Comparison of the postoperative analgesic effects of paracetamol—codeine phosphate and naproxen sodium—codeine phosphate for lumbar disk surgery

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Abstract The aim of this study was to compared the efficacy of paracetamol—codeine phosphate and naproxen sodium—codeine phosphate on postoperative pain and tramadol consumption during the first 24 hours after a lumbar disk surgery. After Ethics Committee approval and informed consent had been obtained, 64 patients were allocated into three groups. Patients received oral paracetamol—codeine (300 mg + 30 mg; Group P), naproxen sodium—codeine (550 mg + 30 mg; Group N), or placebo tablets (Group C) 30 minutes prior to induction of anesthesia. Patient-controlled analgesia was supplied postoperatively using tramadol. Pain intensity, tramadol consumption, and side effects were recorded every 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours after surgery. Whole study period pain intensity (visual analogue scale scores) was lower in Group P (p = 0.007) and Group N (p = 0.001), compared with Group C, however, there was no statistically significant difference between Group P and Group N regarding pain intensity (p > 0.05). Tramadol consumption was lower in Group P and Group N, compared with Group C (p < 0.001), and in turn the lowest incidence of tramadol consumption was detected in Group P compared with Group N (p < 0.001) and Group C (p < 0.001). Side effects were similar between the groups. Preemptive administration of paracetamol—codeine and naproxen sodium—codeine combination significantly reduced tramadol consumption and provided more effective analgesia compared with placebo. The paracetamol—codeine combination was superior to naproxen sodium—codeine with regard to tramadol consumption.

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Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

After surgical intervention, 20–40% of patients report moderate pain, and 50–70% of patients experience severe pain. Effective postoperative pain control decreases postoperative pain-related complications and improves patient outcome [1]. Systemic opioids are regarded as the gold standard for the relief of postoperative pain, however, their use is limited by dose-related side effects [2]. To overcome this problem, the adjunctive administration of analgesics that act via different mechanisms during the preoperative period as a preemptive analgesia is recommended for effective postoperative pain control. Preemptive analgesia reduces peripheral sensitization before noxious stimuli occur by interrupting the noxious perioperative inputs transmission to the spinal cord. Preventing central sensitization reduces pain and analgesic requirements and analgesic-related side effects [3].

The reduced doses of two (or more) drugs from different classes given together can provide adequate pain relief, acting via different targets while reducing dose-dependent adverse events [4]. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are peripherally acting analgesics, whereas codeine is a centrally acting opioid. Used together, these drugs can have additive analgesic effects [5]. Several studies have shown that the combination of an opioid, either NSAIDs or paracetamol, reduces the postoperative opioid requirement and decreases the incidence of opioid-induced side effects [6,7]. However, in studies investigating the effect of a combination of paracetamol and intravenous morphine as a patient-controlled analgesia (PCA), the results are conflicting regarding the opioid-sparing effect of this drug combination [8,9]. NSAIDs also have numerous contraindications and side effects and consequently cannot be used in >25% of postoperative patients [10,11]; however, paracetamol has very few contraindications and is relatively free from side effects at clinical doses [12]. Codeine is commercially available in combination with peripherally acting analgesics such as naproxen sodium or acetylaminoephine.

To our knowledge, no previous study has assessed the effects of naproxen sodium–codeine or paracetamol–codeine orally administered prior to surgery in patients undergoing lumbar disk surgery. Thus, this controlled clinical trial was designed to investigate the analgesic efficacy and opioid-sparing effect of a single dose of oral naproxen sodium–codeine or paracetamol–codeine on postoperative pain in adult patients undergoing lumbar discectomy.

Materials and methods

This study was approved by the Diskapi Yildirim Beyazit Education and Research Hospital ethics committee (2014/20), conducted in accordance with the Declaration of Helsinki, and was registered at http://clinicaltrials.gov (registration number NCT02255955). The study was performed at Diskapi Yildirim Beyazit Education and Research Hospital between October and December 2014. We enrolled 64 consecutive patients, aged 18–65 years and assessed as American Society of Anesthesiologists Physical Status I–II, who underwent general anesthesia for an elective single-level unilateral microsurgical lumbar discectomy. Written informed consent was obtained from all patients prior to randomization. The exclusion criteria were known allergies to any of the drugs used in this study, peptic ulcer disease, hepatic and renal dysfunction, emergency surgery, or inability to provide informed consent (e.g., mental disorders). All patients were instructed regarding the use of PCA pumps [Abbott, Abbott Provider, Pain Manager II (APM II) Single-Channel PCA; Chicago, IL, USA].

The patients were randomly assigned into three groups by computer-generated random numbers. Thirty minutes prior to the surgery, the naproxen sodium–codeine group (Group N, n = 20) received an oral naproxen sodium + codeine phosphate (550 mg + 30 mg) tablet (Apranax Plus Tablet; Abdi Ibrahim, Istanbul, Turkey), the paracetamol–codeine group (Group P, n = 20) received a paracetamol + codeine phosphate (300 mg + 30 mg) tablet (Geralgin Plus Tablet; Münir Şahin, İstanbul, Turkey), and the control group (Group C, n = 20) received an oral placebo. The study drugs were administered by a nurse, and the postoperative data were collected by a blinded anesthesiologist.

In the operating room, after routine monitoring, anesthesia was induced with propofol (1.5–2 mg/kg), rocuronium (0.6 mg/kg), and fentanyl (0.1 μg/kg), and maintained with sevoflurane (1–1.5 mean alveolar concentration) in oxygen/air (fraction of inspired oxygen of 0.40) and remifentanil infusion (0.05–0.1 μg/kg/min). Residual muscle relaxation was reversed with atrопine (0.01 mg/kg) and neostigmine (0.02 mg/kg) at the end of the surgery. All patients received tramadol using a PCA pump for 24 hours postoperatively. The PCA solution was prepared with 500 mg tramadol in 100 mL normal saline. The PCA was set to administer a bolus dose of 20 mg on demand with a lockout period of 10 minutes and no back ground infusion. Because a 10-minute lockout interval was set with the PCA pump if the patient’s pain score was >4, tramadol (1 mg/kg) was administered intravenously.

The patients were assessed for pain at 0 hours, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours postoperatively using a visual analogue scale (100-mm linear scale, where 0 = no pain, 100 mm = worst pain imaginable). Sedation was evaluated on the basis of the Ramsay score [13]. Total tramadol consumption, Ramsay score, postoperative side effects such as constipation, drowsiness, dizziness, nausea, and vomiting, defined by a scale where 0 = absent and 1 = present, were recorded each time the pain intensity was evaluated. The patients did not receive antiemetic prophylaxis. Postoperative nausea and vomiting were treated with 8 mg ondansetron.

Based on a previous study [3] and the assumption that a difference of 20 U in postoperative pain scores on the visual analogue scale is clinically relevant, we carefully defined the effect size to be 2, with an estimated standard deviation of ±2. By setting α = 0.05 and power = 0.9, we calculated a sample size of 18 patients/group. To compensate for possible dropouts, 21 patients/group were included.

The statistical analyses were performed using SPSS 11.5 software (SPSS Inc., Chicago, IL, USA) and R Language (3.1.2). The normality of the distribution was assessed using...
the Shapiro–Wilk test. The nonparametric data (body mass index, age, total drug consumption, and duration of surgery) were analyzed using the Mann–Whitney U test, and one-way analysis of variance was used for the parametric data (duration of anesthesia). The categorical data (sex, American Society of Anesthesiologists) were compared using Fisher’s exact test. Nonparametric longitudinal data analyses were performed by nparLD module at R software package that is an open source statistical software (http://www.R-project.org). The results are given as the mean ± standard deviation and count (percentage). A p value < 0.05 was considered a statistically significant difference.

Results

Sixty-four patients were enrolled in the study. Four patients were excluded during the study. Two patients from Group P, one patient from Group N, and one patient from Group C were excluded owing to a technical failure of the PCA pump. The groups were similar with respect to age, sex, body mass index, and the durations of anesthesia and surgery (Table 1).

When the whole study period was analyzed, the pain intensity was lower in Groups P (p = 0.007) and N (p = 0.001) compared with Group C, however, there was no statistically significant difference between Groups P and N (p > 0.05; Figure 1).

When tramadol consumption was evaluated, tramadol consumption was lower in Groups P (86 ± 39.52 mg) and N (138 ± 52.28 mg) compared with Group C (250 ± 31.46 mg) (p < 0.001). Furthermore, the tramadol consumption level was lower in Group P than in Group N (p < 0.001; Figure 2).

Four (20%) patients in Group P, five (25%) patients in Group N, and five (25%) patients in Group C complained of nausea and vomiting. The hemodynamic values, Ramsey sedation scores, and postoperative nausea and vomiting for all three groups were similar (p > 0.05 for all of the comparisons). There was no adverse aspiration event. No patient complained of constipation during the study period. No patient complained of dizziness or drowsiness.

Discussion

In this study, we evaluated the efficacy of preemptive paracetamol–codeine (300 mg + 30 mg) and naproxen sodium–codeine (500 mg + 30 mg) in patients who underwent single level unilateral microdiscectomy. We demonstrated that preemptive administration of paracetamol–codeine or naproxen sodium–codeine significantly reduced tramadol consumption and provided more effective analgesia compared with placebo. The paracetamol–codeine combination was superior to naproxen sodium–codeine with regard to reducing tramadol consumption. Preemptive NSAIDs and paracetamol have been widely used as multimodal analgesia to treat postoperative pain [14,15].

Paracetamol has both central inhibitor action on cyclooxygenases and interaction with the serotonergic system

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics.</th>
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<tr>
<td>Paracetamol–codeine (n = 20)</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Age (y)</td>
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<tr>
<td>Female sex</td>
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<td>Body mass index (kg/m²)</td>
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<td>Duration of anesthesia (min)</td>
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<td>Duration of surgery (min)</td>
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Data are presented as mean ± SD or n (%). SD = standard deviation.
Paracetamol—codeine and naproxen sodium—codeine

References


