Preemptive Use of Etofenamate in Laparoscopic Cholecystectomy: A Randomized, Placebo-Controlled, Double-Blind Study.

Meral Şen[1], Aydın İnan[1], Hüseyin Sert[2], Ayhan Akpınar[1], Cenap Dener[1]

Fatih University, Medical School, Departments of General Surgery[1] and Anesthesiology[2], Ankara, Turkey

Eur J Gen Med 2010;7(1): 50-55

ABSTRACT

Aim: *To investigate the preemptive effect of etofenomate on postoperative pain and emesis in the first 24 hours after elective laparoscopic cholecystectomy.*

Method: *Patients were randomly assigned to two groups each consisting of 60 patients. Group A was received 1g (2 ml) etofenomate intramuscularly, group B was received 0.9% saline intramuscularly one hour before surgery. All patients were administered meperidine HCl in the patient -controlled analgesia (PCA) intravenous mode in order to treat postoperative pain. Pain intensity was assessed on visual analog scales (VAS) at four times; 1 hour, 6 hours, 12 hours and 24 hours. The total meperidine HCl consumptions, VAS scores and antiemetic requirements were recorded and comparisons among the two groups were evaluated.*

Result: *The mean total meperidine HCl consumptions within first 6 and 24 hours of the group A were significantly less than the group B. The VAS scores at 1 and 6 hours in the group A were significantly lower than that in the group B. There was no significant difference in the postoperative antiemetic requirement among two groups.*

Conclusion: *Preemptive use of etofenamate reduces pain intensity and meperidine HCl requirement, but it doesn't affect the antiemetic requirement in elective laparoscopic cholecystectomy.*

Key words: *Preemptive analgesia, etofenamate, laparoscopic cholecystectomy, nausea, vomiting*

Correspondence: *Hüseyin Sert, MD*
Alparslan Türkeş Caddesi
No: 57 Emek Ankara Turkey
Phone: +903122035555
Fax: +903122213276
E-mail: drhuseyinsert@yahoo.com

INTRODUCTION

Laparoscopic cholecystectomy (LC) is increasingly becoming accepted gold standard technique for symptomatic gallstone disease since 1980s (1). LC produces less postoperative morbidity, less postoperative pain, earlier return to diet and earlier mobilization and discharge home if compared with open cholecystectomy (1-3). Besides these advantages, LC is not pain-free procedure. Sometimes as a result of rapid distension of peritoneum by CO2 can cause rupture in blood vessels, can cause trauma on the nerves and abdominal wall. As a result of these traumas, inflammatory mediators synthesis increase and some patients may experience significant abdominal disturbances and most of patients complain severe abdominal pain and nausea especially during first 24 hours postoperatively (3). Severity of pain decreases after the first 24 hours (3,4).

Preemptive analgesia is defined as an antinociceptive intervention that starts before a surgical procedure and has three goals; to decrease acute pain after tissue injury, to prevent pain-related pathologic modulation of the central nervous system and to inhibit the persistence of postoperative pain (5-10). Many trials have been done using different agents and different methods, but the results relating to pain reduction and analgesic consumption are variable (7,9-11).

Etofenamate is a long-acting nonsteroidal anti inflammatory drug (NSAID) and a rapid-acting intramuscular analgesic that can be used for postoperative pain relief (12,13). To date, as far as we know there has been no other randomized studies in the literature investigating the preemptive analgesic and antiemetic effect of etofenamate in LC.

The aim of this study was to evaluate the effect of preemptive use of etofenamate on postoperative pain, emezis and consumption of opioids and antiemetics in patients who underwent LC.

MATERIAL AND METHODS

Study Design

The protocol for study was approved by the Research Ethics Committee, and all patients gave written informed consent. We carried out a double-blind, randomized, placebo-controlled, prospective study of 120 patients from October 2005 to December 2007 in our hospital. Patients whose physical status was American Society of Anesthesiology (ASA) 1 or 2 underwent elective LC under general anesthesia. Patients were excluded if there was acute cholecystitis, acute pancreatitis, and known history of hypersensitivity to any drug, uncontrolled concomitant medical diseases (diabetes mellitus, hypertension, bronchial asthma, and coagulopaty), chronic opioid therapy, cholelithiasis with known bile duct pathology and the administration of analgesics within 48 hour of the day before surgery. All patients were given an explanation of the VAS and informed how to use of patient-controlled analgesia before surgery. No preanesthetic medication was prescribed and the patients were fasted from midnight before surgery. All patients were hospitalized on the day of surgery. All operations were performed between 9:00 a.m. and 2:00 p.m. and by four surgeons experienced in laparoscopy. Patients were randomised by a computer-generated, blinded randomisation list. The study group was randomly assigned and was balanced at a ratio of 1:1. Group A (the etofenamate group) was received 1g (2 ml) etofenamate (Flexo ampul, Santafarma Drug, İstanbul, Turkey) intramuscularly, group B (the placebo group) was received same dose (2 ml) 0.9% saline intramuscularly one hour before surgery. General anesthesia was given to all patients by the same experienced anesthesiologist. All patients received prophylactic Cefazolin Na 1 g (Cefamezin, 1000 mg flacon, Eczacıbaşı Drug, İstanbul, Turkey).

Anesthesia

Standard monitoring including continuous ECG, pulse oximetry and noninvasive arterial blood pressure was used for all of the patients. Anesthesia was induced with propofol 2 mg/kg and fentanyl 1μg/kg i.v. followed by a non-depolarizing neuromuscular-blocking drug, cisatracurium (150 μg/kg) to facilitate tracheal intubation. General anesthesia was maintained with sevoflurane (end tidal concentration) 1.5-2% according to 20 % variation in blood pressure and/or heart rate compared with basal valves, in combination with nitrous oxide (N2O) 50% in oxygen (02). Mechanical ventilation was adjusted to obtain an end tidal CO2 partial pressure at 30-40 mmHg.

In each case, a gastric tube was inserted for the duration of procedure. Patients were placed in 20-30° head up and 15-20° right side up position. During surgery all patients received infusion of lactated ringer solutions.

Surgical technique

Four trocars were inserted to abdominal cavity for the all patients. CO2 insufflation was executed by a direct trocar insertion into the abdomen. Intraabdominal

pressure was maintained at 10 to 12 mmHg. Standard LC was applied for all patients. All operations were completed with laparoscopic technique. Ondansetron 4 mg i.v. was given to all patients as a prophylactic dose, when the trocars were removed from the abdomen. After completion of surgery, anesthesia was discontinued and residual neuromuscular blockade was antagonized with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg. Patients were extubated when adequate spontaneous ventilation was established.

Postoperative analgesia

Postoperative analgesia was supplied by i.v. meperidine HCl, using PCA. Following the end of the skin closure and extubation an i.v. loading dose of 0.5 mg/kg meperidine was given and the demand bolus injection was set at 10 mg, with a lockout time of 30 min. No basal infusion rate was used. Nausea and vomiting were treated with 4 mg ondansetron i.v. every 6 h if needed.

Intensity of postoperative pain was measured using a 10 cm VAS, anchored at 'no pain' and 'worst pain I can imagine'. All VAS pain scoring was done at postoperatively 1 (T1), 6 (T6), 12 (T12) and 24 (T24) hour and with the patient at rest. The nurses and doctors who applied the preemptive analgesia and VAS scales were blinded to study.

Statistical analysis

Data for age, body weight and duration of surgery were analyzed with student t test and reported as mean±SD. The Mann-Whitney U-test was used the compare for the VAS pain scores, cumulative dose of meperidine HCl and ondansetron between group A and B. P values< 0.05 were considered statistically significant.

RESULTS

Two patients were excluded, one of them group A and the other Group B because of disorientation of study protocol. Thus data from 118 patients were analyzed. No patient was withdrawn from the study because of adverse effects (such as drug toxicity or complication of anesthesia) and there was no significant surgical complication postoperatively. Demographic data (age, gender, and weight) and duration of surgery were shown Table 1. Patient characteristics and operating time did not differ among two groups.

***Table 1**. Demographic findings of both groups**

	Group-A (n:59) (preemptive group)	*Group-B (n:59) (placebo group)*
Age (years)	*53.49 ± 9.74*	*55.24 ± 8.21*
Gender (male/female)	*20/39*	*17/42*
Weight (kg)	*75.35 ± 9.73*	*77.762 ± 11.03*
Duration of surgery (minutes)	*47.71 ± 19.32*	*46.95 ± 19.76*

**Data are expressed as a mean ± SD*

Postoperative pain scores

VAS pain scores were shown Table 2. T1 and T6 scores were significantly lower in group A (p=0.005 and 0.01, respectively). T12 and T24 scores were also lower in group A than group B, but these results were not significant (p=0.25 and 0.88, respectively).

Postoperative meperidine HCl and ondansetron consumption

Total meperidine HCl (within first, second 6 and 24 hours) and ondansetron consumption in group A and B were also shown Table 2. In group A total meperidine consumption in first 6 and 24 hours were significantly lower than Group B (p=0.001 and 0.01, respectively) but there was no difference between group A and B for the total meperidine consumption within second 6 hours postoperatively (p=0.57). There was no difference between group A and B for the total ondansetron consumption (p=0.24).

DISCUSSION

Clinical evidences suggest that surgical damage may induce prolonged changes in both the peripheral and central nervous systems that together magnify postoperative pain (6,8,14,15). Preemptive analgesia means that an analgesic intervention is started before the noxious stimulus arises in order to block peripheral and central nociception (5-7). NSAIDs when given before tissue damage (preemptive) may play an important role in peroperative pain management by reducing the inflammatory response in the periphery and thereby decreasing sensitization of the peripheral nociceptors (6,8,15). Many trials were able to demonstrate that preemptive effect of NSAIDs on the reduction of postoperative pain in LC (9).

Table 2. *Visual analogue scale (VAS) scores at different time intervals, total meperidine HCl and ondansetron consumptions**

Time Period	Group-A (n=59) (preemptive group)	Group-B (n=59) (placebo group)	p values
T1 (Pain score at 1 hour)	4.00 ± 0.87	4.49 ± 0.97	0.005
T6 (Pain score at 6 hour)	2.28 ± 0.58	2.62 ± 0.82	0.01
T12 (Pain score at 12 hour)	1.74 ± 0.57	1.86 ± 0.54	0.25
T24 (Pain score at 24 hour)	1.01 ± 0.60	1.00 ± 0.66	0.88
Total meperidine HCl consumption withinfirst six hour (mg)	79.15 ± 30.92	86.27 ± 20.50	0.001
Total meperidine HCl consumption withinsecond six hour (mg)	20.67 ± 25.04	22.88 ± 10.34	0.57
Total meperidine HCl consumption (mg/24 hour)	110.50 ± 38.48	127.11 ± 36.01	0.01
Total ondansetron consumption (mg/24 hour)	5.55 ± 2.46	5.08 ± 1.94	0.24

*Data are expressed as a mean ± SD and p<0.05 accepted significant.

According to a meta-analysis by Kehlet (9) seven studies (nine arms) were identified comparing a systemic NSAID with placebo in LC. The studies evaluated the preemptive effect of ketorolac, diclofenac, indomethacin and tenoxicam. The meta-analysis showed that VAS scores in eight of the nine study arms reported a significant benefit for NSAIDs versus placebo and also reported that three study arms all reported a significant benefit for systemic NSAIDs versus placebo according the first analgesic request and use of supplementary analgesics. Conversely there are other recent studies showed that some NSAIDs have no preemptive effect in different surgical procedures (16-18).

Etofenomate is a long-acting and potent prostaglandin inhibitor used for the treatment of pain, inflammation, fever and works by none selectively blocking cyclo-oxygenase (COX) enzyme (12,13,19). Prostaglandins are produced by the body in response to the presence of injury or disease and they make the nerves more sensitive to pain impulses (15). Etofenamate is a lipophylic esther derivate of flufenamic acid and slowly released from fat deposits, therefore injections have a longer action time when compared to injections which are water soluble (20). Suggested dosage for adults is 1g/day and analgesic effect starts within 60 min. It has been shown that etofenamate is clinically as effective as fentanyl on pain for patients extracorporeal shockwave lithotripsy (13) and effective and well tolerated as diclofenac in the relief of acute renal colic (19).

Our study is the first clinical investigation to examine the preemptive analgesic and antiemetic effects of etofenomate in LC and our results support the clinical efficacy of preemptive use of etofenamate one hour before surgery versus placebo especially early postoperative period. We administered the etofenamate before one hour surgery, because timing is very important for the effect of NSAIDs in preemptive analgesia. Ong et al. (10) suggested that many of investigations administered the NSAIDs 'just before' the surgical incision and the time that elapsed from the administration of NSAIDs to start of surgery may have been too short to allow sufficient inhibition of the cylooxygenase precluding the de novo synthesis of prostanoids. Consequently, for a preemptive effect, the NSAIDs may require to be administered long before the surgical incision, thus permitting concentration of the drug at the surgical site before the incision (10,15,21). It has been shown that tenoxicam administered 30 min before breast surgery (21) and piroxicam administered two hours before gynecological laparoscopic surgery (22) resulted in better postoperative analgesia than a similar dose administered at induction of anesthesia. Intramuscular administration of etofenamate takes 60 min to reach levels ≥90% of the maximally achieved concentration and usual duration of the analgesic effect after single dose is about 24 hours. We think that, the preemptive administration of etofenamate approximately 60 min before surgery appears rational in order to attain maximal plasma concentration at the

time of surgical stimuli.

The half-life of NSAID is important for the preemptive effect because of shorter acting analgesics do not have a sufficiently long time of action to provide analgesia (22). Although etofenamate has a long half-life (8-10 hours), its preemptive effect of VAS scores and meperidine consumptions diminished late postoperative period. VAS scores at 1 and 6 hours in the etofenamate group were significantly lower, VAS scores at 12 and 24 hours were also lower but the differences between etofenamate and placebo group were not found significant. Our amounts of meperidine consumptions in first six hours were significantly lower in etofenamate group but this significance was lost in second 6 hours parallel. Some investigators made the same observations after using preemptive analgesia with different NSAIDs (23-25). Preoperative administration of intravenous flurbiprofen axetil provided better postoperative analgesia especially early postoperative period than its administration postoperatively and reduced morphine consumption for spinal fusion surgery (23). In another study (25) shown that preemptive administration of ketoprofen improved postoperative analgesia especially during the 3 postoperative hours. Authors explained that this effect could be due to the synergy of the NSAIDs and peroperative opioids. In this study, the mechanism of immediate postoperative analgesia was attributed to peripheral and central effects of etofenamate. We don't think that early postoperative analgesia was contributed to meperidine bolus administration after extubation, because it was very low dose (0.5 mg/kg) for our patients and we didn't use another kind of analgesic postoperatively to avoid any drug interaction. We think that preadministration of etofenamate might reduce or delay the development of peripheral inflammation resulting from the inhibition of PGs plays an important role in immediate postoperative pain and its diminishing analgesic effect could be due to the half-life of etofenamate.

Postoperative nausea and vomiting are common problems and a relatively high incidence (53%-72%) in LC (26). Factors affecting postoperative emesis include the patient-related factors (age, gender, obesity, history of motion sickness and previous postoperative nausea and anxiety), duration of surgery, preanesthetic medication, anesthetic technique and postoperative factors (pain, dizziness, ambulation, oral intake and opioids) (27). Although the etiological mechanism of emesis in LC for this is not quite obvious, increased proinflammatory cytokines as a result of tissue damage, mechanical pressure to gut, stretching of vagal nerve in the peritoneum, hyperalgesia and raised intracranial pressure as a result of vasodilatator effect of CO2 are possible causes (28). In literature, preemptive effect of NSAIDs on postoperative nausea and vomiting is very limited and controversial (24,29,30). In our study preemptive use of etofenamate did not diminish the need for antiemetic requirements. This result might be attributed the prophylactic use of ondansetron at the end of the surgery for all patients. Although some investigators suggested that routine administration of opioids with PCA, prolongs the recovery, in-patient stay and increases the postoperative nausea and vomiting following LC, we didn't see any significant opioid-related adverse effect and delayed recovery in our patients.

In conclusion, in this prospective randomized trial, single dose of etofenamate provides effective postoperative analgesia for LC. The administration of etofenamate 1g one hour before surgery reduces pain intensity and opioid requirement versus placebo especially early postoperative period, but it doesn't affect the antiemetic requirement in LC.

REFERENCES

1. *Cuschieri A, Dubois F, Mouiel J, et al. The European experience with laparoscopic cholecystectomy. Am J Surg 1991;61:385-7*
2. *Victorzon M, Tolonen P, Vuorialho T. Day-case laparoscopic cholecystectomy: treatment of choice for selected patients? Surg Endosc 2007;21:70-3*
3. *Alexander JI. Pain after laparoscopy. Br J Anaesth 1997;79:369-78*
4. *Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. Anesth Analg 1995;81:379-84*
5. *Grape S, Tramer MR. Do we need preemptive analgesia for the treatment of postoperative pain? Best Pract Res Clin Anaesthesiol 2007;21:51-63*
6. *Dahl JB, Moiniche S. Pre-emptive analgesia. Br Med Bull 2004;71:13-27*
7. *Moiniche S, Kehlet H, Dahl JB. A Qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. Anesthesiology 2002;96:725-41*
8. *Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. Am Fam Physician 2001;63:1979-84*

9. Kehlet H, Gray AW, Bonnet F, et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following laparoscopic cholecystectomy. Surg Endosc 2005;19:1396-415

10. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 2005;100:757-73

11. Katz J. Pre-emptive analgesia: importance of timing. Can J Anaesth 2001;48:105-14

12. Guevara-López U, Uscanga-Sánchez S, Márquez J, Bárcenas-Olivares J, Martínez-Arenas A, Palma-Aguirre JA. Comparative clinical multicenter study to evaluate analgesic effectiveness of intramuscular etofenamate and diclofenac in patients with post-surgical pain. Cir Cir 2004;72:483-90

13. Unsal A, Cimentepe E, Bozoklu A, Sağlam R. Comparative study of etofenamate and fentanyl for outpatient extracorporeal shockwave lithotripsy. Scand J Urol Nephrol 2001;35:502-4

14. Reuben SS, Bhopatkar S, Maciolek H, Joshi W, Sklar J. The preemptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery. Anesth Analg 2002;94:55-9

15. Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362-79

16. Munro FJ, Young SJ, Broome IJ, Robb HM, Wardall GJ. Intravenous tenoxicam for analgesia following laparoscopic cholecystectomy. Anaesth Intensive Care 1998;26:56-60

17. Vanlersberghe C, Lauwers MH, Camu F. Preoperative ketorolac administration has no preemptive analgesic effect for minor orthopaedic surgery. Acta Anaesthesiol Scand 1996;40:948-52

18. Buggy DJ, Wall C, Carton EG. Preoperative or postoperative diclofenac for laparoscopic tubal ligation. Br J Anaesth 1994;73:767-70

19. Fraga A, de Almeida M, Moreira-da-Silva V, et al. Intramuscular etofenamate versus diclofenac in the relief of renal colic: A randomised, single-blind, comparative study. Clin Drug Investig 2003;23:701-6

20. Dannhardt G, Laufer S, Lehr M. HPLC determination of etofenamate and flufenamic acid in biological material. Clin Chem 1988;34:2580-1

21. O'Hanlon DM, Thambipillai T, Colbert ST, Keane PW, Given HF. Timing of pre-emptive tenoxicam is important for postoperative analgesia. Can J Anaesth 2001;48:162-6

22. O'Hanlon JJ, Muldoon T, Lowry D, McCleane G. Improved postoperative analgesia with preoperative piroxicam. Can J Anaesth 1996;43:102-5

23. Yamashita K, Fukusaki M, Ando Y, Fujinaga A, Tanabe T, Terao Y, Sumikawa K. Preoperative administration of intravenous flurbiprofen axetil reduces postoperative pain for spinal fusion surgery. J Anesth 2006;20:92-5

24. Norman PH, Daley MD, Lindsey RW. Preemptive analgesic effects of ketorolac in ankle fracture surgery. Anesthesiology 2001;94:599-603

25. Boccara G, Chaumeron A, Pouzeratte Y, Mann C. The preoperative administration of ketoprofen improves analgesia after laparoscopic cholecystectomy in comparison with propacetamol or postoperative ketoprofen. Br J Anaesth 2005;94:347-51

26. Coloma M, White PF, Markowitz SD, et. Dexamethasone in combination with dolasetron for prophylaxis in the ambulatory setting: effect on outcome after laparoscopic cholecystectomy. Anesthesiology 2002;96:1346-50

27. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162-84

28. Feo CV, Sortini D, Ragazzi R, De Palma M, Liboni A. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. Br J Surg 2006;93:295-9

29. Antonetti M, Kirton O, Bui P, et al. The effects of preoperative rofecoxib, metoclopramide, dexamethasone, and ondansetron on postoperative pain and nausea in patients undergoing elective laparoscopic cholecystectomy. Surg Endosc 2007;21:1855-61

30. Newcomb W, Lincourt A, Hope W, et al. Prospective, double-blinded, randomized, placebo-controlled comparison of local anesthetic and nonsteroidal anti-inflammatory drugs for postoperative pain management after laparoscopic surgery. Am Surg 2007;73:618-24