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Comparison of tramadol/acetaminophen fixed-dose combination, tramadol, and acetaminophen in patients undergoing ambulatory arthroscopic meniscectomy

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ABSTRACT

Objectives: Preemptive analgesia is a technique in which analgesics are administered before a surgery to provide better postoperative pain relief with fewer side effects. In this study, we aimed to compare the preemptive efficacy of tramadol/acetaminophen fixed-dose combination, tramadol, and acetaminophen in patients undergoing ambulatory arthroscopic partial meniscectomy.

Methods: We evaluated the patient records of 75 patients who underwent ambulatory arthroscopic partial meniscectomy. We divided the patients into three groups consisting of 20 patients each to equalize the groups. Group A comprised patients who were administered 37.5 mg tramadol/325 mg acetaminophen fixed-dose combination, Group B comprised patients who were administered 50 mg tramadol, and Group C comprised patients who were administered 500 mg acetaminophen. Premedication was not used in any group.

Results: There were no significant differences between the groups in terms of age, sex, BMI, and duration of surgery and anesthesia. All patients in Group B and Group C and 17 patients in Group A required rescue analgesics in the first 6 h. Visual analog scale (VAS) was 4.75 ± 3.05 in Group B at time 0 and was 6.10 ± 1.86 in Group C in the first hour and was higher than the other groups with a statistically significance ($p = 0.030$ and 0.020, respectively). VAS at 24 h postoperatively was ≤3 (1.60 ± 1.63, 1.55 ± 1.84 and 1.70 ± 0.65 respectively in each group), and none of the patients in any group required rescue analgesics. No major side effects, except for slight nausea in one patient requiring no medication, were noted in any group.

Conclusion: The fixed-dose combination of tramadol/acetaminophen or tramadol alone is better than acetaminophen alone as a preemptive analgesic in patients undergoing ambulatory arthroscopic meniscectomy.

Level of evidence: Level III, therapeutic study.

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Introduction

Knee is the most common joint subjected to arthroscopy. Arthroscopic meniscectomy is associated with moderate to severe postoperative pain due to insertion of arthroscopic instruments into the joint, soft tissue dissection, and distension caused by irrigation of the joint.[1–3] Inadequate management of postoperative pain results in increased morbidity, delayed discharge, and decreased patient satisfaction after surgery.[4,5] Preemptive analgesia is a new technique that has been applied over the last two decades. In this technique, analgesics are administered before the painful stimuli to prevent amplification of postoperative pain,

Abbreviations: PACU, post-anesthesia care unit; NNT, number needed to treat; BMI, body mass index.

This study was carried on Süleyman Demirel University School of Medicine Orthopedics and Traumatology and Anaesthesiology and Reanimation Departments after the approval of the ethical committee (2017/115).

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resulting in better postoperative pain relief with fewer side effects, shorter hospital stay, faster recovery, and lesser social burden.[6–10] Among the medications used are local anesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioid, gabapentinoids and magnesium sulfate alone or in combination with local anesthetics.[11–13] In preemptive analgesia, the agents can be used either alone or in combination to increase the analgesic effect via different mechanisms and to reduce the incidence of side effects.[8,14] This approach increases postoperative patient satisfaction, while minimizing systemic narcotic use and reducing the undesirable side effects of narcotics, such as nausea, vomiting, sedation, and respiratory depression.[5,15] Although NSAIDs are mostly used for preemptive analgesia, they are associated with major side effects such as irritation of the gastrointestinal mucosa and inhibition of platelet activation. In addition, they are not an ideal choice as preemptive analgesic in orthopedic surgery owing to perioperative bleeding via cyclooxygenase (COX)-1 isoenzyme.[5,12,16]

Considering the side effects of NSAIDs via COX-1 isoenzyme, selective COX-2 inhibition seems to be a good choice for postoperative pain management.[5] Acetaminophen is the most widely used non-opioid analgesic. It acts centrally, and its pharmacological profile is similar to that of selective COX-2 inhibitors in that it increases pain threshold through nitric oxide system and does not inhibit prostaglandin synthesis or irritate the gastrointestinal mucosa.[17,18]

Orthopedic postoperative patients who have a high incidence of severe pain are responsive to the combination of acetaminophen and opioids as an alternative to NSAIDs.[19] It was reported that almost all patients who underwent arthroscopic meniscectomy were required to be hospitalized for relieving unbearable pain with the help of high-dose opioids. However, many of these patients complained from side effects of opioids, such as sedation and respiratory depression[3,5,15] Considering the side effects and addiction of opioids, tramadol, an inhibitor of both mild μ-opioid receptor binding and norepinephrine and serotonin (5-HT) reuptake, seems to be a good alternative.[19] Furthermore, combining tramadol with acetaminophen provides a unique example of the potential benefits of combination therapy[16,20] The combination of tramadol and acetaminophen results in synergistic analgesia, faster onset, and longer duration of action than either component alone, particularly in orthopedic surgery.[16,19,21]

To the best of our knowledge, no study has so far compared the preemptive analgesic efficacy of tramadol, acetaminophen, and tramadol/acetaminophen fixed-dose combination in the management of postoperative pain within the first 24 h of ambulatory arthroscopic partial meniscectomy. Considering the side effects of opioids and NSAIDs used for pain management after arthroscopic meniscectomy we aimed to compare the preemptive efficacy of opioids and NSAIDs in patients who underwent ambulatory arthroscopic partial meniscectomy as they have fewer side effects in these patients.

Patients and methods

The medical records of 94 patients, who underwent ambulatory arthroscopic partial meniscectomy under general anesthesia and had preemptive analgesia in 2016, were retrospectively evaluated after obtaining the approval of the local ethics committee (year: 2017, no: 115). The inclusion criteria were as follows: age 18–50 years old; underwent ambulatory arthroscopic partial meniscectomy; operation time <1 h, chondral lesions ≤ grade 2, having an American Society of Anesthesiologists (ASA) score ≤ 3, and preoperative visual analog scale (VAS) score < 3 or no pain at rest. The patients with knee instability due to cruciate or collateral ligament injuries or both, cartilage damage requiring surgical interventions, lower extremity mal-alignment due to congenital, acquired, or traumatic lower extremity deformities, missing informed consent, lack of cooperation capability, cancer co-morbidity, osteoarthritis or rheumatoid arthritis, alcohol or drug abuse, previous major surgery on the affected joint, neurologic or psychiatric disease, allergy to any of the drugs, known heart, kidney, liver, or hematological diseases, history of gastrointestinal bleeding, chronic pain, routine use of analgesics, or those who had taken analgesic agents within the last 48 h were excluded from the study.

Seventy-five of the 94 patients who fulfilled the inclusion criteria were included in the study. The evaluation of patient records of these 75 patients showed that preemptive analgesia with 37.5 mg tramadol + 325 mg acetaminophen was administered in 26 patients, 50 mg tramadol in 29 patients, and 500 mg acetaminophen in 20 patients. Based on the results of a previous study[22] and the assumption that a difference of 20 units in postoperative pain scores in VAS is clinically relevant, the effect size was defined as 2, with an estimated standard deviation of ±2. By setting $\alpha = 0.05$ and power to 0.9, we calculated a minimum sample size of 18 patients/group, and the patients were divided into three groups of 20 patients each to equalize the groups.

Group A comprised patients who were administered 37.5 mg tramadol/325 mg acetaminophen fixed-dose combination (Zaldiar® 37.5 mg/325 mg film-coated tablet; Abdi İbrahim, İlaç San. ve Tic. A.Ş., İstanbul/Turkey), Group B comprised patients who were administered 50 mg tramadol (Contramal® 50 mg; Abdi İbrahim), and Group C comprised patients who were administered 500 mg acetaminophen (Parol® 500 mg tablet, Atabay Kimya San. ve Tic. A.Ş., Turkey). Premedication was not used in any group. Preemptive agents were orally administered 1 h before surgery owing to onset of analgesic efficacy.[23]

Anesthesia and surgical procedure

All surgical procedures were performed under general anesthesia after monitoring through standard anteromedial and anterolateral arthroscopic portals under a tourniquet pressure of 300 mm Hg by the same surgical team. After monitoring, 2–3 mg/kg propofol and 3–4 μg/kg remifentanil were administered intravenously for induction. After tracheal intubation, the patients received mechanical ventilation, and the remainder of anesthesia was performed using 1–1.2% isoflurane and a mixture of N_2O and O_2 in equal proportions. Once the operation ended, muscle relaxation was reversed by 0.04 mg/kg neostigmine and atropine intravenously. Postoperative parameters, namely, electrocardiography, non-invasive systolic and diastolic blood pressure, and the duration of anesthesia and surgery were recorded.

Following surgery, the patients were transferred to post-anesthesia care unit (PACU). After the patients regained full consciousness in PACU (time = 0) and at 1, 2, 6, 12, and 24 h after surgery, a VAS assessment was performed by an anesthesiologist. As a rescue analgesic, 8 mg of intravenous lornoxicam (XEFO, Abdi İbrahim, Turkey) at maximum daily doses (2 × 1) were administered to patients with a VAS > 3. All patients were discharged 24 h postoperatively. An anesthetist performed postoperative pain assessment before discharge.

The primary outcomes in the postoperative period (first 24 h) were pain intensity measured by VAS score and time of rescue analgesic consumption. The secondary outcome was side effects of the agents administered in different groups.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences v. 15.0 (SPSS Inc., Chicago, IL, USA). Data were

recorded as the mean ± standard deviation and numerically (*n*, %). To compare age, body mass index (BMI), duration of surgery and anesthesia, and VAS between the groups, one-way ANOVA was used. The values of the three groups were homogenously determined as ($p > 0.05$) 95% after comparing with the homogeneity variance test. The outcomes of the groups were compared using one-way ANOVA Tukey's test. Repeated measures ANOVA and paired *t*-test were conducted to determine the differences in pain scores at each time interval. Chi-square test was used to compare sex distribution and rescue analgesic administration between the groups. A value of $p < 0.05$ was considered statistically significant.

Results

There were 17 women and 3 men (age range 23–50) in Group A, 16 women and 4 men (age range 19–50) in Group B, and 15 women and 5 men (age range 21–47) in Group C. There were no significant differences between the groups in terms of age, sex, BMI, and duration of surgery and anesthesia (Table 1). VAS was significantly higher in Group B at time 0 and in Group C in the first hour ($p = 0.030$ and 0.020, respectively; Table 2). The differences in VAS between the groups disappeared in the second hour ($p = 0.129$; Table 2). The number of patients who required rescue analgesics at time 0 was significantly higher in Group B than in the other groups ($p = 0.041$ Table 3). The number of patients who required rescue analgesics were significantly higher in Group C than in the other groups at the first hour ($p = 0.022$; Table 3). After the second hour, no statistically significant difference in rescue analgesic administration was observed between the groups ($p > 0.05$; Table 3). However, all patients in Group B and Group C and 17 patients in Group A required rescue analgesics in the first 6 h. At the 12th h, 4 patients in Group B and Group C required additional analgesics regardless of earlier administration of rescue analgesics ($p = 0.34$; Table 3). VAS at 24 h postoperatively was ≤3, and none of the patients in any group required rescue analgesics. They were discharged with adequate pain relief even at rest and walking.

No major side effects were noted in any of the groups. Slight nausea requiring no medication was observed only in one patient in Group B.

Discussion

Preemptive analgesia helps to increase analgesic effect via different mechanisms and reduce the incidence of side effects.[8,15] In this study, we compared the preemptive analgesic efficacy of tramadol, acetaminophen, and tramadol/acetaminophen fixed-dose combination in 60 patients who underwent ambulatory arthroscopic partial meniscectomy and had preemptive analgesia. We observed no major side effects in any patient.

The results of the present study show that tramadol/acetaminophen fixed-dose combination is superior to single dose of acetaminophen or tramadol for postoperative pain management in patients who underwent ambulatory partial meniscectomy. This finding is consistent with the results of a meta-analysis by Edwards et al and the study by Smith et al in postoperative patients treated with tramadol plus acetaminophen, particularly in orthopedic patients.[19,24] By combining drugs with different mechanisms of action and pharmacokinetic profiles, one can enhance efficacy even at lower doses of the individual drugs.[1] Treatment with tramadol/acetaminophen combination in patients with moderate to severe pain after oral surgery showed superior performance over treatment with tramadol alone.[21] Similarly, tramadol/acetaminophen combination was reported to show superior pain control over acetaminophen alone after vertebral surgery.[25]

The pharmacological profile of acetaminophen is very similar to selective COX-2 inhibitors.[16] Acetaminophen is widely distributed in different tissues, but not in fatty tissue. It is an inhibitor of nociception, which is dependent on COX-2 derived prostaglandins.[16,17] Tramadol is a centrally acting, atypical opioid analgesic that has two enantiomers.[16] The (+)- enantiomer has higher affinity for μ-receptors and is a more potent inhibitor of 5-HT reuptake. The (−)-enantiomer is a more potent inhibitor of noradrenaline reuptake.[16] The time to maximum concentration (T_{max}) of acetaminophen is 1.25 ± 0.48 h, whereas the T_{max} of tramadol is 2.14 ± 0.99 h. Therefore, acetaminophen provides faster onset of analgesia compared to tramadol (15–30 min *vs.* more than 30 min).[16,17,26] This makes acetaminophen a better choice for acute pain relief and may explain why fewer patients in Group C required less rescue analgesics at time 0 in our study. However, tramadol has a longer half-life than acetaminophen (5–7 *vs.* 4–6 h).[16,27] This may explain why most of the patients in Group C required rescue analgesics in the first hour.

Table 2
Mean pain scores of the groups measured by visual analog scale (VAS) according to time intervals.

	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	p
VAS 0 h	2.10 ± 1.48	4.75 ± 3.05*	1.80 ± 2.46	0.030*
VAS 1 h	3.30 ± 1.71	4.30 ± 2.51	6.10 ± 1.86*	0.020*
VAS 2 h	3.45 ± 1.63	4.95 ± 3.42	3.95 ± 1.43	0.129
VAS 6 h	3.05 ± 1.84	4.05 ± 2.45	3.80 ± 1.90	0.297
VAS 12 h	3.05 ± 2.01	2.55 ± 2.21	2.30 ± 1.21	0.437
VAS 24 h	1.60 ± 1.63	1.55 ± 1.84	1.70 ± 0.65	0.948

*$p < 0.05$ is statistically significant. The values are given as mean ± SD. One-way ANOVA was used.

Table 3
Time of additional analgesic administration after full consciousness was regained in groups.

Time	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	p
0 h (Yes/No)	1/19	7/13*	2/18	0.041*
1 h (Yes/No)	7/13	6/14	14/6*	0.022*
2 h (Yes/No)	6/14	5/15	3/17	0.50
6 h (Yes/No)	3/17	2/18	1/19	0.57
12 h (Yes/No)	0/20	2/18	2/18	0.34

*$p < 0.05$ is statistically significant. Chi-square test was used. h: Hour.

Table 1
Patient demographics and duration of anesthesia and surgery.

	Group A (n = 20)	Group (n = 20)	Group C (n = 20)	p
Age (years)	59.55 ± 10.33	53.85 ± 12.12	53.40 ± 7.74	0.115
Body mass index (kg/m^2)	24.7 ± 4.7	26.6 ± 4.1	27.6 ± 3.5	0.213
Sex (F/M)	17/3	16/4	15/5	0.730
Duration of surgery (min)	30.15 ± 15.18	27.35 ± 10.43	31.90 ± 13.73	0.553
Anesthesia duration (min)	36.75 ± 15.75	39.10 ± 14.89	37.25 ± 13.12	0.867

$p < 0.05$ is statistically significant. The values are given as mean ± SD. Chi-square test and One-way ANOVA tests were used.
kg: kilogram, F: female, M: male, min: minute.

Following oral administration of fixed-dose tramadol/acetaminophen, both tramadol and acetaminophen were absorbed rapidly and almost completely, although the absorption of tramadol was slower than that of acetaminophen.[16] The number needed to treat (NNT) for one person to achieve ≥50% pain relief was significantly better for tramadol/acetaminophen combination than for the components alone, with a similar rate of adverse events.[28] In addition, no significant differences were seen in pharmacokinetic parameters of tramadol or acetaminophen compared to the fixed-dose combination.[16] The onset of pain relief with oral tramadol/acetaminophen combination for acute dental pain was 17 min, while that with tramadol alone was 51 min.[21] Therefore, the combination of tramadol and acetaminophen administered orally is more effective in controlling acute pain via early onset of pain relief with acetaminophen. This can explain why fewer patients required rescue analgesics in Group A and C than in Group B at time 0.

The preemptive analgesic effect of acetaminophen is dosage dependent, and intravenous administration is more effective than oral administration at equal doses.[12] When administered intravenously, acetaminophen plasma concentration reached the peak within 40 min and then decreased slightly. In contrast, when administered orally, acetaminophen plasma concentration was variable and unpredictable.[28]

We did not encounter any major side effects in the present study, and only one case of slight nausea not requiring any medication was observed. The dual mechanism of action of the fixed-dose combination of tramadol/acetaminophen and potential for enhanced efficacy with combined medications decreases the rate of adverse events such as nausea, which is commonly seen, dizziness, vomiting, and respiratory depression.[19] This issue would be expected and consistent with the decreased dose of tramadol and acetaminophen compared to other opioids; thus, paracetamol and tramadol are known to have a lower side effect profile.[19] An advantage of tramadol over morphine and other opioids is its minimal effect on respiratory function.[27] In addition, this feature makes tramadol a better choice for patients with increased risk of impaired respiratory function.[26]

The limitations of this study are the retrospective design, sample size, and oral administration of analgesics, which leads to variability and unpredictability in plasma concentration of drugs. Moreover, there is lack of data on the timing, optimal dosage, and application methods for the administration of preemptive analgesic agents in literature. Therefore, additional prospective comparative studies taking into account the changes in bioavailability depending on administration, dose-dependent effectiveness, and timing should be performed.

In conclusion, in patients undergoing ambulatory partial meniscectomy with general anesthesia, preemptive tramadol/acetaminophen fixed-dose combination may enhance analgesia, particularly for 2 h postoperatively compared to tramadol or acetaminophen alone. However, this combination is not sufficiently effective after 2 h and additional analgesic administration as well as tramadol is required. The fixed-dose combination of tramadol/acetaminophen or tramadol alone is better than acetaminophen alone as a preemptive analgesic.

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