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Original Article

The effect of preoperative intravenous dexketoprofen trometamol on postoperative pain in minor outpatient urologic surgery

Günübirlik küçük ürolojik cerrahide postoperatif ağrıya preoperatif intravenöz deksketoprofen trometamol'ün etkisi

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ABSTRACT

Objective: The aim of this prospective double-blind randomized study was to compare the effectiveness of preoperative dexketoprofen trometamol for acute postoperative pain in patients undergoing minor outpatient urologic surgery.

Material and methods: Sixty male patients (ASA I and II) undergoing varicocelectomy and testicular sperm extraction (TESE) with standard laryngeal mask airway (LMA) anesthesia were randomly divided into two groups. Patients in Group I (n=30) received 50 mg of dexketoprofen trometamol iv before induction, whereas patients in Group II (n=30) received saline. All patients received standard LMA anesthesia (propofol, sevoflurane and N_2O/O_2). Analgesic efficacy was evaluated by self-assessment of pain intensity (VAS) at regular intervals. Vital signs, side effects and time to reach a postanesthesia discharge score (PADS) ≥9 were also recorded. Paracetamol 1 gr iv and tramadol 100 mg iv were used for rescue analgesia.

Results: Demographic data and duration of surgery were similar in both groups. There was no significant difference between groups with respect to postoperative pain scores and side effects. Although more patients in Group II (60%) required rescue analgesia compared to Group I (33.3%), the difference did not reach statistical significance.

Conclusion: Preoperative IV use of dexketoprofen trometamol iv did not decrease the need for rescue analgesia in patients undergoing minor outpatient urological surgery.

Key words: Dexketoprofen trometamol; outpatient; postoperative pain; urologic surgery.

ÖZET

Amaç: Bu prospektif randomize çift kör çalışmada günübirlik minör ürolojik cerrahi geçiren hastalarda akut postoperatif ağrı kontrolü için preoperatif dexketoprofen trometamol uygulamasının etkinliği araştırıldı.

Gereç ve yöntemler: Standart LMA anestezisi ile testiküler sperm ekstraksiyonu (TESE) ve varikoselektomi olacak 60 erkek hasta (ASA I ve II) randomize olarak iki gruba ayrıldı. İndüksiyondan önce Grup I'deki (n=30) hastalara iv 50 mg dexketoprofen trometamol, Grup II'deki (n=30) hastalara iv serum fizyolojik yapıldı. Tüm hastalara standart LMA anestezisi (propofol, sevoflurane ve N_2O/O_2) uygulandı. Analjezi etkinliği düzenli aralıklarla hasta tarafından ağrı şiddeti skalası (VAS) ile değerlendirildi. Aynı zamanda vital bulgular, yan etkiler ve eve gönderilme anestezi sonrası taburcu etme skoru (PADS)'ın ≥9'a ulaşma süresi kayıt edildi. Ek analjezik olarak parasetamol 1 gr iv ve tramadol 100 mg iv kullanıldı.

Bulgular: Demografik veriler ve operasyon süreleri her iki grupta benzerdi. Gruplar arasında postoperatif ağrı skorları ve yan etkiler açısından anlamlı fark yoktu. Grup II'deki hastalarda (%60) Grup I'deki hastalara (%33,3) göre daha fazla ek analjezik gereksinimi olmakla birlikta fark istatistiksel olarak anlamlı düzeyde değildi.

Sonuç: Preoperative iv dexketoprofen trometamol'ün günübirlik minor ürolojik cerrahi geçiren hastalarda postoperatif ağrı kontrolünde ek analjezik gereksinimini azaltmadığı kanısına varıldı.

Anahtar sözcükler: Deksketoprofen trometamol; günübirlik; postoperatif ağrı; ürolojik cerrahi.

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Introduction

When administered properly and adequately, postoperative pain treatment plays an important role in accelerating postoperative recovery, reducing hospitalization time and decreasing treatment expenses in day surgery.[1] However, postoperative pain is still the most frequently observed problem in day surgery. Recent studies have shown that large numbers of patients suffer from moderate to severe pain during the first 24-48 hours depending on the intensity of postoperative pain. Current management includes the use of analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) and tramadol as single drugs or in combination as a part of balanced analgesia regimens.[1]

Dexketoprofen trometamol, the active enantiomer of racemic ketoprofen, is a nonselective NSAID and is a member of the arylpropionic acid group. It is available in Turkey. Dexketoprofen is a more lipophilic agent than ketoprofen, and its maximum plasma concentration (t_{max}) is reached between 0.25 and 0.75 hours. Addition of trometamol (36.9 mg) to dexketoprofen increases its solubility compared to its free acid form, enabling faster absorption. As its elimination is quite fast, dexketoprofen does not accumulate when administered repeatedly.[2] In postoperative analgesia, NSAIDs can be used in different ways. Dexketoprofen trometamol has been used in oral and parenteral forms for postoperative analgesia after different types of surgical operations (dental, abdominal hysterectomy, orthopedic surgery). However, dexketoprofen trometamol administered intravenously has not been evaluated for postoperative pain relief after outpatient surgery.

This prospective, randomized, double-blind study aimed to investigate the effect of the intravenous (iv) administration of dexketoprofen trometamol 50 mg before incision in minor outpatient urological surgery (varicocele, testicular sperm extraction) on early and late postoperative pain control.

Material and methods

The approval of the Ethics Committee of the University Faculty of Medicine (No: 09-7/2, date: 15.10.2009) and the informed consent of each patient were obtained. A total of 60 volunteer, male patients of ASA group I-II between 18 and 65 years of age undergoing minor outpatient urological surgery in the Urology Department were included in this prospective, randomized study. Patients who had heart, kidney or liver failure, a history of allergy to NSAIDs, gastrointestinal bleeding or other active bleeding, hemorrhagic diathesis, clotting disorder or those receiving anticoagulant therapy, those with Crohn's disease or ulcerative colitis, and those using analgesics routinely or who had used them in the last 24 hours were excluded from the study. The patients were informed about the details of the study during the pre-anesthetic evaluation, and each patient was asked to read the informed consent form. They were informed about the VAS (Visual Analogue Scale; 0=no pain and 10=worst pain possible) for postoperative pain management.

Vascular access was established for all subjects, and they were taken to the operating room; standard monitoring (noninvasive arterial pressure, electrocardiography, end-tidal carbon dioxide, pulse oximetry) was then applied. The patients were divided into two groups according to a randomization chart that was prepared on a computer. A nurse who was not included in the study filled a 2 mL injector with the medication or normal saline. Neither the investigator nor the patients knew the contents of the agent in the injector. Before anesthesia induction, Group I patients were administered 50 mg (2 mL) of dexketoprofen trometamol in an iv bolus, and Group II patients received 2 mL of normal saline as placebo in not less than 15 seconds.

Atropine 0.5 mg, propofol 2-2.5 mg/kg and remifentanil 1 µg/kg were used for anesthesia induction. After a laryngeal mask airway (LMA) was placed, anesthesia was maintained using a remifentanil 0.05-1 µg/kg/min. infusion, 50% oxygen-50% air and sevoflurane 1-2%. Hemodynamic changes were recorded in 5-minute intervals during the operation. The remifentanil infusion dose was adjusted so that systolic arterial pressure (SAP) would not drop 30% or more and the mean arterial pressure (MAP) would not drop below 60 mmHg; intervention was performed using ephedrine when necessary. When the HR reached <50/min., atropine 0.5 mg was administered in an iv bolus. Five minutes before the end of the operation, remifentanil infusions were stopped, and the subjects' LMAs were removed before their laryngeal reflexes became active. The subjects were ventilated with a mask under fresh gas flow, and when their spontaneous breathing and reflexes were sufficient, they were taken to the postoperative recovery room. The total amount of remifentanil used was recorded at the end of the operation.

In the postoperative recovery room, the subjects' VAS scores, vital signs and side effects (nausea, vomiting, etc.) were recorded every 5 minutes in the first 15 minutes and every 15 minutes thereafter (i.e., 0, 5', 10', 15', 30', 45', 60', 75', 90', 105', 120'). If a patient in either group had a postoperative VAS value of 4 and over when their pain was questioned, they were administered a 1 gr/100 mL paracetamol iv infusion to control their pain, and the time of first analgesic requirement was recorded. In patients whose pain could not be controlled despite this treatment, a slow iv infusion of tramadol 100 mg was administered. Home readiness after surgery was evaluated with the PADS (postanesthesia discharge score). The time to reach a PADS ≥9 was recorded. The subjects were informed verbally and in writing about their pain diary and the analgesic treatment they would use in the first two postoperative days. They were given a follow-up form for

pain assessment and side effects at six different times within two days.

The assessment times for postoperative pain were planned as follows:

Day 1:
1. When leaving the hospital
2. 3 hours after leaving the hospital
3. When going to bed at night

Day 2:
4. Upon waking up in the morning
5. At 16:00 hours
6. When going to bed at night

The subjects were instructed to take a 500 mg paracetamol tablet every 6 hours at home. If the pain could not be controlled with this treatment [Visual Analogue Scale (VAS)≥4], they were allowed to orally take 25 mg of dexketoprofen trometamol at 8-hour intervals (3x1). All the patients completed the postoperative follow-up form, which was explained to them previously. At the end of the study, the overall analgesia quality of the subjects during the first two postoperative days, the amount of analgesic medicine they used daily, all side effects and patient satisfaction were determined through phone interviews and were recorded.

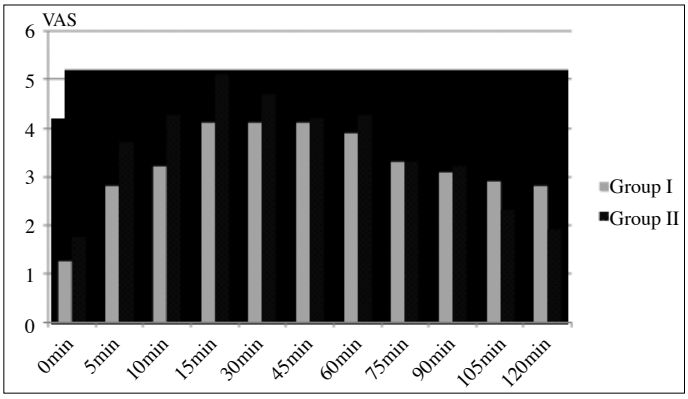

Figure 1. Postoperative pain scores

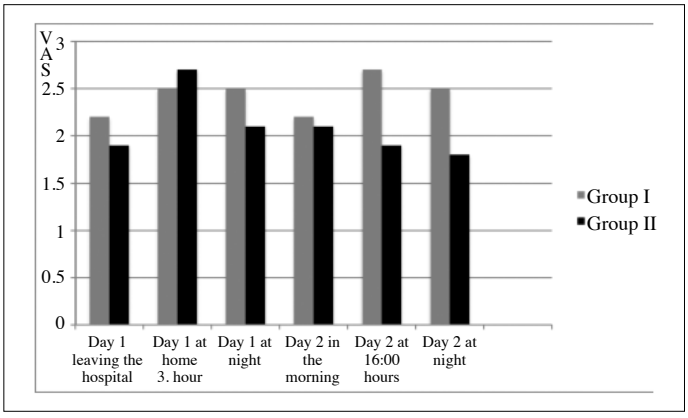

Figure 2. Postoperative pain scores at home

Statistical analysis

For statistical evaluations, the t-test was used for demographic data, durations of anesthesia and surgery, intraoperative remifentanil requirement, postoperative and home pain scores, times at which paracetamol and tramadol were required, time to reach a PADS ≥9 and the amount of analgesics planned to be used at home for pain. The chi-square test was used for side effects occurring in the postoperative period and home follow-up and type of surgical intervention. The Mann-Whitney U test was used for patient satisfaction.

Results

No statistically significant differences were found between the groups in terms of demographic data (age, weight), durations of anesthesia and surgery or type of surgical intervention (Table 1).

The total intraoperative remifentanil infusion dose was found to be 0.134±0.045 μg/kg/min. in Group I and 0.144±0.086 μ/kg/min. in Group II; no statistically significant difference was found between the groups. No statistically significant difference was found between the two groups in terms of postoperative pain scores (Figure 1).

The 22 patients in Group I (73.3%) and 28 patients in Group II (93.3%) were administered an iv paracetamol infusion for postoperative pain control. Because sufficient postoperative pain control could not be achieved in 10 patients in Group I (33.3%) despite the intravenous paracetamol administration, they were administered an iv tramadol infusion; 18 patients in Group II (60%) were administered an iv tramadol infusion. Although Group I required less analgesic medication, during immediate postoperative period, and less time for the PADS to become ≥9 compared to Group II, the differences were not statistically significant (Table 2).

No significant difference was found between the groups in terms of home pain scores (Figure 2). When the amounts of analgesic

Table 1. Demographic data, type of surgical intervention and durations of anesthesia and surgery (mean±SD)

	Group I (n=30)	Group II (n=30)
Age (yr)	30.5±7	29.5±6
Weight (kg)	75±10	77±14
Duration of anesthesia (min)	44±13	43±15
Duration of surgery (min)	33±12	30±14
TESE (n)	18	18
Unilateral varicocelectomy (n)	6	8
Bilateral varicocelectomy (n)	6	4

TESE: Testicular sperm extraction

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Table 2. Data on early postoperative pain treatment in both groups

	Group I (n=30)	Group II (n=30)
i.v. paracetamol requirement (n)	22	28
i.v. tramadol requirement (n)	10	18
Time of paracetamol requirement (min)	11±8	9±9
Time of tramadol requirement (min)	51±8	49±19
Time to a PADS ≥9	58±32	68±32

Table 3. Data on postoperative pain treatment at home

	Group I (n=30)	Group II (n=30)
Paracetamol tablets used on Day 1 (n)	1.3±0.9	1.3±0.6
Paracetamol tablets used on Day 2 (n)	2.3±1.2	2.2±1.12
Dexketoprofen tablets used on Day 1 (n)	0.3±0.5	0.4±0.5
Dexketoprofen tablets used on Day 2 (n)	0.7±0.9	0.3±0.7
Total paracetamol tablets used (n)	3.7±1.9	3.5±1.6
Total dexketoprofen tablets used (n)	1.0±1.4	0.7±1.0

medication the patients used for postoperative pain control at home were compared, no statistically significant difference was found between the two groups (Table 3).

There was no statistically significant difference between the two groups during the study in terms of the side effects (nausea, vomiting, dizziness, headache, constipation, diarrhea, stomach bloating, abdominal pain, dryness of the mouth, fatigue) that emerged in the postoperative period and at home (Table 4).

No significant difference was found between the two groups in terms of general analgesic quality.

Discussion

Adequate postoperative pain control is a prerequisite for day surgery. Effective pain control shortens the discharge time, increases patient satisfaction and reduces the cost.[3] However, the most recent studies have shown that the incidence of pain is still high in day surgery. This situation may be explained by the fact that although important scientific developments have been realized in the field of multimodal analgesia, these concepts have not been adapted to routine clinical practice.[4]

Extensive use of opioids in postoperative pain control for outpatient surgery causes complications. Opioids have side effects such as nausea and vomiting and negatively affect discharge

Table 4. Side effects emerging in the early and late postoperative periods

	Group I (n=30)		Group II (n=30)	
	Postoperative	at home	Postoperative	at home
Nausea	0	3	1	5
Vomiting	0	3	0	3
Dizziness	0	1	0	1
Constipation	0	0	0	0
Diarrhea	0	1	0	5
Stomach Bloating	0	2	0	1
Abdominal Pain	1	2	1	1
Dry Mouth	1	0	1	1
Fatigue	1	2	2	1

time and the re-hospitalization rate. It has been reported that the second most frequent reason for re-hospitalization after inadequate pain treatment in outpatient surgery is the side effects associated with opioids.[5]

Nonopioid analgesics are the most frequently used medication group in the world. They are used alone for mild and moderate pain and are an important component of multimodal analgesia; using them in multimodal analgesia reduces the opioid dose required and the incidence of their side effects.[6] The use of nonopioids in day surgery is very common; a large-scale study reported that paracetamol was used at a rate of 95% and NSAIDs at a rate of 73% for postoperative analgesia in day surgery.[2]

Many trials have demonstrated that the oral form of dexketoprofen is effective for acute pain such as dental and postoperative pain.[2] Tuncer et al.[7] orally administered 25 mg of dexketoprofen to 50 patients (aged 47.6±6.6 years) who underwent elective abdominal hysterectomy one hour before the operation and at the 8th and 16th hours after the operation and found that both the postoperative pain scores and the amount of tramadol used in postoperative analgesia were lower compared to the placebo group. The researchers concluded that oral dexketoprofen administered pre- and postoperatively for abdominal hysterectomy reduced the need for opioids and produced an analgesic effect. Berti et al.[8] compared the administration of oral dexketoprofen (25 mg, 3 times per day), ketoprofen (50 mg, 3 times per day) and paracetamol (500 mg, 4 times per day) in postoperative pain treatment in 45 patients who underwent knee arthroscopy accompanied by a combined sciatic-femoral block in day surgery conditions. Pain was assessed during movement and rest in the groups administered oral analgesic agents before surgery. Although pain control was adequate in all the groups, the pain scores measured during movement in the paracetamol group

were observed to be higher compared to the other two groups. The researchers concluded that the analgesic effect of dexketoprofen administered at 75 mg/day was similar to ketoprofen administered at 150 mg/day and that both agents were more effective than paracetamol for pain control during movement.

Iohom et al.[9] administered oral dexketoprofen (25 mg, 3 times per day) to 30 patients (aged 45-70 years) undergoing hip arthroplasty 24 hours before the operation and continued the practice for 48 hours postoperatively. In the group taking dexketoprofen, the researchers reported more effective pain control, a lower need for opioids, fewer side effects associated with opioids and lower plasma interleukin-6 levels compared to the control group. Although this study demonstrated that dexketoprofen administration may suppress the postoperative pro-inflammatory response, these results require further study.

The parenteral form of dexketoprofen started to be used clinically in 2003.[2] In studies including patients who underwent orthopedic surgery, the ability of im or iv dexketoprofen administration to control postoperative pain was compared to those of ketoprofen and placebo.[10,11] In the studies performed with parenteral formulations, its analgesic efficacy was similar to those of other agents from the same group; it reduced the amount of opioids required for postoperative analgesia, decreased the incidence of nausea and vomiting, improved the quality of sleep and caused less sedation.[2,10,11] The parenteral form of dexketoprofen was reported to be a major alternative to other drugs more commonly administered parenterally due to its fast onset of action, effectiveness and safety.[2]

We have not encountered any studies related to the intravenous use of dexketoprofen in outpatient surgery. However, Inanoglu et al.[12] compared the preoperative and postoperative efficacies of iv lornoxicam in their study on 44 patients who underwent varicocele surgery under local anesthesia. The researchers reported that the pain scores were lower in the group administered 8 mg of iv lornoxicam preoperatively compared to the group administered lornoxicam after the completion of the operation, and they required fewer analgesics in the following 24 hours. In that study, the iv administration of lornoxicam before surgery was found to be more advantageous than the postoperative administration. That study differed from ours in that local anesthesia was chosen as the anesthetic technique. One of the most important advantages of regional techniques is that they enable more effective postoperative analgesia. The lower pain scores in that study compared to our study and the lack of need for opioids to control pain may be associated with the use of long-acting local anesthetics.

Side effect profiles are one of the most important points in the use of NSAIDs. A multicenter study evaluating the side effects associated with NSAIDs analyzed the incidence of bleeding in the upper gastrointestinal system associated with a gastric or duodenal ulcer in individuals over 18 years of age.[13] In that study, the risk of upper gastrointestinal bleeding associated with the administration of dexketoprofen was found to be lower compared to other similar NSAIDs. In other studies evaluating the risk of postoperative surgical bleeding, no difference was found between dexketoprofen and control groups in terms of the amount of bleeding and coagulation parameters.[10,14] Dexketoprofen was stated to have a fast onset of action, induce effective analgesia and have a safe profile with respect to side effects.[2] Despite the side effects that may develop due to dexketoprofen, we did not encounter any serious side effects in the group administered a single dose of dexketoprofen preoperatively in our study, and the groups were similar in terms of side effects.

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[15] It has biological, psychological and social components. Therefore, postoperative pain is influenced by several factors including education, anxiety, somatization, coping strategies and sleep disturbances.[16] One of the limitations of our study is that the effect of these factors was not evaluated. Kain et al.[17] showed that preoperative midazolam 5 mg administered intramuscularly decreases postoperative pain scores and the need for rescue analgesia in patients undergoing outpatient surgery. Therefore, future studies are needed to evaluate the effects of different psychosocial factors on postoperative pain in surgical patients.

In conclusion**,** dexketoprofen trometamol administration of intravenous dexketoprofen prior to the incision did not significantly differ from placebo in terms of early postoperative analgesia, discharge time or need for analgesics at home. However, because fewer subjects in the dexketoprofen group required additional tramadol and this can be important in the avoidance of tramadol-related side effects, particularly in outpatient surgery, further studies that include larger numbers of patients are needed to demonstrate the efficacy of the preoperative administration of iv dexketoprofen in outpatient surgery.

Conflict of Interest
No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University School of Medicine (15.10.2009, 09-7/2).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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