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ORIGINAL ARTICLE

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.

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-releated 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 acetaminophen.

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 İbrahim, Istanbul, Turkey), the paracetamol—codeine group (Group P, $n = 20$) received a paracetamol + codeine phosphate (300 mg + 30 mg) tablet (Geralgine Plus Tablet; Münir Şahin, Istanbul, 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 atropine (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 $\alpha = 0.05$ 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.

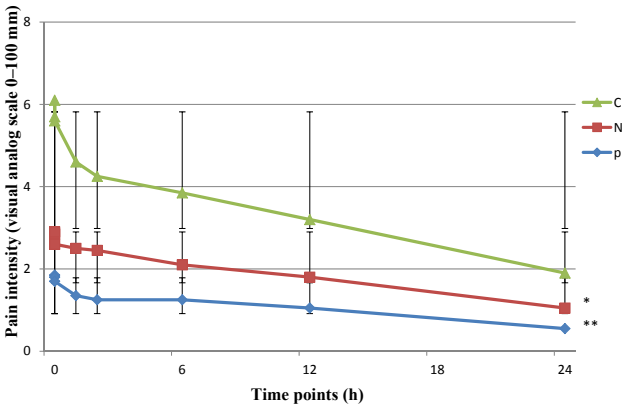

Figure 1. Pain intensity at each of the indicated time intervals (mean ± SD). Consecutive visual analogue scale measurements for the whole study period were analyzed by Package 'nparLD'. Group P and group N versus group C, *$p < 0.05$; group P versus group N, **$p > 0.05$ for 24 hours.

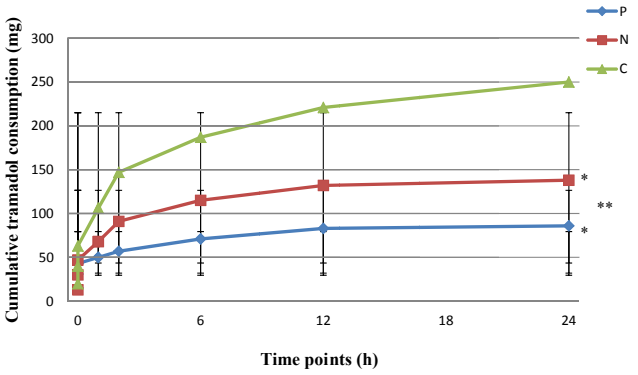

Figure 2. Cumulative tramadol consumption in groups during the postoperative 24 hours (mean ± standard deviation). Group P and N versus Group C, *$p < 0.001$; Group P versus Group N, **$p < 0.001$.

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 1 Patient characteristics.

	Paracetamol–codeine ($n = 20$)	Naproxen sodium–codeine ($n = 20$)	Control ($n = 20$)	p
Age (y)	44.95 ± 10.08	45.05 ± 9.68	43.10 ± 10.82	0.910
Female sex	10 (50)	9 (45)	8 (40)	0.627
Body mass index (kg/m^2)	25.80 ± 4	27.06 ± 2.82	26.25 ± 2.99	0.594
Duration of anesthesia (min)	93.95 ± 10.84	91.75 ± 8.94	89 ± 10.12	0.3
Duration of surgery (min)	81.45 ± 11.12	77.80 ± 7.98	73.75 ± 8.99	0.079

Data are presented as mean ± SD or n (%).
SD = standard deviation.

[16]. It may be used alone or in combined analgesic regimens for the PCA device treatment of mild and moderate postoperative pain [8,17]. Seymour et al [18] demonstrated that 1 g paracetamol was safe and effective at providing significant pain relief after third molar surgery. However, the efficacy of paracetamol in postoperative reduction of opioid consumption after major surgery remains controversial. In a study by Tunali et al [6], oral administration of 1 g paracetamol every 6 hours for 24 hours following lumbar disk surgery was not effective at reducing pain scores or morphine consumption compared with placebo; similar results were reported by Uzun et al [14]. A paracetamol—opioid combination is recommended for pain not controlled by paracetamol alone. Tramadol exhibits both mild μ-opioid receptor binding and norepinephrine and serotonin reuptake inhibition. A study conducted by Emir et al [19] demonstrated that a preemptive combination of 0.75 mg/kg tramadol and 1 g of paracetamol was effective at reducing postoperative pain intensity in patients who underwent spinal vertebral surgery despite the fact that only a low postoperative dose of infused tramadol was used.

Codeine is a prodrug with well-known analgesic efficacy, and it is frequently used in pain management. It is metabolized to its active form, morphine, by the liver. The recently published Cochrane review that includes 14 clinical trials states that combining paracetamol (600—1000 mg) with codeine (30—60 mg) provides clinically useful levels of pain relief in approximately 50% of patients with moderate to severe postoperative pain and that this combination prolonged the duration of analgesia compared with paracetamol alone [20]. In this work, we found that paracetamol—codeine (300 mg + 30 mg) reduced the pain intensity and also reduced tramadol consumption by approximately 65% when used as a supplemental analgesic with a tramadol PCA pump. In our study, we were able to provide effective analgesia with a lower dose of paracetamol than was used in the study by Emir et al [19]. These differences may be explained by the difference in the type of surgery; spinal vertebral surgery is more invasive than disk surgery.

NSAIDs reduce peripheral nociception by reducing the inflammatory response to surgical trauma and modulating the central response to painful stimuli by inhibiting prostaglandin synthesis in the spinal cord. The analgesic efficacy of NSAIDs for postoperative pain has been investigated in many studies, and their analgesic efficacy is considered to be as high as that of opioids [6,11,12].

Naproxen sodium, a peripherally acting anti-inflammatory drug, is used to treat various painful conditions, including postoperative pain [7,21]. However, in the literature we found only a small number of studies that had investigated the analgesic efficacy of a naproxen—codeine combination on postoperative pain. For this reason, we compared naproxen sodium—codeine and paracetamol—codeine in patients undergoing unilateral single level lumbar microdiscectomy.

The analgesic efficacy of naproxen—codeine may be attributable to the prevention of sensitization in peripheral and central pathways. Forbes et al [22] compared the effect of naproxen sodium—codeine, naproxen sodium, and placebo on postoperative pain 12 hours after oral surgery. They demonstrated that the naproxen sodium—codeine combination was superior to placebo or naproxen sodium alone. In another study, Bali et al [23] compared the efficacy of preemptive 550 mg naproxen sodium and naproxen sodium—codeine (550 mg + 30 mg) in patients undergoing arthroscopic meniscectomy, and they also found that the combination of naproxen sodium—codeine provided more effective analgesia and lower meperidine consumption than naproxen sodium alone. Similarly, in our study, we found that naproxen sodium—codeine reduced the pain intensity and also reduced tramadol consumption by almost 50% compared with placebo when used as a supplemental analgesic to tramadol PCA. The higher efficacy of naproxen—codeine compared with placebo may be related to the well-known analgesic efficacy of codeine.

Codeine, a centrally acting opioid, can have additive analgesic effects when combined with peripherally acting agents. In a review by Derry et al [17], which included 35 clinical trials comparing codeine (60—90 mg) with placebo in postoperative pain management, codeine alone at 60 mg provided better analgesia than placebo. However, this analgesia was not as effective as when it was used in combination with paracetamol and NSAIDs. We also found that both naproxen sodium—codeine and paracetamol—codeine combinations provided effective analgesia.

The effective dose of codeine phosphate is 30—60 mg; at doses >60 mg, there is a significant increase in the incidence of side effects, such as constipation, nausea, and respiratory depression. In our study, we did not encounter constipation or respiratory depression, perhaps because of the codeine dose that was used. We propose that a combination of tramadol and supplemental analgesics containing codeine might reduce the amount of systemic tramadol consumption and therefore the incidence of side effects, such as sedation, nausea, and vomiting.

Although we were not able to demonstrate a difference in the pain scores between the two treatment groups, we did find a significant difference in the amount of tramadol consumption. The incidence of postoperative adverse effects was similar between the treatment groups.

Conclusion

Both preemptive oral naproxen sodium—codeine and paracetamol—codeine combinations provided better pain relief than the placebo following lumbar disk surgery. Although both drug combinations also reduced the amount of postoperative tramadol consumption, paracetamol—codeine was more effective than naproxen sodium—codeine in this regard.

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