### Table 1 Patient characteristics. Data are median (range) or mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group A (placebo)</th>
<th>Group B (pregabalin)</th>
<th>Group C (pregabalin + dexamethasone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>38</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Age</td>
<td>66 (63–71)</td>
<td>67 (62–71)</td>
<td>68 (64–71)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (9)</td>
<td>170 (9)</td>
<td>170 (8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (14)</td>
<td>73 (13)</td>
<td>81 (13)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>18/20</td>
<td>14/26</td>
<td>22/20</td>
</tr>
<tr>
<td>Preoperative VAS pain at rest (mm)</td>
<td>2 (0–16)</td>
<td>5 (0–21)</td>
<td>7 (2–19)</td>
</tr>
<tr>
<td>Preoperative VAS pain at mobilization (mm)</td>
<td>21 (8–30)</td>
<td>15 (5–27)</td>
<td>21 (14–31)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>60 (52–67)</td>
<td>52 (46–60)</td>
<td>60 (50–71)</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>425 (300–600)</td>
<td>375 (263–500)</td>
<td>400 (300–600)</td>
</tr>
<tr>
<td>Isotonic sodium chloride (ml)</td>
<td>825 (600–1000)</td>
<td>400 (800–1000)</td>
<td>810 (800–1000)</td>
</tr>
<tr>
<td>Voluven (ml)</td>
<td>250 (0–500)</td>
<td>275 (0–500)</td>
<td>425 (0–500)</td>
</tr>
<tr>
<td>Type of alloplastic No cement</td>
<td>36</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Total cement</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hybrid</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Glucocorticoids have both anti-inflammatory and anti-emetic properties and have demonstrated prolonged postoperative analgesic effects in several procedures. Dexamethasone has been shown to reduce postoperative analgesic requirements in both dental (8 and 16 mg), laparoscopic (8 mg), and breast (8 and 16 mg) surgery. 

The main results of our study could not confirm our hypothesis that pregabalin and dexamethasone would demonstrate prolonged and additive analgesic effects. We observed reduced morphine requirements in the groups receiving pregabalin, but no additional opioid-sparing or clinically significant prolonged pain-relieving effects of adding dexamethasone to pregabalin. We only have data on accumulated morphine requirements at 2, 4, and 24 h after operation, and our results cannot document if the opioid-

**Fig 2** Consumption of morphine in 0–24 h after operation in placebo, pregabalin, and pregabalin+dexamethasone groups. *P<0.003 compared with placebo.

**Fig 3** Pain score (VAS) at rest at 2, 4, and 24 h after operation in placebo, pregabalin, and pregabalin+dexamethasone groups. There were no differences between the groups.
sparing effect of pregabalin was prolonged beyond the expected clinical duration of action, or if it took place during the first few postoperative hours. Future studies with more frequent assessments are needed to answer this question.

In spite of the relatively large reduction in morphine consumption, we did not observe any reduction of nausea or vomiting with pregabalin. The incidence of nausea and vomiting in this population was very low, and our study is most likely underpowered to detect any difference. The well-known anti-emetic effect of dexamethasone \(^1\) was seen as a significant reduction in vomiting in patients receiving the combination of pregabalin and dexamethasone compared with pregabalin alone in our study.

Sedation and dizziness are well-known side-effects of gabapentinoids \(^7\), and we observed increased sedation in patients receiving pregabalin alone in the early postoperative period. The clinical relevance is arguable as most patients were only slightly sedated at this stage and all patients were able to follow the postoperative routine of care and mobilization. When adding dexamethasone to pregabalin (Group C), sedation diminished and we observed no significant differences in mean sedation score between Group A and Group C. In a previous study, dexamethasone 8 mg significantly reduced postoperative fatigue scores after laparoscopic cholecystectomy \(^1\)\. Consequently, dexamethasone may have important beneficial effects other than analgesia in multimodal regimens.

The combination of pregabalin and dexamethasone had no effect on pain or opioid requirements compared with pregabalin alone. One reason for this finding could be that the dose of dexamethasone was too low. We used 8 mg of dexamethasone, but a somewhat higher dose of 0.2–0.4 mg kg\(^{-1}\) dexamethasone i.v. is recommended by some authors \(^1\)\. Another reason could be the low pain score at most time points in all groups (<30 mm on the VAS), since adequate sensitivity in trials of analgesics for acute pain may only be achieved when patients are experiencing at least moderate pain \(^2\), \(^2\)\. In a recent procedure-specific systematic review, recommendations were provided for optimal pain treatment after total hip arthroplasty. \(^2\) These recommendations included acetaminophen and in addition, a number of medications, including gabapentinoids, were suggested to have potential usefulness, but procedure-specific data were not yet available. \(^2\) Our study presents procedure-specific data for pregabalin in hip arthroplasty. However, in spite of the opioid-sparing effect demonstrated, general recommendations for the use of pregabalin in hip alloplastic surgery cannot be made based on this single study. The optimal dosing regimen for pregabalin is unsolved, and the potential clinical benefit from the opioid-sparing was not demonstrated.

The mechanisms of action of \(N\)-methyl-\(d\)-aspartic acid (NMDA) antagonists and gabapentinoids differ from that of ‘traditional’ anti-nociceptive drugs. Whereas the latter reduce the afferent input from both intact and traumatized tissue, NMDA antagonists and gabapentinoids have no effect on nociception per se, but reduce the hyperexcitability of dorsal horn neurones induced by tissue damage.
This effect seems equally effective irrespective of the timing of administration, that being if the drugs are administered before or after the injury.\textsuperscript{22}

The term ‘anti-hyperalgesic’ has been suggested for NMDA antagonists, gabapentinoids, and other medications with similar mechanisms of action. Accordingly, the term ‘protective analgesia’ has been suggested for preoperative administration of anti-hyperalgesics, since these medications block the sensitization process in dorsal horn neurones.\textsuperscript{3} ‘Protective’ was suggested in order to differentiate this concept from ‘pre-emptive’ analgesia. Although both concepts share the same objective, reduction of pain or opioid requirements could be demonstrated.

In conclusion, we have demonstrated that a single, preoperative dose of pregabalin 300 mg resulted in a nearly 50% reduction in 24 h postoperative morphine requirements in patients undergoing hip surgery. This opioid-sparing was not, however, associated with a reduced incidence of nausea or vomiting. In contrast, pregabalin resulted in increased levels of sedation. The combination of pregabalin and dexamethasone 8 mg reduced vomiting and sedation compared with pregabalin alone, but no additional effects on pain or opioid requirements could be demonstrated.

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