Preemptive meloxicam for postoperative pain relief after abdominal hysterectomy

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Summary

Objective: This study was conducted to evaluate the analgesic efficacy of meloxicam in abdominal hysterectomy.

Methods: The study population consisted of 52 patients scheduled for total abdominal hysterectomy who were ASA 1 or 2 physical status female. Patients were allocated randomly to receive orally either 15 mg of meloxicam (Group M, n = 27) or placebo (Group P, n = 25) before anesthesia induction. After intravenous administration of 1.5 mg kg^{-1} of tramadol, anesthesia was induced with an intravenous loading dose of 1-2 mg kg^{-1} propofol. Anesthesia was maintained on intravenous infusion of propofol at 6-12 mg kg^{-1} h^{-1} plus tramadol at 1 mg kg^{-1} h^{-1}, vecuronium, and a 2:1 nitrous oxide-oxygen mixture.

Results: The relative propofol consumption was lower in Group M than in Group P, ($p < 0.05$). The time for analgesic rescue decreased in the order Group M > Group P ($p < 0.01$). The degree of sedation was similar between the groups ($p > 0.05$) and the visual analog scores (10-cm scale) and verbal rating scale data differences were present in the first 2 h only ($p < 0.05$). When side-effects were evaluated nausea and vomiting were found to be lower in group M than in group P ($p < 0.05$).

Conclusion: Preemptive meloxicam provided better postoperative analgesia than placebo.

Key words: Meloxicam; Abdominal hysterectomy.

Introduction

The goal of postoperative pain relief is to achieve optimal analgesia, facilitating a speedy return to normal physiological organ function with minimal side-effects. Preemptive analgesics can be used to control postoperative pain relief. Preemptive analgesia has been used to describe the phenomenon by which analgesia administered before a painful stimulus decreases the intensity of the subsequent pain [1, 2]. By administering an analgesic before the painful stimulus, the development of pain hypersensitization may be reduced or abolished, thus resulting in less poststimulus pain. A wide variety of agents have been examined for their possible preemptive analgesic effects, including systemic opiods and neuroaxial blocker agents and systemic NSAIDs, In this randomized controlled trial, we examined the efficacy and safety of preemptive meloxicam for total abdominal hysterectomy surgery performed with tramadol [3-7]. The preemptive meloxicam dose was administered 30-40 minutes before the operation was started in one group of patients and placebo dose was administered to the other group of patients. This study describes the potential effects of preemptive analgesia by using meloxicam, an enolic acid derivative of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs), whose mechanism of action may be related to prostaglandin (cyclooxygenase) synthetase inhibition.

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Materials and Methods

Patients

Fifty-two ASA 1 or 2 physical status females scheduled for gynecological abdominal hysterectomy were included in the study. Patients with clinically significant hepatic-renal failure, platelet dysfunction, chronic pain, non-steroid antinflammatory drug administration or drug abuse, allergy to NSAIDs, age older than 60, mental defects, significant cardiopulmonary dysfunction and those whose body weight was 30% above or below their ideal weight were excluded. The study was approved by the Ethics Commitee of Ege University Hospital. Written informed consent was obtained from all patients. Fifty-two randomized patients aged between 35 and 60 years were divided into two groups: meloxicam group (n = 27) and placebo group (n = 25). Patients were premedicated with 5 mg oral diazepam 8 h preoperatively. The premedication was either a placebo tablet (Group P) or a 15 mg meloxicam tablet (Group M), administered orally 30-40 minutes before anesthesia induction. During surgery the patients were monitored using the Datex-Ohmeda system. The standard noninvasive monitorization was applied to both groups. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation monitoring were established before induction of anesthesia. Two intravenous lines were established for each group. After intravenous administration of 1.5 mg kg^{-1} tramadol, anesthesia was induced with an intravenous loading dose of 1-2 mg kg^{-1} propofol until the patient lost consciousness and eyelash reflex. A nondepolarizing neuromuscular block of 0.1 mg kg^{-1} vecuronium was administered to facilitate tracheal intubation and mechanical ventilation. Patients were ventilated to obtain an end-tidal carbon dioxide concentration of 30-40 mm Hg and anesthesia was maintained at an intravenous infusion of propofol at 6-12 mg kg^{-1} h^{-1} plus tramadol at 1 mg kg^{-1} h^{-1}, nitrous

oxide 60% and 40% oxygen. Intravenous 0.5 mg atropine was to be given if bradycardia developed (a drop in heart rate below 50 beats/min^{-1}). If hemodynamic data increased 30% above the baseline, it was considered the clinical sign of inadequate anesthesia and increments of IV propofol and vecuronium were given as indicated. Tramadol infusion was continued until 15 minutes to the end of the surgery, and propofol infusion was continued until the *last suture was made*.

Postoperative analgesia

If analgesia was inadequte in the 24-hour postoperative period in the recovery room – a visual analog scale (VAS) at rest of 4 or higher and verbal rating score (VRS) at rest of 2 or higher – tramadol was planned to be given at 50 mg IV (2x1) and also diclofenac-Na 1 mg kg^{-1} IM, until adequate pain relief was achieved. The subsequent 24 h, and up to five days if necessary, 7.5 mg meloxicam (x 2) was planned to be given. Patients were observed by an anesthetist at least eight times during the subsequent postoperative 24 hours and two times over five days. The postoperative study records included assessment of pain relief according to a VAS and VRS. Side-effects such as nausea, vomiting and sedation scores were recorded for 24 hours. Vital function monitoring included continuous pulse oximetry (SpO_2) and hourly counting of respiratory rate, noninvasive blood pressure and heart rate with an electrocardiogram.

Data collection

Preoperatively, a VAS pain score, VRS and nausea-vomiting (NV) score were recorded by each subject. The VAS was a 10-point scale, with 10 signifying the "worst possible pain" and 0 representing "no pain." The VRS was a 4-point scale, with 4 signifying the "worst possible pain" and 0 representing "no pain." The NV score was based on the following scale: 1 = no nausea; 2 = mild nausea; 3 = moderate nausea; 4 = severe nausea; and 5 = severe nausea plus vomiting. Postoperatively, eight times in 24 h in post anaesthetic care unit (PACU) and afterwards between 24 hours and the fifth day, the pain and NV scores were repeated, and the use of tramadol and diklofenac-Na, and the first analgesic requirement in PACU were recorded. The meloxicam requirements were also recorded between 24h and five days.

Statistics

The demographic data, propofol consumption, tramadol and diclofenac usage and VAS/VRS pain scores were analyzed by the Student's t-test. Side-effects data were analyzed by the chi-square test. All tests were performed using Systat 10.0 (SPSS) and statistical significance was defined as $p < 0.05$.

Table 1. — *Patient characteristcs and duration of anesthesia.*

	Group M (n = 27)	Group P (n = 25)
Age (yrs)	48 ± 4*	46 ± 5
Weight (kg)	68 ± 10*	65 ± 7
ASA I/II	25/2*	23/2
Duration of anesthesia (min)	110 ± 20*	115 ± 17

Values are mean ± SD, *p > 0.05.

Table 2. — *Propofol consumption.*

	Group M (n = 27)	Group P (n = 25)
Induction propofol (mg)	150 ± 22*	169 ± 21
Total propofol (mg)	712 ± 113*	826 ± 224

Values are mean ± SD, *p < 0.05.

Table 3. — *Postoperative rest and cough VAS values.*

	Group M (rest)	Group M (cough)	Group P (rest)	Group P (cough)
1 min.	1.3 ± 1.0*	2.7 ± 2.4*	3.1 ± 0.4	4.3 ± 0.6
15 min.	1.2 ± 1.2*	2.9 ± 1.9*	3.3 ± 0.1	3.9 ± 0.5
30 min.	1.5 ± 1.3*	2.7 ± 1.5*	3.7 ± 1.9	6.8 ± 2.1
2 h	1.2 ± 1.4*	2.9 ± 1.6*	3.4 ± 1.5	3.9 ± 1.8
4 h	1.9 ± 1.5	2.3 ± 1.7	2.1 ± 1.53	3.2 ± 1.45
6 h	2.4 ± 1.1	2.6 ± 1.35	2.7 ± 1.01	2.8 ± 1.9
12 h	2.6 ± 1.1	2.6 ± 1.5	2.48 ± 0.5	2.6 ± 0.8
24 h	2.3 ± 1.4	2.7 ± 1.59	2.6 ± 0.8	2.63 ± 0.9

Values are mean ± SD, *p < 0.05.

Table 4. — *Postoperative rest and cough VRS values.*

	Group M (rest)	Group M (cough)	Group P (rest)	Group P (cough)
1 min.	0.9 ± 0.7*	1.5 ± 0.5*	2.1 ± 0.6	2.1 ± 1.1
15 min.	0.9 ± 0.5*	1.6 ± 0.6*	1.3 ± 1.3	2.1 ± 0.5
30 min.	0.7 ± 0.2*	1.6 ± 0.3*	1.5 ± 0.9	2.2 ± 0.8
2 h	0.7 ± 0.1*	1.2 ± 0.5*	1.3 ± 0.9	1.5 ± 0.6
4 h	0.8 ± 1.1	1.2 ± 0.7	1.3 ± 0.5	1.3 ± 0.7
6 h	0.9 ± 1.2	1.1 ± 1.1	1.1 ± 0.6	0.9 ± 0.8
12 h	0.9 ± 1.8	1.0 ± 0.5	0.9 ± 0.9	0.9 ± 0.8
24 h	0.8 ± 1.7	1.1 ± 1.1	0.9 ± 0.8	1.2 ± 0.7

Values are mean ± SD, *p < 0.05.

Table 5. — *First analgesic time, total tramadol and diclofenac sodium consumption.*

	Group M (n = 27)	Group P (n = 25)
First analgesic time (h)	21.5 ± 10*	4 ± 1.9
Total tramadol (mg) (24 h)	25 ± 25*	80 ± 25
Diclofenac (mg) (24h)	0*	75 ± 25

Values are mean ± SD, *p < 0.01.

Results

The demographic data for both groups were similar. There were no significant differences statistically ($p > 0.05$) (Table 1). In group M induction and total propofol consumption was significantly lower than group P ($p < 0.05$) (Table 2). Pain scores (VAS at rest/on coughing and VRS at rest/on coughing) were significantly higher in the placebo group ($p < 0.05$). VAS and VRS data are presented in Tables 3 and 4. Graphic analysis revealed that postoperative differences were present the first two hours only ($p < 0.05$). The first analgesic time was 21.5 ± 10 h in group M and in group P 4 ± 1.9 h ($p < 0.01$) (Table 5). Amount of total tramadol was 25 ± 25 mg and 80 ± 25 mg in the meloxicam and placebo groups, respectively ($p < 0.01$) (Table 6). Patients for whom analgesia was inadequate with tramadol used diclofenac-Na which was given in group P (75 ± 25 mg). Diclofenac-Na was not applied in group M ($p < 0.01$) (Table 6). The amount of meloxicam was found to be lower during the last five postoperative days in group M ($p < 0.01$) (Table 6). When evaluated, the side-effects nausea and vomiting were found to be lower in group M than in group P ($p < 0.05$) (Table 7).

Table 6. — *Amount of meloxicam (mg) the last 5 postoperative days.*

	Group M (n = 27)	Group P (n = 25)
24-48 h	7.5 ± 0*	15 ± 0
48-72 h	6.9 ± 2*	12 ± 3.7
72-96 h	6.1 ± 3*	7.5 ± 0
96-110 h	3.6 ± 3*	7.5 ± 0

Values are mean ± SD, *p < 0.01.

Table 7. — *Incidence of nausea and vomiting.*

	Group M (n = 27) (n/%)	Group P (n = 25) (n/%)
Nausea	6 (22.2%)*	11 (44%)
Vomiting	1 (37%)*	7 (28%)

* p < 0.05.

Discussion

Nonopioids are of benefit in multimodal analgesia and allow acute rehabilitation of surgical patients. Acetaminophen, NSAIDs, alpha 2-antagonists, and NMDA antagonists are in routine use as components of multimodal analgesia, in combination with opioids or local anesthetic techniques [8]. Surgical tissue trauma results in the release of a vast number of inflammatory mediators, including prostanoids. These mediators affect nociceptors, altering their firing threshold and sometimes causing direct stimulation [9]. NSAIDs block the synthesis of prostaglandins by inhibiting the enzyme cyclooxygenase (COX), thereby reducing the production of mediators of the acute inflammatory response. The effectiveness of nonsteroidal antiinflammatory drugs (NSAIDs) in alleviating pain and reducing requirements for opioids in the postoperative period has been well documented [10-12]. COX-2 inhibitors are being increasingly used as non-opioid adjuvants to minimize pain during the perioperative period. Early studies evaluated the use of COX-2 inhibitors for preventative analgesia when administered for oral premedication [13-15]. Both preoperative [16] and postoperative [17] administration of this investigational COX-2 drug seems to exert significant opioid-sparing effects, and these preliminary studies suggest that it can improve the quality of recovery and patient satisfaction with postoperative pain management.

In our study, for patients with total abdominal hysterectomy (ATH) we found analgesia time to be 21.5 ± 10 hours in group M (COX-2 inhibitors NSAIDs-meloxicam) and 4 ± 1.9 hours in group P (p < 0.01). Total tramadol dose was found to be signifacantly low (p < 0.01) in the preoperative meloxicam group in 24 hours. Diklofenac-Na was given to group P in whom the analgesic effect of the IV tramadol dose was not enough.There was no need for diklofenac-Na in group M (p < 0.01). According to PACU, 24-hour pain score evaluations on rest and coughing for the VAS and VRS were found to be statistically low for the first two hours in group M (p < 0.01). Because of the use of more analgesia with tramadol and diklofenac-Na when VAS > 4 or VRS > 2, VAS and VRS values were not found to be different between the two groups after two hours.

Reuben and *et al.* [18] reported that patients who received rofecoxib preoperatively experienced less postoperative pain at rest and with movement, and required less analgesia than patients who received rofecoxib postoperatively. The study included 60 patients. Group I patients were given a placebo both before and after surgery, group 2 patients were given of 50 mg rofecoxib one hour before surgery and placebo 15 minutes after surgery, and group 3 patients were given a placebo one hour before surgery and 50 mg of rofecoxib 15 minutes after surgery. The analgesic duration was 318 minutes for group 1 (placebo), 461 minutes for group 2 (post-op rofecoxib), and 803 minutes for group 2 (pre-op rofecoxib, p < 0.001). A dramatic and statistically significant reduction in the use of oxycodone and acetaminophen over 24 hours was noted: 5.5 tablets, 3.3 tablets and 1.5 tablets for groups 1, 2 and 3, respectively (p < 0.05). Furthermore, all patients in groups 1 and 2 required postoperative opioids for pain, while seven patients (35%) in group 3 did not require any (p < 0.05).

Thompson *et al.* [19] reported that the use of meloxicam preoperatively in ATH patients had significantly reduced the dose of PCA-morphine and the VAS values within 24 hours on rest, movement and coughing. There have been different conclusions on studies about pain relief by using a combination of tramadol and NSAID. Lauretti *et al.* [20] found the preoperative use of tramadol and NSAID (betacyclodextrin piroxicam) combinations provided better perioperative analgesia then tramadol alone. Intramuscular lornoxicam offers a useful alternative to tramadol in the treatment of moderate to unbearable postoperative pain following arthroscopic reconstruction of the anterior cruciate ligament using the patella bone-tendon-bone technique [21]. Striebel *et al.*, however, found insufficient pain reduction in multimodal analgesic treatment in their study; satisfactory pain relief occurred rather late despite high doses of both tramadol/metamizole and tramadol/ibuprofen [22]. Preoperative administration of meloxicam is a safe and effective method of controlling postoperative pain in experimental animal surgery [23].

When side-effects were evaluated the the incidence of nausea-vomiting in group M was less than in group P (p < 0.01). In experimental studies, lipopolysaccharide-induced emesis was abolished with COX inhibition by using both meloxicam and indomethacin when they were administered before the lipopolysaccharide [24]. The anti-emetic activity of two COX inhibitors suggests that prostaglandins contribute to the activation of the emetic reflex in response to cisplatin [25]. Clinically the most common side-effects of NSAIDs are seen in the gastrointestinal system (GIS) [26, 27]. There was not any GIS-related complaint in either group. The use of selective COX-2 inhibitors in patients with osteoarthritis and rheumatoid arthritis has resulted in less gastric erosion than that seen when using earlier NSAIDs at dosages that have an antiinflammatory effect [28, 29]. The potent antiinflammatory effect of meloxicam, accompanied with low gastric toxicity, may be related to its relative selec-

tivity for COX-2 over COX-1 [30]. The results with human mucosa pieces would suggest that the better gastric tolerability of meloxicam compared to indomethacin is related to its relatively lower inhibition of gastric mucosal PGE synthesis by COX-1 [31].

Surgical tissue trauma results in the release of a vast number of inflammatory mediators, including prostanoids. These mediators affect nociceptors, altering their firing threshold and sometimes causing direct stimulation. Traditional non-selective NSAIDs are used widely in the perioperative period as they decrease opioid requirements and improve analgesia. If effective in this setting, the use of COX-2 specific NSAIDs may provide advantages over traditional NSAIDs, particularly in the elderly and those at risk of the adverse gastrointestinal or renal effects of these drugs. Preemptive analgesia with meloxicam is efficacious in the management of postoperative pain after total abdominal hysterectomy.

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