

Comparison of efficacy of dexketoprofen versus paracetamol on postoperative pain and morphine consumption in laminectomy patients

Laminektomilerde preoperatif uygulanan deksketoprofenin postoperatif ağrı ve morfin tüketimi üzerine etkilerinin parasetamol ile karşılaştırılması

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Summary

Objectives: The aim of this prospective randomized, double-blind study was to evaluate the analgesic efficacy and opioid-sparing effects of preemptive single dose of dexketoprofen trometamol in comparison with that of paracetamol or placebo for elective lumbar disc surgery, over a 24-hour (h) investigation period.

Methods: After institutional approval and informed consent had been obtained, 75 patients scheduled for single level lumbar disc surgery were randomly allocated into three equal groups. Patients received oral dexketoprofen 25 mg (Group D), 500 mg paracetamol (Group P) or placebo tablets (Group C) 30 minutes (min) before induction of standard anesthesia. Patient-controlled analgesia was supplied postoperatively using morphine. Hemodynamics, visual analogue scale (VAS), sedation score, morphine consumption, and side effects were recorded every 15 min in the first hour and at 2, 6 and 24 h after surgery.

Results: The mean pain scores were similar among groups ($p>0.05$). The cumulative (SD) 24-h morphine consumption was 28.1 mg, 40.6 mg, and 43.6 mg for Groups D, P and C, respectively. The amount of morphine use at 2, 6 and 24 h was significantly lower in Group D ($p<0.006$). Hemodynamic parameters, sedation scores and side effects did not differ among the groups ($p>0.05$).

Conclusion: The study demonstrated that preemptive dexketoprofen trometamol 25 mg is associated with a decrease of up to 35% in morphine consumption compared with placebo over the first 24 h following lumbar disc surgery; however, paracetamol 500 mg did not show the expected opioid-sparing effect comparatively.

Key words: Dexketoprofen trometamol; lumbar disc surgery; morphine; paracetamol; preemptive; patient-controlled analgesia.

Özet

Amaç: Ameliyat öncesi uygulanan tek doz deksketoprofen trometamol ile parasetamolün laminektomi sonrası 24 saatlik dönemde postoperatif ağrı ve opioid tüketimi üzerine etkisinin randomize, çift kör, plasebo-kontrollü çalışma olarak araştırılması amaçlandı.

Gereç ve Yöntem: Elektif tek seviye lomber disk cerrahisi geçirecek ASA I-II grubundan 75 hasta çalışmaya dahil edildi. Hastalar rastgele 3 gruba ayrıldı. Grup D: Anestezi induksiyonundan 30 dk önce oral 25 mg deksketoprofen; Grup P: Anestezi induksiyonundan 30 dk önce oral 500 mg parasetamol ve Grup C: Anestezi induksiyonundan 30 dk önce oral plasebo tablet uygulaması sonrasında standard genel anestezi verilen tüm hastalara ameliyat sonrasında HKA ile iv morfin başlandı. Üç grubun hemodinamik verileri, postoperatif ağrı durumu (VAS), sedasyon düzeyi, morfin tüketimi ve yan etkileri ilk 1 saatte her 15 dakikada bir, sonrasında 2., 6. ve 24. saatlerde karşılaştırıldı.

Bulgular: Gruplar arasında ortalama VAS skorları arasında anlamlı fark gözlenmedi ($p>0.05$). 24 saatlik toplam morfin tüketimi Grup D, P ve C'de sırasıyla 28.1 mg, 40.6 mg ve 43.6 mg idi. Grup D'de tüketilen morfin miktarı 2., 6. ve 24. saatlerde anlamlı olarak düşük bulundu ($p<0.006$). Hemodinamik bulgular, sedasyon skorları ve yan etkiler gruplar arasında benzer bulundu ($p>0.05$).

Sonuç: Çalışmamızın sonucunda, elektif lomber disk ameliyatlarında preemptif 25 mg deksketoprofen trometamol uygulamasının plaseboya kıyasla postoperatif morfin tüketiminde %35'lere varan azalma sağladığı, ancak parasetamolün bu açıdan beklenen etkinliği göstermediği kanaatine varıldı.

Anahtar sözcükler: Dexketoprofen trometamol; lomber disk cerrahisi; morfin; parasetamol; preemptif; hasta kontrollü analjezi.

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Introduction

Lumbar disc surgery is associated with moderate to severe back and radicular pain postoperatively, which has unfavorable effects on patient's recovery and procedure's outcome. Administration of opioid analgesics is routinely practiced but is limited with dose-related adverse effects.^[1] Within this concept, combining an opioid with different analgesics acting by different mechanisms as multimodal analgesia is recommended for effective post-operative pain control. The adjunctive administration of non-steroidal anti-inflammatory drugs (NSAIDs) during the preoperative period reduces the need for opioid analgesics and improves the control of postoperative pain.

Paracetamol is one of the most widely used analgesics and is generally recognized as a safe and effective drug in treating postoperative pain with a favorable adverse effect profile. In several studies, it has been widely demonstrated to reduce morphine consumption significantly after different types of surgeries.^[2,3]

Dexketoprofen trometamol is a newly developed, centrally acting NSAID with potency similar to that of μ -opioid agonists.^[4] In a number of studies in different pain models, it has been proven to have a good analgesic efficacy and tolerability profile after oral administration.^[5,6] Preclinical studies have found that dexketoprofen trometamol was effective even at very low doses however; most of the clinical investigations showing a benefit have demonstrated that 25 mg dexketoprofen was advocated to improve analgesia.^[7]

To our knowledge, no previous controlled study has assessed the effects of orally administered dexketoprofen trometamol or paracetamol in patients after lumbar disc surgery. Thus, this controlled clinical trial was designed to investigate the analgesic efficacy and opioid-sparing activity of a single dose of oral dexketoprofen trometamol 25 mg in comparison to that of oral paracetamol 500 mg administered preoperatively.

Materials and Methods

Following local hospital ethics committee approval, and informed consent, 75 patients (ASA physical

status I or II; age, 18-65 years), scheduled for elective lumbar disc hernia operation were enrolled in this prospective, randomized, double-blind, placebo-controlled clinical trial. Exclusion criteria were as follows: pregnancy; drug or alcohol abuse, history of allergic reaction to any of the study drugs; ongoing opioid, and non-steroidal anti-inflammatory analgesic therapy; cardiac, respiratory, hepatic and/or renal failure; history of peptic ulcer disease and coagulopathy, use of corticosteroids within the last 7 days; and use of anticoagulants within the last month, patients who are unable to use the patient-controlled analgesia (PCA) device (APM®, Abbott Laboratories, North Chicago, IL, USA) because of mental or cultural condition. At the preoperative visit instructions about the use of the PCA device and a visual analogue scale (VAS) for pain were fully explained. This scale consisted of an unmarked 10 cm line on which 0 cm representing no pain and 10 cm representing the worst pain imaginable. The double-blind design was achieved using a sealed envelope for each patient from a list of random numbers, so that the 75 patients matching the working criteria were assigned to one of three treatment groups before surgery: dexketoprofen 25 mg (tablet) orally (group D); paracetamol 500 mg (tablet) orally (group P) and placebo (lactose) tablet orally (group C).

A single dose of appropriate study medication was administered orally (po) 30 min before induction of standard general anesthesia. All medicines were administered by an anesthetist who had no other involvement in the study. The anesthetist who managed anesthesia was blind to the treatment group. All observations and data collection were carried out by a single investigator who was also blind to the treatment group. On admission to the operating room, a 20 G intravenous cannula was inserted on the dorsum of the hand and a 5 ml.kg⁻¹.h⁻¹ infusion of lactated Ringer's solution was started. After standard anesthesia monitorization, baseline measurements of heart rate (HR), non-invasive blood pressure, peripheral oxygen saturation (SpO₂) and respiratory rate (RR) were recorded. Subsequently anesthesia was induced with 1-2 μ g.kg⁻¹ fentanyl and 2-2.5 mg.kg⁻¹ propofol intravenous (IV). Endotracheal intubation was facilitated with 0.15 mg.kg⁻¹ cisatracurim. Mechanical ventilation with

an equal mixture of oxygen and nitrous oxide was used in all patients to maintain an end-tidal carbon dioxide concentration of 32-36 mmHg. Anesthesia was maintained with 1-2% sevoflurane. Additional muscle relaxant and fentanyl were administered throughout the operation according to clinical need and the anesthesiologist's discretion; however, in the last 30 min of the operation, fentanyl was not administered. At the end of the operation, residual neuromuscular blockade was reversed with neostigmine 0.04 mg.kg⁻¹ combined with atropine 0.02 mg.kg⁻¹ and tracheal extubation was carried out.

In the postanesthesia care unit, all patients were connected to a PCA device containing morphine 1 mg.ml⁻¹ and received IV analgesia. PCA device was set as demand dose of 1 mg; with a lock-out time of 15 min; and 0.3 mg.h⁻¹ continuous background infusion without a 4-hour limitation. All patients were kept in the recovery room for 60 minutes before being discharged to the ward. Pain was assessed with VAS at every 15 min in the first hour and 2, 6 and 24 h after surgery and total morphine consumption and side effects were also recorded at the same time points. Side effects were treated as necessary.

The morphine consumption by PCA at the end of 24 hours was the primary outcome variable on which sample size estimation was based at the beginning of the study. A sample size of 25 per group was required to detect at least 5 mg difference between Group D and any of the other two groups with a power of 90% at the 5% significance level. The difference of 5 mg was taken from both pilot study and clinical experience. Sample size estimation was performed by using NCSS and PASS 2000 software. Data analysis

was performed by using SPSS 11.5 software (SPSS Inc., Chicago, IL, United States). Shapiro-Wilk test was used to test the normality of distribution for continuous variables. Data were expressed as mean ± standard deviation or median (minimum-maximum), where applicable. While the mean differences among groups were compared by One-Way ANOVA, otherwise, Kruskal Wallis test was applied for the comparisons of the median values. When the p-value from the variance analyses were statistically significant to know which group differs from which others, post hoc Tukey for One-Way ANOVA and multiple comparison test for Kruskal Wallis were used. Nominal data were analyzed by Pearson Chi-square test. The repeated hemodynamic parameters were analyzed by Repeated Measures of Variance Analysis with Bonferroni Adjustment for multiple comparisons; otherwise, Friedman test with Bonferroni Adjusted Wilcoxon Sign Rank test was applied for the evaluation of VAS and Ramsey scales. A p value less than 0.05 was considered statistically significant. The Bonferroni Correction was applied for all possible multiple comparisons controlling Type I error.

Results

Thirty three women and forty two men aged between 18 to 65 yr with a mean of 42.9 yr were enrolled into the study. The demographic data of the patients and surgical characteristics were similar in each group (Table 1). The baseline pain intensity as determined according to the VAS score, preoperative analgesics administered and intraoperative use of fentanyl, mean arterial pressure, heart rate, SpO₂ and ETCO₂ changes were not statistically signifi-

Table 1. Demographic data and surgical characteristics

	Group D (n = 25)	Group P (n = 25)	Group C (n = 25)	p
Sex (F/M)	10/15	11/14	12/13	NS
Age (Yr)	45.2±8.7	42.7±12.1	40.9±13.4	NS
Height (cm)	167.6±6.4	169±7.8	169.9± 8.1	NS
Weight (kg)	74.9± 12.9	76±11.5	79.8±15.6	NS
Duration of surgery (min)	84.2±30.3	83.4±25.8	85.4±28.7	NS
Duration of anaesthesia (min)	106.8±30.7	110.2±23.1	111.8±27.6	NS

NS: Not significant, values are mean ± SD or n.

cant when compared among groups ($p > 0.05$). The mean VAS at PACU was 6.2 ± 2.4 and 7.1 ± 1.8 in the dexketoprofen and paracetamol groups, respectively, compared with 7.1 ± 1.4 in the placebo group ($p > 0.05$). The pain scores in Group D were significantly lower at 45 min postoperatively compared to the scores at PACU. In both Group P and Group C, VAS scores decreased significantly at 1 hr after surgery ($p < 0.0005$) (Figure 1). The PCA demand frequencies were lower in Group D, particularly at 30, 45 min and 1, 2 and 24 h ($p < 0.001$). Additionally, the cumulative (SD) 24-hour morphine consumption was 28.1 (15.6) mg, 40.6 (10.9) mg, and 43.6 (12.9) mg for groups D, P and C, respectively and so that it was significantly lower in patients treated with dexketoprofen at 2, 6 and 24 hr compared to those treated with paracetamol or placebo ($p < 0.006$) (Figure 2). However, there was no statistically significant difference between Group P and Group C ($p > 0.05$). During the first 24 hours, the three groups exhibited a similar sedation score and the degree of sedation of all patients was generally mild. Side-effects, such as hypotension and bradycardia, were not observed in either group throughout the study period. The incidences of nausea or vomiting, pruritis, and urinary retention were similar in the three groups ($p > 0.05$). No patient complained of respiratory depression or postoperative bleeding during the study period.

Discussion

The results of this study showed that a single dose of dexketoprofen trometamol 25 mg administered 30 min before surgery improved analgesia relative to placebo and that dexketoprofen more effectively reduced morphine consumption. However, a similar

benefit could not be demonstrated by preemptively administered paracetamol 500 mg.

NSAIDs have long been used for their analgesic properties and several studies have shown a pain relief equal to or better than opioids.^[8] In this study, we did not use NSAID in combination with morphine as part of a multimodal approach to postoperative analgesia, but tried to assess the analgesic efficacy of dexketoprofen using morphine as a rescue medication.

In the previous studies, 30-50% reduced morphine consumption with NSAIDs after major surgery was reported.^[9] Although in preclinical studies, dexketoprofen has been shown to be a more potent analgesic than ketoprofen, recent evidence has proposed little information on the comparative efficacy of the drug because clinical investigations comparing dexketoprofen 10 to 25 mg with placebo in a postoperative setting are few.^[10] In a study by Hanna et al.,^[10] dexketoprofen 50 mg administered as two intramuscular doses 12 h apart provided one third reduction in mean cumulative amount of morphine compared to placebo. In another study, Iohom et al.^[11] demonstrated a significant reduction in opioid consumption in dexketoprofen given patients in comparison to placebo, at 6 and 48 h postoperatively. Moreover, it was reported that, a single dose of dexketoprofen trometamol provided sufficient analgesia over a 24 h study period in surgical dentistry although the need for rescue medication was significantly more than the other active drug.^[12] Recently, Zippel et al.^[13] evaluated the analgesic efficacy and tolerability of dexketoprofen in comparison to ketoprofen administered by iv route after orthopedic surgery and re-

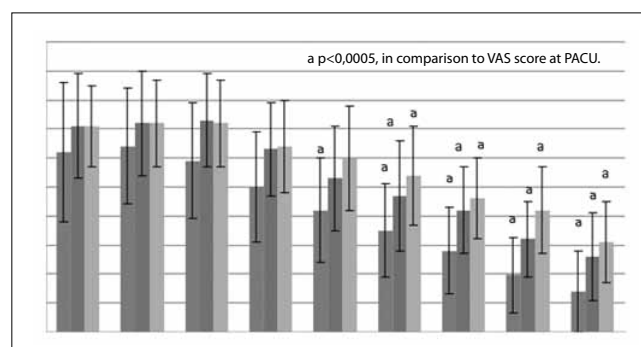


Figure 1. The visual analog scale scores in three groups during postoperative 24 hours. Values are mean \pm SD.

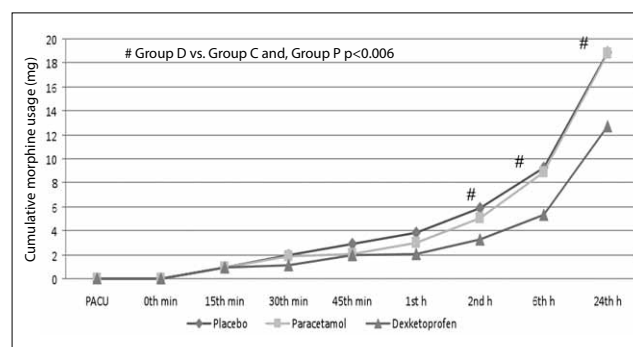


Figure 2. The cumulative (SD) 24-hour morphine consumptions (mg) in three groups. Values are mean \pm SD.

ported equivalent activity between the two drugs. In another study, Tuncer et al.,^[14] demonstrated a significant analgesic benefit and decreased morphine requirement with iv 50 mg dexketoprofen, at time points as 1 h before surgery and 2 h after surgery in abdominal hysterectomy patients. Because there are no data regarding the effect of preemptive dexketoprofen on opioid consumption during the postoperative first 24 hours after lumbar spine surgery, we considered the results of trials in other major surgical procedures. In our study, clinically relevant in previous publications, dexketoprofen clearly demonstrated a morphine-sparing effect up to 35%. However, there is no clear explanation of the analgesic efficacy obtained in our study by 25 mg oral dexketoprofen that is almost equivalent to the one obtained at higher doses of dexketoprofen applied in other trials. In this study, the dose of dexketoprofen trometamol was selected according to data from clinical trials.^[7,15,16] In the literature, we noticed that 25 mg dexketoprofen was almost equal to 50 mg ketoprofen in analgesic efficiency, and although 12,5 mg dexketoprofen was proven to be less effective, 50 mg dexketoprofen provided no superiority to 25 mg. Additionally, pharmacokinetic studies have indicated that the onset of effect of this drug is 0.25 to 0.75 h following oral administration,^[17] thus all of our patients received dexketoprofen exactly 30 min before anesthesia induction.

Paracetamol has both central inhibitor action on cyclooxygenases and interaction with the serotonergic system.^[18] In addition, it does not have the adverse effects of NSAIDs or opioids.^[19] However, the efficacy of paracetamol in postoperative opioid reduction after major surgery remains speculative. In some of the studies, it was demonstrated to exert a beneficial effect.^[8,20] While in other studies, paracetamol did not show any opioid-sparing effect.^[21,22] In two of these studies, IV paracetamol was demonstrated to exert a significant opioid-sparing effect.^[23,24] Also, Seymour et al.^[25] concluded that paracetamol 1000 mg was effective and safe in providing significant pain relief after third molar surgery. Pettersson et al.^[26] showed a limited opioid-sparing effect after coronary artery bypass graft surgery. Similarly, in another study, Remy et al.^[20] reported that paracetamol administered 1 g every 6 h had an opioid-sparing effect of less than 10% in 24 h.

In the current literature, we found that 1 g paracetamol has been administered preemptively in lumbar disc surgery in four recent publications.^[27,28] In one of these studies, paracetamol 1 g IV was administered as additional analgesic to PCA morphine in the postoperative period and provided effective analgesia equivalent to metamizol 1g.^[29] Recently, both Toygar et al.^[27] and Grundman et al.^[30] failed to demonstrate a beneficial preemptive analgesic effect of 1 g IV paracetamol. In the other study in which the analgesic efficacy and opioid-sparing effect of paracetamol were evaluated by Cakan et al.,^[28] it was reported that paracetamol 1 gr IV administered at the end of the operation and at 6 hr intervals over 24 hours, did not decrease narcotic requirements but improved the quality of pain relief in the early postoperative period. From an evaluation of the overall results obtained in our study, we could not find any beneficial effect of administering paracetamol prior to surgery. By contrast with other authors, we administered oral form of paracetamol at a dose of 500 mg at once 30 min before operation. The cause of the discrepancy between our findings and those of other investigators may be the different form and insufficiency of the dose we used. Indeed, there exists a controversy about the optimal dose of paracetamol. In a study by Karvonen et al.,^[31] fentanyl consumption was not affected by paracetamol 1.33 g administered 1 h prior to surgery and at 8 and 16 h after the initial dose following major orthopedic surgery. Moreover, Issioui et al.,^[32] failed to show a statistically significant analgesic effect with oral premedication of a larger dose of paracetamol (2000 mg) after ambulatory ENT surgery. It is difficult to compare these contradictory results because of differences in the localization of the pain, type of surgery and mode of administration of the active drug.

In our study, no significant difference was found in the pain relief scores among groups during the first 24 hours. This could be related to titration of more morphine by paracetamol and placebo groups to reach the same analgesic level. Thus, increased morphine usage by the PCA system due to lack of dexketoprofen's analgesic effect could have masked any potential increases in VAS in the other two groups. Besides, we detected a shorter time interval in dexketoprofen group until statistically significant

lower pain scores were observed comparatively with the scores at arrival to PACU.

In our study, the hemodynamics remained unchanged in all patients throughout the study period. We found no statistically significant differences with regard to the respiratory parameters, sedation score or side-effects among the groups, but side-effects were more frequently recorded in group P and C than in group D.

In conclusion, preemptive administration of dexketoprofen trometamol 25 mg provided sufficient analgesia with a significant decrease in morphine requirements following lumbar disc surgery. Nevertheless, we acknowledge that; before suggesting a final result as dexketoprofen 25 mg is effective in lumbar disc surgery, whether the optimal dose of this NSAID is selected or not should be taken into consideration. On the other hand, our findings do not encourage the opioid-sparing effect of paracetamol 500 mg. Thus, further comparative and controlled studies of the effects of higher doses of both drugs in larger study sizes are needed before final recommendations can be made.

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