Surgery Journal 3 (5): 108-112, 2008
ISSN: 1816-3211

Effect of Intra-peritoneal Tenoxicam Prior to Pneumoperitineum on Post-Laparoscopic Cholecystectomy Pain: A Randomized, Clinical Trial

[1]Seyed Mehdi Jalali, [2]Karamollah Toulabi, [1]Shahraz Golbabaee and [1]Amir Hussein Lebaschi
[1]Department of Surgery, [2]Department of Anesthesiology,
Imam Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

Abstract: To assess the effect of preemptive administration of intra-peritoneal tenoxicam with or without lidocaine before CO_2 insufflation on the post-operative abdominal pain after laparoscopic cholecystectomy. Sixty patients were enrolled in a double-blind, randomized clinical trial. Patients were randomized into three groups of equal size: group A (infusion of 200 mL normal saline alone), group B (intra-peritoneal infusion of 20 mg tenoxicam in 200 mL normal saline) and group C (intra-peritoneal infusion of 20 mg tenoxicam and 200 mg lidocaine in 200 mL normal saline). Abdominal and shoulder pain were evaluated using VAS after surgery and at 6, 12 and 24 h post-operatively. Patients in group A and B had significantly lower abdominal and shoulder pain compared to group C. Patients in group B had significantly lower pain scores than group A. Incidence of nausea/vomiting and the time of GI function resumption were not significantly different among three groups. No adverse reaction was observed in any patient. Preemptive intra-peritoneal administration of tenoxicam as an anti-inflammatory agent, especially when combined with lidocaine, can significantly decrease pain after laparoscopic cholecystectomy.

Key words: Intra-peritoneal, post-laparoscopic, cholecystectomy pain, patients, abdominal and shoulder pain

INTRODUCTION

The majority of patients suffering from gall stone can be managed successfully by Laparoscopic Cholecystectomy (LC). Laparoscopic procedures, as compared to open surgeries, are associated with lesser degrees of tissue manipulation and damage and inflammatory responses of lower intensity, which translate into less post-operative pain and morbidity and a faster recovery (Attwood *et al*., 1993).

Theoretically, these features make LC an ideal procedure to be performed on an ambulatory basis (Mjaland *et al*., 1997), but in practice this end has not been achieved and most patients will stay overnight in the hospital (Berggren *et al*., 1994).

LC is yet a painful procedure. LC-associated pain is of such significant intensity that most patients still require opiod analgesia post-operatively (Mouton *et al*., 1999).

Post-LC pain seems to be multi-factorial. Bodily sites that are most subject to post-operative pain are port sites, right-upper quadrant (RUQ) and shoulder pain (Joris *et al*., 1995; Ure *et al*., 1994).

Factors that affect pain intensity include residual gas volume (Jackson *et al*., 1996), type of insufflated gas (Aitola *et al*., 1998), pneumo-peritoneum pressure (Wallace *et al*., 1997), gas temperature (Mraovic *et al*., 1997), gas volume and duration of the operation (Korell *et al*., 1995).

Many of the above-mentioned variables have been subject of active research. Two sets of studies have formed the basis of this article. The first set includes the work by Pasqualucci *et al*. (1996), who examined the concept of preemptive analgesia. They infused bupivacaine intra-peritoneally after creation of pneumopertoneum and compared the effect with the same intervention after completion of LC.

Later, Maestroni *et al*. (2000) infused ropivacaine intra-peritoneally before creation o f pneumo-pertoneum and compared the effect with the same intervention using placeboin patients undergoing LC.

The second set includes research by Elhakim *et al*. (2000), who examined the effect of intra-peritoneal infusion of tenoxicam after completion of LC.

The aim of this study is to examine the novel idea of the preemptive effect of an anti-inflammatory agent (tenoxicam) on post-LC pain.

Corresponding Author: Karamollah Toulabi, Department of Surgery, Imam Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

MATERIALS AND METHODS

The study protocol was approved by our local ethic committee and all the participants signed an informed consent.

Sixty patients were enrolled in Imam Hospital complex between January 2008 and March 2008. The inclusion criteria were ASA class I or II, pure gall stone disease without any other stone involvement and elective setting. Patients with history of asthma, gastric bleeding, renal impairment or concurrent non-steroidal anti-inflammatory drugs (NSAIDs) therapy, allergy to local anesthetics and general contra-indications for laparoscopic surgery.

This study was performed in a randomized, double blind fashion. Patients were randomized into three equal size groups. Group A was the control group, who received only 200 mL normal saline. Group B recived 200 mL normal saline plus 20 mg tenoxicam. Group C received 200 mL normal saline plus 20 mg tenoxicam and 200 mg lidocaine. Randomization was conducted using a computer program. Sixty small opaque envelopes, on which a number (1-60) was printed were used. Each envelope contained a small piece of paper denoting control, tenoxicam, or tenoxicam + lidocaine. Allocation was done by a technician outside study protocol, who picked the remaining envelope with the lowest number. After allocation, she prepared the serum bag and handed the tubing to the surgeon in a sterile fashion. Since, tenoxicam solution has a yellow tinge, all serum bags were covered with a black sac. The tinge was not discernible when the fluid flowed through the tubing.

Pre-operative data were recorded on a special dataform. The severity of biliary symptoms was graded according to McSherry *et al.* (1985), on a scale from 0-3: gastrointestinal symptoms not caused by gall stones; infrequent episodes of biliary colic without cholecystitis; frequent episodes of biliary colic, at intervals of about 1 month; acute cholecystitis or obstructive jaundice without acute cholecystitis.

Anesthesia was induced with 5-7 $\mu g\ kg^{-1}$ of fentanyl, 1-2 $mg\ kg^{-1}$ of propofol and 0.1 $mg\ kg^{-1}$ of vecuronium bromide. After tracheal intubation, general anesthesia was maintained with isoflorane and 50% air with oxygen.

Local anesthetic or placebo solution were administer before creation of the pneumoperitoneum in the abdominal cavity.

All surgeries were performed by a single surgeon. All procedures were carried out using 4 ports: a 10 mm umbilical, a 10 mm epigastric and two, 5 mm lateral ports. 0.5% bupivacaine was infiltrated at the site of each port before port insertion. First port was inserted using closed technique. After infusion, the patients was sequentially put into trendelenburg, anti-trendelenburg, left and right lateral position. Patient was allowed to stay in each position for 1 min. Then the abdomen was insufflated with CO_2, keeping the pressure between 12 and 15 mmHg. After the completion of the procedure, the gas was evacuated as much as possible and no attempt was made to suction the residual fluid. In the recovery room, all patients received 25 mg intra-muscular meperidine. During the post-operative period, all patients received dclofenac suppository (100 mg) 8 h after arrival to the ward. If required by the patient, 5 mg of intra-muscular morphine was administered. This was repeated just once as required.

Post-operative RUQ and shoulder pain were assessed using a 10 cm vertical Visual Analogue Scale (VAS), ranging from no pain at all to the worst pain imaginable, at recovery from anesthesia (T_0), 6, 12 and 24 h. Presence of nausea/vomiting and return of GI function (defined as audible bowel sound or presence of oral tolerance) were also recorded at these intervals. Occurrence of any adverse events was also noted. The assessors were ward nurses, who were not aware of the patient allocation. They were trained to record the data consistently.

Data were analysed using ANOVA and chi-square (χ^2) test using SPSS 12.00. 0.05 was considered statistically significant.

RESULTS

Demographic data as well as operative time in the three groups are summarized in Table 1. Patients of the three groups were not different regarding these variables. There was no difference between groups in this regard.

Figure 1 depicts the VAS scores for abdominal pain at various post-operative intervals. These scores were different among groups ($p<0.001$). The lowest scores

Table 1: Demographic data and operative time

	Group			
Variable	Tenoxicam +lidocaine	Tenoxicam	Control	p-value
Gender				
Male	5 (25%)	6 (30%)	3 (15%)	0.315
Female	15 (75%)	14 (70%)	17 (85%)	
Age (year)	53.62	44.64	47.08	0.364
Underlying condition				
Symptoms not caused by gall stones	0	7.1%	0	0.868
Infrequent episodes of colic	38.5%	28.6%	41.7%	
Frequent episodes of colic	53.8%	50%	50%	
Acute cholecystitis	7.7%	14.3%	8.3%	
Operative time (min)	25.62	23.27	23.57	0.577

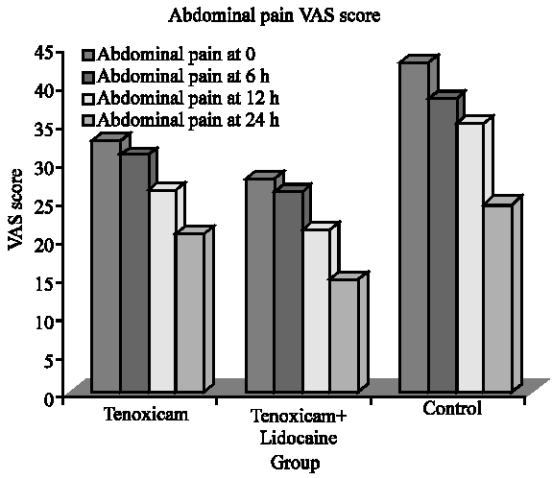

Fig. 1: Post-operative VAS scores for abdominal pain

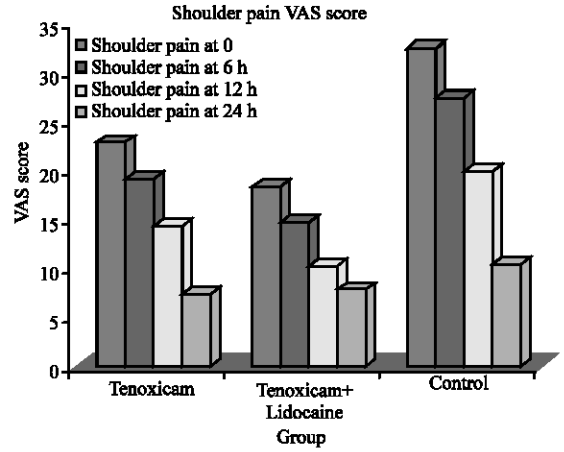

Fig. 2: Post-operative VAS scores for shoulder pain

belong to the combined tenoxicam plus lidocaine group. VAS scores were lower in the tenoxicam-only group compared to the control group.

Figure 2 demonstrates the VAS scores for shoulder pain at various post-operative intervals. These scores were different among groups ($p<0.001$). The lowest scores belong to the combined tenoxicam plus lidocaine group. VAS scores were lower in the tenoxicam-only group compared to the control group.

Incidence of post operative nausea/vomiting was not s ignificantly different among the three groups ($p = 0.266$). Also, time of resumption of the GI function was not significantly different among patients of different groups ($p = 0.206$).

All the patients received equal doses of analgesic during the 24 h after surgery. Only 2 patients in the control group received an additional dose of morphine.

No adverse event attributable to tenoxicam or lidocaine administration was noted. There was no difference in the time of discharge between groups.

DISCUSSION

Data obtained in this study shows that preemptive administration of an anti-inflammatory agent can lead to a lower degree of post-operative pain in LC patients. This could be due to decreased local levels of pro-inflammatory mediators that will cause pain either directly or indirectly through inflammation and tissue damage. Local application of tenoxicam may lead to rapid effective concentration in the inflamed tissues with less systemic effects.

Another finding was that addition of a local anesthetic to tenoxicam led to even lower intensities of pain. Lidocaine can block afferent impulses from sensory nerve endings regardless of the causation of the pain stimuli. These observations reinforce the multi-factorial genesis of post-laparoscopic pain and support the fact that each intervention can possibly alter pain experience of the patients in a unique or overlapping way.

Local application of NSAIDs have been found to be effective. In dental procedures, local application of aspirin has been effective to reduce pain (Moore *et al*., 1992).

Ketorolac has been demonstrated to be effected to reduce post-herniorrhaphy pain when applied locally and this analgesic effect was superior compared to intr-venous route (Ben-David *et al*., 1995).

There are some specific aspects of tenoxicam that merit mentioning. This agent is an oxicam NSAID that is highly hydrophilic with 99% protein binding (Heintz and Guentert, 1984; Nilsen, 1994).

These properties may help this drug to remain in the site of administration (e.g., inside peritoneal cavity) and lower the risk of adverse reactions subsequent to systemic absorption.

We did not observe any adverse reaction attributable to tenoxicam administration (e.g., gastric bleeding or renal impairment). The surgeon did not note increased bleading from surgical site and not bleeding event was observed post-operatively.

We also used 200 mg lidocaine for each patient that is well below the average dose of 5 mg kg^{-1}. In a report by Narchi *et al*. (1991), it was observed that systemic absorption of intra-peritoneal lidocaine is relatively slow after laparoscopy. In any case authors believe that the sample size of this study may not be

sufficiently large to make a definite conclusion about the safety of intra-peritoneal administration of tenoxicam and lidocaine.

In this study, it could be observed that preemptive intra-peritoneal administration of an anti-inflammatory agent could reduce the intensity of post-LC abdominal and shoulder pain. In the research by Elhakim *et al.* (2000), in which intra-peritoneal tenoxicam was administered after completion of the procedure, similar results were noted. They reported lower analgesic requirements and faster bowel function recovery in patients who received tenoxicam and Although, it has been shown in animal studies that interference with prostaglandin synthesis through intra-peritineal administration of tenoxicam may decrease post-operative adhesions and bowel distension (Celebioglu *et al*., 1999; Yilmazlar *et al*., 1996), these latter results were not noted in this study.

CONCLUSION

In this study, the authors attempted to examine a novel concept of preemptive analgesia and extend this technique to include an anti-inflammatory agent. Some theoretical expectations including reduced need for post-operative analgesia and shorter interval before resumption of GI function were not observed in this study. Further trials enrolling larger number of patients may help to resolve these issues.

REFERENCES

Aitola, P., I. Airo, S. Kaukinen and S. Ylitalo, 1998. Comparison of N_2O and CO_2 pneumoperitoneums during laparoscopic cholecystectomy with special reference to postoperative pain. Surg. Laparos Endosc., 8: 140-144. PMID: 9566570.

Attwood, S.E., A.D. Hill, K. Mealy and R.B. Stephens, 1993. A prospective comparison of laparoscopic versus open cholecystectomy. Ann. R. Coll. Surg. Engl., 75 (4): 299. PMID: 8379639.

Ben-David, B., E. Katz, I. Gaitini and Z. Goldik, 1995. Comparison o f I.M. and local infiltration of ketorolac with and without local anaesthetic. Br. J. Anaesth., 75 (4): 409-412. PMID: 7488478.

Berggren, U., T. Gordh, D. Grama, U. Haglund, J. Rastad and D. Arvidsson, 1994. Laparoscopic versus open cholecystectomy: Hospitalization, sick leave, analgesia and trauma responses. Br. J. Surg., 81 (9): 1362-1365. PMID: 7953415.

Celebioglu, B., N.R. Eslambouli, E. Olcay and S. Atakan, 1999. The effect of tenoxicam on intraperitoneal adhesion and prostaglandin E_2 levels in mice. Anesth. Analg., 88 (4): 939-942. PMID: 10195553.

Elhakim, M., H. Amine, S. Kamel and F. Saad, 2000. Effects of intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after laparoscopic cholecystectomy. Acta Anaesthesiol. Scand., 44 (8): 929-933. PMID: 10981568.

Heintz, R.C. and T.W. Guentert, 1984. Pharmacokinetics oftenoxicam inhealthyhuman volunteers. Eur. J.Drug. Metab.Pharmacokinet., 12 (1): 59-63. PMID: 3497039.

Jackson, S.A., A.S. Laurence and J.C. Hill, 1996. Does post-laparoscopy pain relate to residual carbon dioxide? Anaesthesia, 51 (5): 485-487. PMID: 8694166.

Joris, J., E. Thiry, P. Pris, J. Weerts and M. Lamy, 1995. Pain after laparoscopic cholecystectomy: characteristics and effects of intraperitoneal bupivacaine. Anesth. Analg., 81: 379-384. PMID: 7618731.

Korell, M., F. Schmaus, T. Strowitzki, S.G. Schneeweis and H. Hepp, 1995. Pain intensity following laparoscopy. Surg. Laparosc. Endosc., 6: 375-379. PMID: 8890423.

Maestroni, U., D. Sortini, C. Devito, P.M.K.F. Brunaldi, G. Anania, L. Pavanelli, A. Pasqualucci and A. Donini, 2002. A new method of preemptive analgesia in laparoscopic cholecystectomy. Surg. Endosc., 16 (9): 1336-1340. PMID: 11988800.

McSherry, C., H. Ferstenberg, F. Calhoun, E. Lahman and M. Virshup, 1985. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. Ann. Surg., 202: 59-63. PMID: 4015212.

Mjaland, O., J. Reader, V. Aasboe, E. Trondsen and T. Buanes, 1997. Outpatient laparoscopic cholecystectomy. Br. J. Surg., 84 (7): 958-961. PMID: 9240135.

Moore, U.J., R.A. Seymour and M.D. Rawlins, 1992. The efficacy of locally applied aspirin and acetaminophen in postoperative pain after third molar surgery. Clin. Pharmacol. Ther., 52: 292-296. PMID: 1526087.

Mouton, W.G., J.R. Bessel, K.T. Otten and G.J. Maddern, 1999. Pain after laparoscopy. Surg. Endosc., 13 (5): 445-448. PMID: 10227938

Mraovic, B., T. Jurisic, V. Kogler-Majeric and A. Sustic, 1997. Intraperitoneal bupivacaine for analgesia after laparoscopic cholecystectomy. Acta. Anaaesthesiol. Scand., 41: 193-196. PMID: 9062598.

Narchi, P., D. Benhamou and H. Fernandez, 1991. Intraperitoneal local anaesthetic for shoulder pain after day-case laparoscopy. Lancet., Dec 21-28; 338 (8782-8783): 1569-1570. PMID: 1683981.

Nilsen, O.G., 1994. Clinical pharmacokinetics of tenoxicam. Clin. Pharmacokinet., 26 (1): 16-43. PMID: 8137596.

Pasqualucci, A., V. de Angelis, R. Contardo, F. Colo, G. Terrosu, A. Donini, A. Pasetto and F. Bresadola, 1996. Preemptive analgesia: Intraperitoneal local anaesthetic in laparoscopic cholecystectomy; a randomized double-blind, placebo-controlled study. Anesthsiology, 85: 11-20. PMID: 8694355.

Ure, B.M., H. Troidl, W. Spangenberger, E. Dietrich, R. Lefering and E. Neugebauer, 1994. Pain after laparoscopic cholecystectomy: Intensity and localization of pain and analysis of predictors in preoperative symptoms and intraoperative events. Surg. Endosc., 8: 90-96. PMID: 8165491.

Wallace, D.H., M.G. Serpell, J.N. Baxter and P.J. O'swyer, 1997. Randomized trial of different insufflation pressures for laparoscopic cholecystectomy. Br. J. Surg., 84: 455-458. PMID: 9112891.

Yilmazlar, T., E. Kaya, E. Gurpinar and H. Emiroglu, 1996. Efficacy of tenoxicam on intraabdominal adhesion prevention in a rat model. J. Int. Med. Res., 24 (4): 352-357. PMID: 8854289.