The efficacy of paracetamol versus tenoxicam on postoperative pain and morphine consumption after abdominal hysterectomy: a placebo-controlled, randomized study

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Summary

Objective: The purpose of this study was to determine the analgesic efficacy and side-effects of paracetamol and tenoxicam in comparison with placebo in patients with postoperative pain after elective abdominal hysterectomy. *Material and Methods:* A total of 120 patients were randomly divided into three groups to receive either paracetamol 1 g, tenoxicam 20 mg or placebo intravenously at the end of surgery, and then morphine was administered by a patient-controlled analgesia device postoperatively. *Results:* Tenoxicam was associated with lower pain scores at the 2nd, 4th, 6th and 24th hour postoperatively. Total morphine consumption was 44.8 ± 17.4 mg, 64.6 ± 19.6 mg, 69.2 ± 22.1 (tenoxicam, paracetamol and placebo group, respectively) and there was a significant difference in the tenoxicam group compared with the other two groups ($p < 0.05$). Side-effects except for nausea were similar. *Conclusion:* A single dose of 20 mg tenoxicam provided effective analgesia and reduced total morphine consumption in comparison with paracetamol and placebo after abdominal hysterectomy.

Key words: Paracetamol; Tenoxicam; Morphine; Postoperative pain; Abdominal hysterectomy.

Introduction

Acute postoperative pain is a complex and multifactorial symptom that requires a thoughtful approach using a variety of treatment modalities to obtain an optimal outcome after surgery [1]. Single analgesics, such as opioid, nonsteroidal anti-inflammatory drugs (NSAIDs), are not able to provide effective pain relief without side-effects such as nausea, vomiting, sedation, or bleeding. Therefore, multimodal analgesia involving administration of a combination of opioid and nonopioid analgesics represents a popular approach to preventing postoperative pain [2, 3]. Morphine is often combined with NSAIDs or paracetamol as part of multimodal analgesia after surgery to decrease side-effects, and also to improve the quality of postoperative analgesia [3, 4]. Tenoxicam is a thienothiazide derivative of the oxicam class of NSAIDs, making it extremely suitable for postoperative analgesia [5, 6]. Studies have demonstrated the analgesic efficacy of 20 mg tenoxicam IV after third molar extraction [7], thoracic surgery [8] and cesarean section [9]. However, the use of NSAIDs are limited by contraindications and potential side-effects, such as gastrointestinal and perioperative bleeding, renal impairment, bronchospasm and homeostatic dysfunctions [10]. Paracetamol is a well established analgesic drug for the postoperative period, as an alternative to NSAIDs because it has a better record regarding adverse reactions [11]. Although it is widely used as a basis for pain treatment and after minor surgery [10, 12], some studies indicated that paracetamol might be effective in postoperative pain and opioid consumption after major gynecologic abdominal surgery [4, 13].

There are a lot of studies about multimodal analgesia with NSAIDs and/or paracetamol in the literature; however, no study has compared the analgesic efficacy of intravenous (IV) paracetamol and tenoxicam given intraoperatively, both compared with placebo after abdominal hysterectomy.

We aimed to assess postoperative morphine consumption, pain scores, and side-effects in patients who received 1 g paracetamol or 20 mg tenoxicam IV and to compare the results with the control patients who received placebo.

Materials and Methods

After ethics committee approval and having obtained written informed consent, 120 women, aged 44-65 years old, with the American Society of Anesthesiologist (ASA) physical status of class I or II, scheduled for elective abdominal hysterectomy were included in this randomized double-blind clinical trial. Patients with renal and hematopoietic disease, known gastric ulcer, asthma, hypersensitivity to NSAIDs and paracetamol, hepatic and cardiac dysfunction, bleeding disturbances, a history of drug or alcohol abuse, administration of an NSAID or opioid during 24 hours preceding surgery were excluded from the investigation.

By visiting the patients one day before the operation, related information and training was given about the anesthesia method to be applied, usage of the PCA (patient-controlled analgesia) device (Abbott Laboratories, North Chicago, IL, USA) and a visual analog scale (VAS). All patients were premedicated with 5 mg oral diazepam one night before surgery and two hours preoperatively. On arrival in the operating room, Lactated Ringer's solution, with a rate of 10 ml/kg/h, was started through an 18-gauge (G) IV cannula and antacid prophylaxis consisted of 50 mg ranitidine and 10 mg metoclopramide IV. The women were then randomly allocated into one of three groups; 1 g of parac-

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etamol (Perfalgan, 100 ml, IV, Bristol Myers Squibb, Group P), 20 mg of tenoxicam (Tilcotil, into 100 ml saline, Roche Laboratories, Group T) and placebo (100 ml saline, Group C), according to a computer-generated randomization table. All patients received standard general anesthesia which was induced with propofol 2 to 3 mg/kg, fentanyl 1 to 2 μg/kg and rocuronium 0.6 mg/kg and maintained with desflurane (3-6%) with N2O (66%) in oxygen (33%). The doses of the study drug in all groups were administered, IV infusion, for over 15 min at the end of surgery and then paracetamol 1g (Group P) or placebo (100 ml saline, Group T and Group C) were given every six hours for 24 hours. The study drugs as previously randomized were prepared by an anesthetic nurse who was not otherwise involved in the care of the patient and were administered by the same anesthetist not involved in the study follow-up.

At the end of the operation, the patients were transferred to the recovery room and all were given IV PCA with morphine (0.3 mg/ml morphine and a PCA device programmed for a 0.1 mg/kg loading dose, 0.02 mg/kg bolus with a 15-min lockout interval and no basal infusion). Postoperative pain was assessed using a 10 cm visual analog scale (VAS) with 0: no pain and 10: the worst imaginable pain. The patients were applied an additional 1 mg/kg of tramadol intramuscularly if VAS was ≥ 4. Side-effects, such as nausea, vomiting, itching, respiratory depression, sedation and stomach irritation were recorded. Nausea and vomiting were treated with 8 mg ondansetron. The sedation levels of the patients were defined in accordance with the Ramsay sedation scale [14]. Postoperatively, all measurements were performed by another blinded and independent anesthetist.

The power analysis was based on a variation of morphine consumption from our pilot data. Sample size was calculated to detect a difference of 20% among groups in which morphine consumption was the lowest and the highest (α: 0.05, and β: 0.8), and 35 patients for each group were determined. Statistical analyses were performed with the SPSS (SPSS for Windows Release 13.0) Statistical Package. The results are presented as mean ± standard deviation (SD), median (range) or n (%) as appropriate. Age, weight, height, duration of anesthesia and surgery, intraoperative fentanyl requirement, morphine consumption, sedation and pain scores among the groups were compared using one-way analysis of variance. Side-effects and additional analgesic requirements were analyzed using chi-square and Fisher's exact test. All post hoc comparisons were performed using Bonferroni correction. A p value < 0.05 was considered statistically significant.

Results

There were no differences among the groups in the demographic and baseline hemodynamic data, anesthesia and surgical time and intraoperative analgesic (fentanyl) requirement (Table 1).

VAS scores were lower in Group T at the 2nd, 4th, 6th and 24th hour than the other two groups ($p < 0.05$); there was no statistically significant difference between Group C and P (Figure 1).

Total morphine consumption at the 24th hour was 44.8 ± 17.4 mg, 64.6 ± 19.6 mg and 69.2 ± 22.1 mg, Group T, Group P and Group C, respectively. Additional analgesic requirement was also lower in Group T (Table 2). There was a statistically significant difference between Group T and the other two groups ($p < 0.0001$) (Figure 2).

Table 1. — *Patient, anesthesia, and surgical characteristics*.

	Group C (n = 40)	Group P (n = 40)	Group T (n = 40)	p value
Age (years)	48.3 ± 5	47.8 ± 4.9	49.8 ± 6.6	025
Weight (kg)	71.2 ± 9.6	70.7 ± 9.7	74.2 ± 12.2	0.27
Height (cm)	162.2 ± 4.4	160.7 ± 5.1	161.3 ± 4.9	0.4
Duration of anesthesia (min)	116.8 ± 20.3	119.7 ± 18.5	122.3 ± 17.3	0.42
Duration of surgery (min)	105.2 ± 20.1	107.6 ± 18.2	110 ± 17.7	0.52
Baseline SBP (mmHg)	144.4 ± 14.6	139.7 ± 15.1	140.8 ± 11.8	0.29
Baseline DBP (mmHg)	85.9 ± 11.9	82.7 ± 8.2	87.6 ± 11	0.11
Baseline MBP (mmHg)	105.5 ± 10.4	101.5 ± 9.3	104.4 ± 9.1	0.16
Baseline HR (beats min-1)	93.6 ± 13.1	88.8 ± 10.8	89.6 ± 11.3	0.15
Fentanyl requirement (μg)	72.1 ± 65	71.6 ± 57.1	76.3 ± 60.7	0.93

Data are mean ± SD, SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, HR: heart rate, Group T: tenoxicam group, Group P: paracetamol group, Group C: placebo group.

Table 2. — *Analgesic requirement and side-effects*.

	Group C	Group P	Group T	p value
Additional analgesic requirement (%, n)	80 (32)	72.5 (29)	40 (16)*	$p < 0.01$*
Nausea (%, n)	67.5 (27)	60 (24)	40 (16) †	0.02 †
Vomiting (%, n)	37.5 (15)	40 (16)	25 (10)	0.31
Itching (%, n)	22.5 (9)	25 (10)	10 (4)	0.18

Data are mean ± SD, n: number of patient, *$p < 0.05$ Group T versus Group C and P, †$p < 0.05$ Group C versus Group T, Group T: tenoxicam group, Group P: paracetamol group, Group C: placebo group.

Sedation scores were similar among groups except for the 30th min, at this time Group T was lower than Group C ($p = 0.02$). No patient suffered from oversedation at any time nor had respiratory depression. Although nausea was only statistically significant difference in Group T compared with Group C, vomiting and itching were similar among groups (Table 2).

Discussion

The results of this study demonstrated that 20 mg of tenoxicam provided effective analgesia with less additional analgesic requirements compared to paracetamol and placebo in the first 24 hours after abdominal hysterectomy. The incidence of side-effects was similar among groups except for nausea which was lower in the tenoxicam group than in the placebo group.

Single or multiple doses of intravenous paracetamol (1 g) generally provided significantly better analgesic efficacy than placebo treatment in adult patients who underwent dental, orthopedic or gynecological surgery [15, 16]. On the other hand, in some studies which compared paracetamol with NSAIDs, the analgesic efficacy of paracetamol in the postoperative period was found to be controversial since both effective [13] and ineffective [17, 18] results were reached. Varrassi *et al*. [13] indicated that propacetamol and ketorolac, combined with patient-controlled analgesia morphine, showed similar analgesic efficacy after gynecologic surgery. However, Munishankar *et al*. [17] demonstrated that patients given paracetamol were less satisfied than the patients given diclofenac alone and the combination of these after cesarean section. In this study, patients given a combination of diclofenac and paracetamol used 38% less mor-

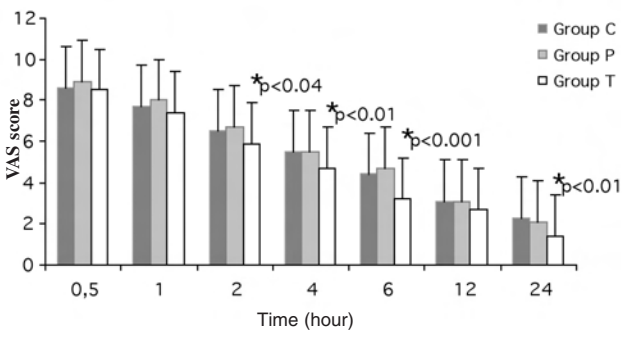

Figure 1. — VAS scores among groups.
VAS: visual analog scale, $*p < 0.05$ Group T versus Group C and P.

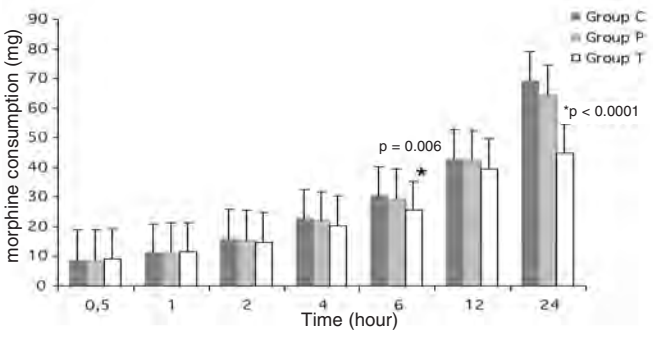

Figure 2. — Postoperative morphine consumption
$*p < 0.05$ Group T versus Group C and P.

phine compared to patients given paracetamol alone. Recently, a systematic review [19] reported that 24-hour morphine consumption decreased by 6.3 mg to 10.9 mg compared to placebo, when paracetamol, NSAID or COX-2 inhibitors were added to PCA morphine following major surgery. In the study, the authors concluded that NSAIDs seemed to be superior for postoperative pain management although there were differences in the efficacies of paracetamol and NSAIDs depending on the type of surgery performed. A qualitative review also determined that the efficacies of paracetamol and NSAIDs may depend on type of surgery [20]. The analgesic effect of paracetamol may be dependent on the rate and amount of active drug reaching the central nervous system, where its analgesic effect takes place [21]. Piguet *et al*. [22] indicated that intravenous paracetamol exerted a dose-dependent central antinociceptive effect in healthy subjects. A study by Juhl *et al*. [23] compared 1 g and 2 g paracetamol in dental surgery and found that the analgesic efficacy of a 2 g starting dose of IV paracetamol was superior over the recommended dose of 1 g in terms of magnitude and duration of analgesic effect for postoperative pain. Sinatra *et al*. [16] showed that the total morphine doses received over 24 h were 38.3 ± 35.1 mg for paracetamol 1 g and 57.4 ± 52.3 mg for placebo, corresponding decreases of 33% (19 mg) after major orthopedic surgery. However, we found that 24-hour morphine consumption decreased by 4.6 mg compared to placebo when paracetamol was added to PCA morphine in accordance with the literature [19]. Different results in studies may depend on the types of surgeries and different pain scores of the patients [19, 20].

Tenoxicam potentiates an opioid analgesic effect on the somatic and visceral types of pain to different extents [24]. Intravenous tenoxicam administration is preferable both in the immediate postoperative period to avoid any delay in absorption from either intramuscular or enteral routes. The drug is recommended at a once daily dosage of 20 mg [5]. A study showed that intraoperative injection of 20 mg tenoxicam decreased the demand ratio for PCA and 24-hour morphine consumption by approximately 30%. The authors suggested that intraoperative injection of 20 mg tenoxicam was sufficient to enhance intravenous PCA morphine on uterine cramping pain for the first 24 hours after cesarean section [24]. Munro *et al*. [5] reported that intraoperative intravenous administration of 40 mg tenoxicam during laparoscopic cholecystectomy, when compared with placebo, was associated with a significant reduction in consumption of morphine at six hours and 12 hours ($p < 0.05$) but not at 24 hours, when assessed by patient-controlled analgesia. There was no difference between the groups in pain scores, either at rest or on movement, nor in the incidence of nausea and vomiting. In contrast, Danou *et al*. [25] showed that the administration of 20 or 40 mg IV tenoxicam did not reduce fentanyl consumption via PCA compared with placebo after total abdominal hysterectomy. A difference between placebo and 40 mg tenoxicam groups was noted in VAS scores, both at rest and during coughing, at the 4th hour postoperatively but still failed to reach statistical significance. Furthermore, Merry *et al*. [8] performed a placebo-controlled trial using 20 mg tenoxicam in patients following thoracotomy and there was no significant difference between groups in terms of pain scores or side-effects. However, in other studies by the same authors, 20 mg and 40 mg of tenoxicam were superior to the control group regarding pain score and morphine consumption [26, 27]. There were no significant differences between study groups postoperatively in pain during coughing, opioid consumption, nausea, vomiting or sedation. The authors reported that these data support the inclusion of 20 mg tenoxicam IV in the management of pain, but do not show additional benefits for a higher dose.

Munishankar *et al*. [17] determined that morphine-related side-effects were similar in paracetamol, diclofenac, or the combination of diclofenac and paracetamol groups. Vandermeulen *et al*. [6] showed that morphine consumption in a control group was higher than in a 40 mg tenoxicam group at 24 h after hysterectomy. In the study, there were no important differences between placebo and tenoxicam groups in the incidence and severity of adverse events. In a study by Danou *et al*. [25], the incidence of nausea

was similar in patients receiving 20 mg tenoxicam IV and 40 mg IV compared with placebo, but mild gastrointestinal symptoms were exhibited in tenoxicam groups. The authors reported that tenoxicam may increase intraoperative bleeding and gastrointestinal side-effects.

In our study, vomiting and itching were similar among groups although nausea was the only difference. Morphine sparing resulted in parallel reductions in opioid-related side-effects such as nausea in the tenoxicam group. Pain score and morphine consumption in placebo and paracetamol groups were higher at 6 h, probably because our patients were mobilized at the time. We believe that tenoxicam provided effective analgesia compared with the other two groups even on movement although VAS scores of the patients were evaluated only at rest.

One of our few limitations was that pain scores of the patients were only recorded at rest, not on movement and when coughing. Moreover, the amount of preoperative bleeding was not assessed but no patient was re-operated for bleeding or hematoma and received blood transfusions postoperatively.

In conclusion, tenoxicam provided reliable analgesia with comparable pain scores and reduced morphine consumption and nausea which is an opioid-related side effect after abdominal hysterectomy. Although paracetamol is claimed to be effective in postoperative pain after major abdominal surgery, we found no difference between paracetamol and placebo groups.

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