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SCIENTIFIC ARTICLE

Comparison of the postoperative analgesic effects of naproxen sodium and naproxen sodium-codeine phosphate for arthroscopic meniscus surgery☆

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KEYWORDS
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Abstract
Background and objectives: Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to control arthroscopic pain. Addition of oral effective opioid ''codeine'' to NSAIDs may be more effective and decrease parenteral opioid consumption in the postoperative period. The aim of this study was to compare the efficacy and side effects of naproxen sodium and a new preparation naproxen sodium-codeine phosphate when administered preemptively for arthroscopic meniscectomy.
Methods: Sixty-one patients were randomized into two groups to receive either oral naproxen sodium (Group N) or naproxen sodium-codeine phosphate (Group NC) before surgery. The surgery was carried out under general anesthesia. Intravenous meperidine was initiated by patient-controlled analgesia (PCA) for all patients. The primary outcome measure was pain score at the first postoperative hour assessed by the Visual Analogue Scale (VAS). Sedation assessed by Ramsey Sedation Scale, first demand time of PCA, postoperative meperidine consumption, side effects and hemodynamic data were also recorded.
Results: The groups were demographically comparable. Median VAS scores both at rest and on movement were significantly lower in Group NC compared with Group N, except 18th hour on movement ($p < 0.05$). The median time to the first demand of PCA was shorter in Group N compared with Group NC ($p < 0.001$). Meperidine consumption was higher in Group N compared with Group NC ($p < 0.001$). There was no difference between groups with respect to side effects ($p > 0.05$).
Conclusions: The combination of naproxen sodium-codeine phosphate provided more effective analgesia than naproxen sodium and did not increase side effects.

☆ This study was carried out in Baskent University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Adana, Turkey.
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PALAVRAS-CHAVE
Artroscopia;
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Naproxeno sódico;
Fosfato de codeína

Comparação dos efeitos analgésicos pós-operatórios de naproxeno sódico e naproxeno sódico-fosfato de codeína em artroscopia de menisco

Resumo
Justificativa e objetivos: Os anti-inflamatórios não esteróides (AINEs) são frequentemente usados para controlar a dor após artroscopia. A adição de um opiáceo oral eficaz (codeína) aos AINEs pode ser mais efetiva e diminuir o consumo de opiáceo parenteral no pós-operatório. O objetivo deste estudo foi comparar a eficácia e os efeitos colaterais de naproxeno sódico e uma nova preparação, naproxeno sódico-fosfato de codeína, quando administrados preventivamente para meniscectomia artroscópica.
Métodos: Sessenta e um pacientes foram randomicamente divididos em dois grupos para receber naproxeno sódico por via oral (Grupo N) ou naproxeno sódico-fosfato de codeína (Grupo NC) antes da cirurgia. A cirurgia foi realizada sob anestesia geral. Meperidina intravenosa foi iniciada por meio de analgesia controlada pelo paciente (ACP) para todos os pacientes. O desfecho primário foi o escore de dor na primeira hora de pós-operatório, avaliada com a Escala Visual Analógica (EVA). A sedação foi avaliada usando a Escala de Sedação de Ramsey. A primeira demanda de ACP, o consumo de meperidina no pós-operatório, os efeitos colaterais e os dados hemodinâmicos também foram registrados.
Resultados: Os grupos foram demograficamente comparáveis. As medianas dos escores EVA tanto em repouso quanto em movimento foram significativamente menores no Grupo NC comparado ao Grupo N; exceto para movimento na avaliação de18 horas ($p < 0,05$). A mediana do tempo até a primeira demanda de ACP foi menor no Grupo N em comparação com o Grupo NC ($p < 0,001$). O consumo de meperidina foi maior no Grupo N em comparação com o Grupo NC ($p < 0,001$). Não houve diferença entre os grupos em relação aos efeitos colaterais ($p > 0,05$).
Conclusões: A combinação de naproxeno sódico-fosfato de codeína forneceu analgesia mais efetiva que naproxeno sódico, sem aumentar os efeitos colaterais.

Introduction

Arthroscopic knee surgery is a common surgical intervention. There is evidence that effective postoperative pain management facilitates discharge and more rapid functional improvement of these patients.[1,2] Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for controlling arthroscopic pain[1,2] and have been administered alone or as intraarticular combinations with local anesthetics or opioids for these procedures.[2,3] This group of drugs have been demonstrated to reduce pain and inflammation due to arthroscopy, as well as effusions related to inflammation, by inhibiting prostaglandin synthesis.[4] The preoperative administration of NSAIDs may be more effective in reducing postoperative pain by inhibiting prostanoid production before the development of tissue injury.[1]

Although the efficacy of oral naproxen sodium as a preemptive medication has been shown for arthroscopic knee surgery,[5] the preemptive efficacy of oral naproxen sodium-codeine phosphate has not yet been investigated to our knowledge. 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.[6]

This study aims to compare the efficacy of single preemptive dose of oral naproxen sodium versus a new combination of oral naproxen sodium-codeine phosphate on postoperative pain in adult patients undergoing arthroscopic meniscectomy.

Materials and methods

The Baskent University Institutional Review Board and Ethics Committee approved this prospective, randomized, double-blind study (Project number: KA12/268). The study was supported by Baskent University Research Fund and was completed within 6 months. Patients undergoing arthroscopic meniscectomy were included in the study. The exclusion criteria were as follows: ≤18 years of age, hypersensitivity to NSAIDs and/or codeine, history of a peptic ulcer, gastritis, upper gastrointestinal bleeding, a coagulation disorder, hepatic failure, renal impairment, pregnancy, and the use of NSAID, opioid and other analgesic agents up to the time of the surgery.

During the preoperative examination, patients were informed about the study parameters, including pain management methods to be used during the study, drugs involved and potential side effects. Written informed consent was obtained from all patients.

The randomization scheme automatically created by a computer was kept in closed envelopes. These envelopes were prepared by an anesthesiologist who was not part of the study. Before surgery, patients were assigned to either Group N or Group NC according to the randomization scheme. Drugs were given orally to both groups by a nurse unaware of the study 60 min before surgery. Patients in Group N ($n = 30$) received naproxen sodium 550 mg (Apranax Fort®, Abdi Ibrahim Ilac, Istanbul/Turkey) and patients in

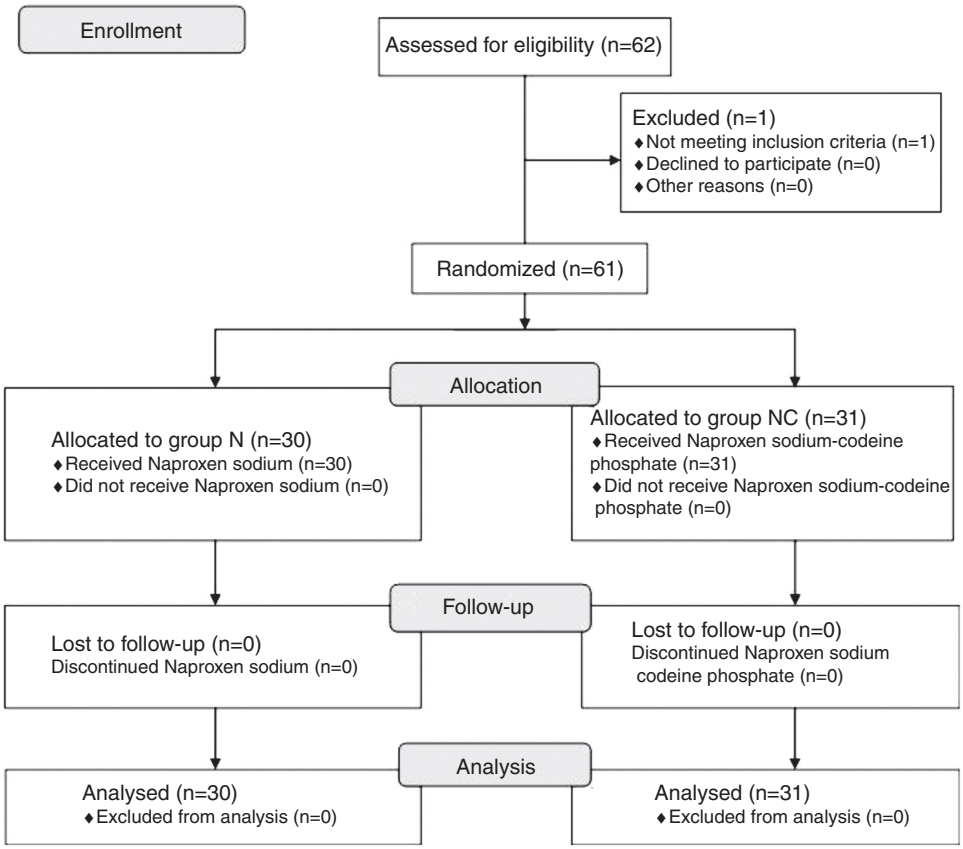

Figure 1 Study flow chart. Group N, naproxen sodium group; Group NC, naproxen sodium-codeine phosphate group.

Group NC ($n = 31$) received naproxen sodium-codeine phosphate 550 mg + 30 mg tablets (Apranax Plus®, Abdi Ibrahim Ilac, Istanbul/Turkey) (Fig. 1).

Following transfer to the operating room, patients were monitored by pulse-oximetry, electrocardiography and non-invasive blood pressure. Induction and maintenance of anesthesia were performed by an anesthesiologist blinded to the study. Intravenous propofol (2 mg/kg) and fentanyl (0.5 μg/kg) were used for induction and intravenous rocuronium was used as a muscle relaxant (0.6 mg/kg). Following endotracheal intubation, anesthesia was maintained with isoflurane (1–1.5%) and a mixture of nitrous oxide and oxygen (50% + 50%). At the end of the operation, neuromuscular blockade was reversed with neostigmine (0.05 mg/kg) and atropine (0.015 mg/kg). Patients were then extubated and transferred to the recovery room.

In the recovery room, intravenous meperidine was initiated by patient-controlled analgesia (PCA; 10 mg bolus, 20 min lockout, no basal infusion and 4 h limit) for all patients.

Data were recorded by an anesthesia technician blinded to the study drugs. Postoperative pain levels at rest and on movement were evaluated using the Visual Analogue Scale (VAS; 0 = no pain and 10 = the worst pain possible) and recorded at 15 and 30 min and at 1, 2, 4, 6, 12 and 18 h postoperatively.

Sedation scores were assessed using the Ramsey Sedation Scale (1: anxious and agitated; 2: cooperative, oriented and calm; 3: drowsy, responsive to orders; 4: asleep, but responsive to a glabellar tap; 5: sleeping and slowly responsive to tactile stimuli; and 6: patient unresponsive to painful stimuli) and were recorded at the same time points.

Hemodynamic data (systolic, diastolic and mean blood pressure; heart rate) and peripheral oxygen saturation were recorded before anesthesia and at 5, 10, 15, 30, 45 and 60 min following anesthetic induction; before and after the surgical incision; and at 15 and 30 min and 1, 2, 4, 6, 12 and 18 h postoperatively.

Time to the first demand of PCA, total meperidine consumption, and postoperative side effects such as sedation, respiratory depression, constipation, urinary retention, nausea, vomiting, gastric complaints and bleeding in the surgical area were recorded.

Statistical analysis

The primary outcome parameter of this study was visual analog score for pain at the first postoperative hour. Power analysis of the study was based on a study by Code et al.[5] Win-Epi 2.0 was used for sample size calculation; a total of 60 patients with 30 patients in each group was considered to be an appropriate number following sample size calculation for a 95% confidence interval and power of 80%.

The compact program SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data. Categorical variables were expressed as numbers and percentages, whereas numerical variables were expressed as mean and

Table 1 Demographic characteristics.

	Group N Mean ± SD (n = 30)	Group NC Mean ± SD (n = 31)
Age (years)	39.70 ± 13.21	42.03 ± 13.66
Weight (kg)	77.26 ± 12.84	78.35 ± 12.95
Height (cm)	171.13 ± 10.77	169.41 ± 10.03
Sex (female/male)	15/15	16/15
ASA (I-II)	17/13	15/16
Duration of surgery (min)	33.43 ± 7.19	30.61 ± 6.08

Group N, naproxen sodium group; Group NC, naproxen sodium-codeine phosphate group; Data show the number of cases or mean ± SD, mean ± standard deviation; ASA, American Society of Anesthesiologists; min, minute.

standard deviation (and as median and minimum–maximum when necessary). The intergroup comparison of numerical variables was performed using Student's t-test when the assumptions were fulfilled and the Mann–Whitney U test when the assumptions were not fulfilled. For parameters with normal distribution, repeated measures analysis and the paired t-test were used to compare dependent variables whereas the Wilcoxon test or the Friedman tests were otherwise used. p-Values less than 0.05 were considered significant for all comparisons.

Results

Sixty-two patients were invited to participate. During screening, one patient was found to not meet the inclusion criteria, so sixty-one patients were enrolled in the study (Fig. 1). The groups had comparable demographics, including age, body weight, height, gender, ASA (American Society of Anesthesiologists) status and surgery time (Table 1).

There were no significant differences regarding systolic and diastolic blood pressure, heart rate and peripheral oxygen saturation values between groups. None of the patients exhibited hypotension, hypertension, bradycardia or tachycardia.

Median VAS scores at rest were significantly lower in Group NC compared with Group N at all measured postoperative time points (15 min through 18 h) (Table 2). Median VAS scores on movement were also significantly lower in Group NC compared with Group N except for the score at 18th h postoperatively (Table 3).

Table 2 Visual Analogue pain scores at rest.

Postoperative Times	Group N Median (min–max)	Group NC Median (min–max)	p
15 min	3 (0–4)	1 (0–3)	0.0001
30 min	3 (0–4)	1 (0–3)	0.0001
1 h	3 (0–4)	2 (1–3)	0.0001
2 h	3 (0–4)	2 (0–3)	0.001
4 h	2 (1–4)	2 (0–3)	0.0001
6 h	2 (0–4)	1 (0–6)	0.0001
12 h	2 (0–3)	1 (0–3)	0.0001
18 h	2 (0–3)	1 (0–2)	0.0001

Group N, naproxen sodium group; Group NC, naproxen sodium-codeine phosphate group; min–max, minimum–maximum.

Table 3 Visual Analogue pain scores on movement.

Postoperative Times	Group N Median (min–max)	Group NC Median (min–max)	p
15 min	3 (0–5)	1 (0–3)	0.0001
30 min	3 (0–5)	2 (0–4)	0.0001
1 h	3 (0–5)	2 (0–4)	0.001
2 h	3 (1–4)	2 (0–4)	0.001
4 h	2 (1–5)	2 (0–3)	0.0001
6 h	3 (0–6)	1 (0–6)	0.0001
12 h	2 (0–4)	1 (0–3)	0.0001
18 h	2 (0–3)	1 (0–3)	>0.05

Group N, naproxen sodium group; Group NC, naproxen sodium-codeine phosphate group; min–max; minimum–maximum.

The median time to patients' first demand of PCA was 29 min in Group N (10–240 min) versus 135 min (20–600 min) in Group NC; this time period was significantly shorter in Group N ($p < 0.001$). Consumption of intravenous meperidine during the 18 h postoperatively was 20 mg in Group NC (10–50 mg) versus 95 mg (10–160 mg) in Group N ($p < 0.001$).

Both groups had similar sedation scores; the incidence of nausea and vomiting did not significantly differ between groups ($p > 0.05$). Bleeding in the surgical area, gastric complaints, respiratory depression, constipation, and urinary retention were not observed in any patients in either group.

Discussion

In this study, we evaluated the efficacy of preemptive naproxen sodium and naproxen sodium-codeine phosphate in patients who underwent arthroscopic meniscectomy. We have demonstrated that preemptive administration of naproxen sodium-codeine phosphate significantly reduced postoperative opioid consumption and provided more effective analgesia compared with naproxen sodium alone.

NSAIDs are commonly administered for arthroscopic procedures. Faster recovery, more rapid return of movement and quadriceps function, and more quick return to work were reported when NSAIDs were administered for arthroscopic surgeries.[4,7] NSAIDs suppress the acute inflammatory response by blocking prostaglandin synthesis via inhibition of the enzyme cyclooxygenase.[8] NSAIDs may reduce peripheral nociception by reduction of the inflammatory response to surgical trauma,[8] and they may also modulate the central response to painful stimuli by inhibiting prostaglandin synthesis in the spinal cord.[9] 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.[10–13]

Preemptive analgesia is a technique that enables more effective postoperative pain control. It produces effective analgesia through a reduction in peripheral sensitization before the occurrence of the noxius stimuli and by interrupting the transmission of noxious peri-operative inputs to the spinal cord. Preventing central sensitization reduces

pain and analgesic requirements even after the analgesic effects of the preemptive agents have worn off.[14] Studies have shown that the preemptive administration of naproxen sodium provides improved postoperative pain control, a reduction in analgesic usage, or both.[5,15–17]

Although the preemptive administration of naproxen sodium has been studied, there are no other studies on the preemptive efficacy of the naproxen-codeine combination since this preparation is a new agent on the market. Codeine, a prodrug with well-known analgesic efficacy, is frequently used in pain management in combination with parasetamol.[18] For this reason, we compared naproxen sodium and naproxen sodium-codeine phosphate in patients undergoing arthroscopic meniscectomy. In our study, VAS scores were significantly lower in Group NC compared with Group N, and meperidine consumption was significantly higher in Group N.

The analgesic efficacy of naproxen-codeine may be due to the prevention of sensitization in peripheral and central pathways before tissue injury. The higher efficacy of naproxen-codeine relative to naproxen sodium may be due to the well-known analgesic efficacy of codeine. The effective dose of codeine phosphate is 30–60 mg, with higher doses opioid-related side effects become visible, constipation, nausea, and respiratory depression.[18] A previous review that includes data from 14 clinical trials showed that the combination of paracetamol (600–1000 mg) and codeine (30–60 mg) provided effective analgesia in approximately 50% of patients with moderate to severe postoperative pain and that this combination prolonged duration of analgesia compared with patients receiving paracetamol alone.[19] In another review, which included 35 clinical trials comparing codeine (60–90 mg) with placebo in postoperative pain management, single agent codeine at 60 mg provided better analgesia than placebo. However, this analgesia was not sufficient when a comparison was made between codeine alone and its use in combination with paracetamol and NSAIDs.[20] Similarly, our study showed more effective postoperative analgesia and lower meperidine consumption with the naproxen sodium-codeine phosphate combination. In previous studies, codeine and other drugs were administered as different pills to patients, whereas our study used single pills that included both naproxen sodium and codeine. This may be an advantage for patients, as it contributes to usage facility. In both meta-analyses, opioid-related side effects such as drowsiness and somnolence were more frequent in the groups receiving codeine, although this was not statistically significant.[19,20] Forbes et al. compared naproxen sodium, codeine sulfate, naproxen sodium and codeine sulfate for postoperative pain after oral surgery.[21] In this paper codeine dose was 60 mg in groups receiving codeine which was twice the dose of our study. Accordingly they reported more side effects with codeine. Although our study was not powered to show any difference between the groups regarding side effects, we may roughly state that side effects such as sedation, drowsiness, nausea and vomiting were similar between the groups. This may be interpreted that the dosing of codeine in this commercially available preparation was tolerable by the patients of this study.

Codeine is metabolized in the liver to its active form morphine by the cytochrome P-450 isoenzyme 2D6 (CYP2D6).[22,23] CYP2D6 is highly polymorphic. These polymorphisms create different phenotypes for codeine metabolism, from ultra-rapid metabolism to poor metabolism. Ultra-rapid metabolism may cause high levels of morphine and toxicity.[22] Serious adverse events and deaths were reported in children with obstructive sleep apnea (13 cases in an estimated >22 million pediatric tonsillectomies) who received codeine after a tonsillectomy and/or adenoidectomy. Since these children had already underlying breathing problems and also some of them were ultra-rapid metabolizer, the U.S Food and Drug Administration (FDA) warns about codein use in all children after tonsillectomy and/or adenoidectomy.[22,23] But there is no warning about codein use in adults.

Although the beneficial effects of NSAIDs have been demonstrated, there are some concerns about negative effects, such as gastrointestinal mucosal damage, renal tubular damage and platelet dysfunction.[24,25] In our study, no such problems occurred related to NSAID use.

Conclusions

Preemptive oral naproxen sodium-codeine phosphate is an effective analgesic option in patients undergoing arthroscopic meniscectomy when compared with oral naproxen sodium, and it carries the advantages of ease of administration and lack of serious side effects at this dose. We suggest that naproxen sodium-codeine phosphate may be a valuable option for clinical use for arthroscopic procedures.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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