# INTRAPERITONEAL BUPIVACAINE-KETOROLAC FOR POSTOPERATIVE PAIN CONTROL AFTER LAPAROSCOPIC COLORECTAL SURGERY: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

Ahmed H. Bakeer[1], Nasr M. Abdallah[2] and Mahmoud A. Kamel[3]

## Abstract

**Background**: The study aimed to evaluate the antinociceptive effect of intraperitoneal ketorolac combined with bupivacaine in patients undergoing laparoscopic colectomy.

**Methods**: This prospective randomized double-blind controlled trial included 60 adults scheduled for laparoscopic colectomy randomized into one of two groups according to the analgesic instilled intraperitoneally at the end of surgery. Group B (n = 30) received 50 ml of intraperitoneal (IP) bupivacaine 0.25% + 5 ml of normal saline. Group KB (n=30) received 50 ml of intraperitoneal bupivacaine 0.25% + 30 mg ketorolac in 5 ml of normal saline. Postoperative pain intensity was measured by visual analogue scale (VAS) score. The time to the first request of analgesia and total morphine consumption were recorded in addition to PONV score.

**Results:** During the whole postoperative period, compared to group B, the VAS score was significantly lower ($p < 0.001$), time to first request of analgesia was significantly longer ($p < 0.001$) and total morphine consumption was significantly lower in KB group ($p < 0.001$). Postoperative nausea and vomiting score was significantly higher in Group B ($p = 0.001$).

**Conclusion**: Intraperitoneal instillation of a combination of bupivacaine 0.25% and ketorolac is a safe and effective option for postoperative analgesic following laparoscopic colectomy in cases colon cancer.

**Keywords:** NSAIDs, Intraperitoneal, Laparoscopy, Colorectal surgery

## Introduction

Open colectomy is considered the principal operation for colorectal (CR) cancer. However currently laparoscopic surgery is often considered a treatment option for several malignant and benign colorectal diseases[1]. Laparoscopic colectomy has been shown to be associated with less postoperative analgesic requirement, more rapid bowel function recovery, and shorter hospital stay[2].

1 Lecturer of Anesthesia and Pain Relief, National Cancer Institute, Cairo University.
2 Assistant Professor of Anaesthesia, Faculty of Medicine, Cairo University
3 Lecturer of Anesthesia and Pain Relief, National Cancer Institute, Cairo University.
**Corresponding Author:** Ahmed H. Bakeer: Department of Anaesthesia and Pain Relief, National Cancer Institute, Egypt. Address: 13 Mohamed Shokry street - Agouza - Giza. Tel: +20233360906. E-mail address: mailbox_mcs@yahoo.com

Numerous randomized controlled trials (RCTs) suggested that the short- and long-term outcomes of laparoscopic and open surgery for CR cancer were comparable[3-6]. The Japan Clinical Oncology Group (JCOG) reported that the survival outcomes were similar following laparoscopic versus open dissection for stage II or III colon cancer[7].

Optimal postoperative pain control is vital for both patients' comfort and rapid recovery. Return of bowel function and consequently tolerance of oral feeding is influenced by postoperative pain following CR resection[8]. It is recommended to avoid opioids after CR surgery due to their known gastrointestinal side effects including nausea and vomiting and delayed bowel motility[9].

For open CR surgery, pain relief methods include thoracic epidural analgesia (TEA), patient-controlled analgesia (PCA), intrathecal analgesia, systemic lidocaine infusions, wound infiltration, and transversus abdominis plane block[9]. Conversely, there is no sufficient evidence for postoperative analgesia after laparoscopic CR surgery. A meta-analysis of 7 RCTs reported that epidural analgesia is a good analgesic option during the initial period after laparoscopic CR surgery with no significant benefit in return of bowel function[10].

Intraperitoneal instillation of local anesthetics has been used in other types of laparoscopic surgery. A systematic review of 13 trials comparing local anesthetics after laparoscopic cholecystectomy showed a significant reduction in pain scores in seven studies[11]. A pilot case-control study investigated the analgesic efficacy of intraperitoneal irrigation of bupivacaine following gynecological operative laparoscopy in 20 women. The authors found that this method can reduce postoperative pain and analgesic requirements at least during the first 10 hours after surgery[12].

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent antinociceptive agents widely used as adjuncts in post-surgical pain. According to published findings, peripheral and central mechanisms are involved in the antinociceptive action of these drugs. NSAIDs inhibit prostaglandin synthesis at the site of peripheral inflammation and in the CNS as well[13]. Ketorolac, a NSAID with localized anti-inflammatory and analgesic properties is currently used as a perioperative analgesic alone or combined with local anesthetics[14,15].

Therefore, the aim of this study was to evaluate the antinociceptive effects of intraperitoneal ketorolac combined with bupivacaine in patients undergoing laparoscopic colectomy.

## Patients and Methods

This prospective randomized double-blind controlled trial was done in the National Cancer Institute, Cairo, Egypt during the period from April 2017 to November 2017. After approval from the local Institutional Ethical Committee (IRB approval number 201617012.2P), 60 adult patients scheduled for laparoscopic colorectal surgery were included in the study and all patients provided written informed consents before surgery. Patients aged 18-60 years, American Society of Anesthesiologists (ASA) physical status class I, II or III with satisfactory laboratory findings (CBC, liver functions, renal functions and coagulation profile) were included in the study. Exclusion criteria were allergy to study drugs (Bubivacaine and ketorolac), impaired liver or renal functions, severe cardiopulmonary impairment and patients underwent open colectomy after laparoscopic starting.

Preoperatively, in the preparation area, an intravenous catheter (18-gauge) was introduced to all patients and 500 ml Ringer's solution were infused, then 3 mg midazolam were given before patients being transported to the operating room. Intraoperatively, basic monitoring was connected to patients (non-invasive blood pressure, capnography, pulse-oximetry and 5-leads ECG), radial artery (in either hand) was then cannulated and invasive blood pressure was monitored, baseline findings were recorded.

General anesthesia was induced by giving fentanyl 1.5 µg/kg, propofol 2.5 mg/kg followed by atracurium besylate 0.5 mg/kg to facilitate orotracheal intubation with cuffed tube of appropriate size. Patients' ventilation was then maintained mechanically by GE anesthesia machine. Anesthesia was maintained with 100% oxygen with 1.2-2% isoflurane. Intermittent boluses of atracurium 0.1 mg/kg were given to achieve muscle relaxation.

Tidal volume of 6 ml/kg with respiratory rate 14 per minute was adjusted and manipulated according to end-tidal carbon-dioxide ($EtCO_2$) to maintain normocapnia, i.e. ($EtCO_2$) between 34 and 38 mmHg. A nasogastric tube of appropriate size was then inserted and secured in place with plaster tape.

Ringer acetate solution was given to cover fasting, deficit and lost fluids. Blood and plasma were given if there was major blood loss. Blood pressure fluctuations (Hypotension/hypertension) were defined as (fall/rise) in mean arterial pressure MAP of >20% from the baseline values. These fluctuations were managed as per our clinical standard practice.

Patients were placed in supine position with legs apart. During laparoscopy, after induction of pneumoperitoneum, a 10 mm trocar is inserted in the upper midline, and a laparoscopic exploration of the abdomen performed in order to choose the most suitable procedure and position of the remaining trocars. Other trocars were then inserted to facilitate introduction of surgical tools until resection is completed. Intra-abdominal $CO_2$ insufflation was adjusted to maintain intra-abdominal pressure at 14 mm Hg.

Patients were randomly grouped into two groups according to randomization table. Group B (n = 30) received 50 ml of intraperitoneal (IP) bupivacaine 0.25% + 5 ml of normal saline. Group KB (n=30) received 50 ml of intraperitoneal bupivacaine 0.25% + 30 mg ketorolac in 5 ml of normal saline. The anesthesiologist who prepared the study drugs was not involved in the study. On the other hand the anesthesiologist and the surgeon who observed the patient were unaware of the study group until the end of the study. After removal of the specimen and after adequate hemostasis, the prepared solutions of the study drugs were instilled diffusely intraperitoneally then the trocar was removed and incisions were sutured. The neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and atropine 0.01 mg/kg and endotracheal tube was removed. Patients were then transferred to post-anesthesia care unit (PACU) until criteria of discharge were fulfilled. Pulse and blood pressure were monitored during the first 24 postoperative hours.

The primary outcome was postoperative pain intensity measured by visual analogue scale (VAS) score. The secondary outcomes were time to the postoperative first analgesic request, total morphine dose given in the 1st postoperative day and any adverse effects, the percentage increase of MAP compared to baseline readings. **Postoperative nausea and vomiting was evaluated with** PONV score (0 none, 1 mild, 2 moderate, 3 severe).

Before surgery, patients were informed about VAS score (VAS score 0 - no pain, VAS score 10 - worst possible pain). The VAS score was recorded at 1, 2, 6, 12, 24 h after surgery.

IV morphine dose of 0.05 mg/kg was given to patients who reported VAS score of 3 or more and asked for analgesia. Paracetamol 1 gm infusion was given to patients who asked for analgesia with VAS score less than 3 or as an adjuvant to morphine.

Postoperative nausea and vomiting was observed and patients who suffered nausea or vomiting were given ondansetron 4 mg IV. Time to the first analgesic request (considering the extubation as time 0), total dose of morphine given and adverse effects like nausea and vomiting, sedation over 24 h postoperatively were noted.

## Sample Size Estimation

In a previous study[16], the addition of ketorolac to intraperitoneal bupivacaine reduced VAS score of abdominal pain from 4.0±1.5 to 2.7±1.9. Based on the results of this study, a sample of 29 patients in each group is required to elicit the difference at an alpha level of 0.05 and a power of the study of 80%. Sample size was calculated using the G*Power© software (Institutfür Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany) version 3.1.9.2.

## Statistical Analysis

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Comparison between the two groups was done using independent sample t-test or Mann-Whitney test as

*Table 1*

*Age, body mass index, and duration of the procedure of the two studied groups. Data is presented as mean ± standard deviation*

| | **Group B (n=30)** | **Group KB (n=30)** | **p-value** |
|---|---|---|---|
| Age (years) | 58.4±4.5 | 59.0±3.7 | 0.575 |
| Body mass index (kg/m$^2$) | 24.4±3.7 | 24.7±3.1 | 0.742 |
| Baseline mean arterial pressure (mmHg) | 83±8 | 82±8 | 0.701 |
| Duration procedure (min.) | 145±11 | 138±19 | 0.086 |

appropriate. All tests were two-tailed. A p-value < 0.05 was considered significant.

## Results

Table (1) shows baseline characteristics of the two studied groups. There was no significant difference between the two groups regarding age, BMI and procedure duration. Left colectomy was done in 22 patients and the remaining eight had right colectomy.

During the whole postoperative period, the VAS score was significantly lower in Group KB compared to Group B (Table 2). The time to first request of analgesia was significantly longer in Group KB compared to Group B (p < 0.001).The total morphine consumption during the first postoperative 24 hours was significantly lower in Group KB compared to group B (p < 0.001).

The percentage increase of MAP compared to baseline readings was significantly higher in Group B compared to Group KB after 2 and 12 hours (Table 2). Postoperative nausea and vomiting score was significantly higher in Group B compared to Group KB (p = 0.001).

## Discussion

The results of this study demonstrated analgesic effectiveness of intraperitoneal instillation of a

*Table 2*

*Pain score, morphine consumption and PONV score in the two studied groups. Data is presented either as median (range) or mean ± standard deviation*

| | **Group B (n=30)** | **Group KB (n=30)** | **p-value** |
|---|---|---|---|
| VAS score | | | |
| After 1 hour | 4 (1-8) | 2 (1-5) | < 0.001 |
| After 2 hours | 4 (2-7) | 2 (1-4) | < 0.001 |
| After 6 hours | 4 (2-6) | 2 (1-4) | < 0.001 |
| After 12 hours | 4 (2-6) | 2 (1-4) | < 0.001 |
| After 24 hours | 4 (2-7) | 3 (1-6) | 0.005 |
| Percentage increase of MAP | | | |
| After 2 hours | 22.1±8.9 | 15.8±5.9 | 0.009 |
| After 6 hours | 19.2±5.5 | 15.6±7.0 | 0.128 |
| After 12 hours | 23.7±9.3 | 17.2±6.2 | 0.013 |
| After 24 hours | 21.9±8.0 | 23.8±9.4 | 0.273 |
| Time to first request of analgesia (hrs) | 6 (4-18) | 16 (4-24) | < 0.001 |
| Total Morphine consumption (mg) | 5 (0-6) | 0 (0-3) | < 0.001 |
| PONV score | 2 (0-3) | 1 (0-3) | 0.001 |

combination of bupivacaine 0.25% and ketorolac following laparoscopic CR surgery for colon cancer. The addition of ketorolac to intraperitoneal local anesthesia produced better analgesia and more reduction of opioid consumption and postoperative nausea and vomiting.

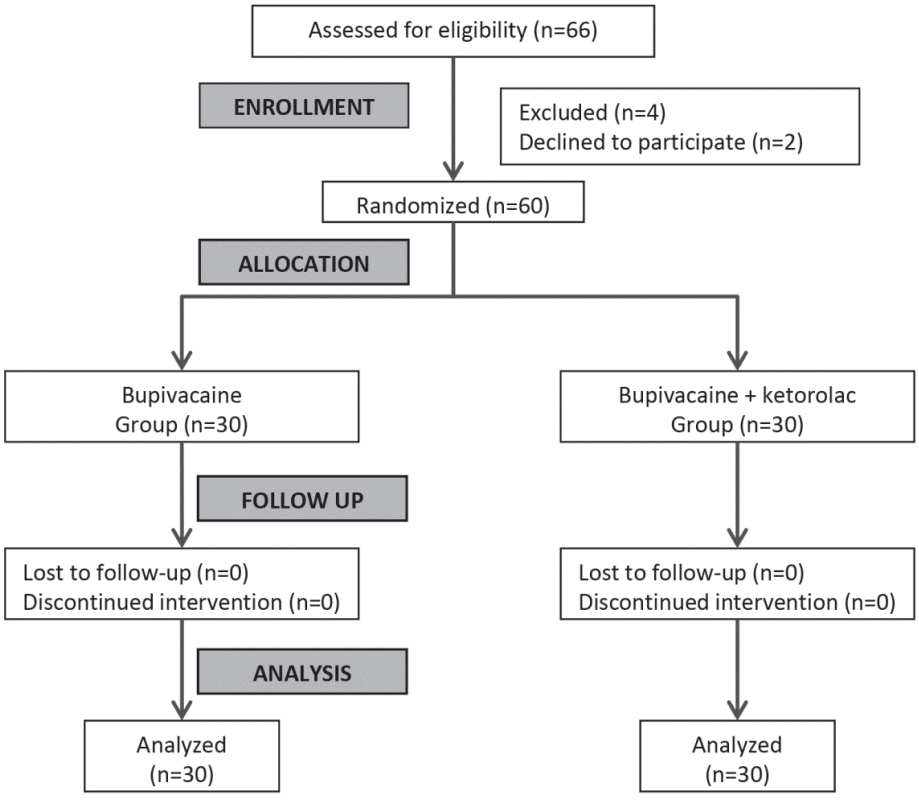
The optimal analgesic modality after laparoscopic CR surgery is yet to be determined. The most popular type used after open CR surgery is TEA. One meta-analysis included 7 RCTs that compared the effect of TEA and PCA following laparoscopic colectomy. TEA resulted in significantly lower pain intensity and lower risk in nausea and vomiting with no significant benefits in return of bowel function[10]. On the other hand, another systematic review of six RCTs for the effect of TEA on laparoscopic CR surgery found that it significantly reduced pain and improved return of bowel function[17].

A retrospective review of CR cases managed laparoscopically in the United States identified limited use of epidural analgesia. But, it was more likely to be used in cancer cases. Epidural analgesia was associated with a longer hospital stay, higher hospital costs and higher rate of urinary tract infection[18].

Successful analgesic management is based on better understanding of mechanisms of pain. Pain after laparoscopy is believed to be multifactorial. These factors include the volume of residual gas[19], the pressure created by the pneumoperitoneum[20], and the temperature of insufflated gas[21]. The rate and total volume of insufflated carbon dioxide can influence the incidence of postoperative pain[22,23]. Other proposed mechanisms include diaphragmatic stretching, with phrenic nerve neuropraxia[20], neuropathic pain elicited by chemical irritation, ischemia and compression, Intraperitoneal acidosis has also been documented in humans after carbon dioxide pneumoperitoneum[24].

Therefore, these suggested mechanisms persuade the use of IP analgesics to combat the local effects of pneumoperitoneum that may be the principal source of pain following laparoscopy. Based on the controversial results of analgesic benefit of IP local anesthetics in different types of laparoscopic surgery, the current

*Fig. 1*
*CONSORT Flow Diagram*



study proposed a multimodal local analgesia using a combination of bupivacaine and ketorolac.

Nonsteroidal anti-inflammatory drugs(NSAIDs) have shown localized anti-inflammatory and analgesic properties through the inhibition of prostaglandin synthesis directly at the site of tissue trauma[25]. The topical application of NSAIDs was found to inhibit peripheral N-methyl D-aspartate (NMDA)activity[26].

Elhakim et al.[27] have reported comparable pain reduction with IP and IV tenoxicam combined with lidocaine after laparoscopic cholecystectomy. The IP route only reduced the time to first analgesic request. However, Jabbour-Khoury et al.[16] found IP local anesthesia combined with IV ketoprofen was better than IP ketoprofenin terms of reduced requirements for rescue analgesia and reductions in nausea and vomiting.

More recently, Murdoch et al. compared the postoperative analgesic effect of 30 mg of ketorolac administered IP vs. the same dose intravenously following laparoscopic cholecystectomy. The authors concluded that IP and IV ketorolac had comparable analgesic efficacy[28]. Compared to control placebo group, IP ketorolac reduced opioid consumption and delayed the time to first request of analgesia. However, the analgesic effect of ketorolac was relatively short and reduction of pain score was small.

In conclusion, in cases of colon cancer undergoing laparoscopic colectomy, intraperitoneal instillation of a combination of bupivacaine 0.25% and ketorolac is a safe and effective option to provide a good postoperative analgesia along the first 24 postoperative hours with minimal adverse effects. The addition of the NSAID ketorolac to the intraperitoneal local anesthetic augments its analgesic efficacy with reduced opioid consumption and postoperative nausea and vomiting.

## References


1. Luglio G, De Palma GD, Tarquini R, Giglio MC, Sollazzo V, Esposito E, Spadarella E, Peltrini R, Liccardo F, Bucci L: Laparoscopic colorectal surgery in learning curve: Role of implementation of a standardized technique and recovery protocol. A cohort study. *Ann Med Surg (Lond)*; 2015, 4:89-94.
2. Ahad S, Figueredo EJ: Laparoscopic colectomy. *Med Gen Med*; 2007, 9:37.
3. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM: MRC CLASICC TRIAL group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet*; 2005, 365:1718-1726.
4. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM: UK MRC CLASICC Trial Group. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol*; 2007, 25:3061-3068.
5. Colon Cancer Laparoscopic Or Open Resection Study Group, Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ: Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol*; 2009, 10:44-52.
6. Nakao T, Shimada M, Yoshikawa K, Higashijima J, Tokunaga T, Nishi M, et al: Propensity score-matched study of laparoscopic and open surgery for colorectal cancer in rural hospitals. *J Gastroenterol Hepatol*; 2016, 31:1700-1704.
7. Kitano S, Inomata M, Mizusawa J, Katayama H, Watanabe M, Yamamoto S, et al: Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol*; 2017, 2:261-268.
8. Cali RL, Meade PG, Swanson MS, Freeman C: Effect of Morphine and incision length on bowel function after colectomy. *Dis Colon Rectum*; 2000, 43:163-168.
9. Patel S, Lutz JM, Panchagnula U, Bansal S: Anesthesia and perioperative management of colorectal surgical patients - A clinical review (Part 1). *J Anaesthesiol Clin Pharmacol*; 2012, 28:162-171.
10. Liu H, Hu X, Duan X, Wu J: Thoracic epidural analgesia (TEA) vs. patient controlled analgesia (PCA) in laparoscopic colectomy: a meta-analysis. *Hepatogastroenterology*; 2014, 61:1213-1219.
11. Møiniche S, Jørgensen H, Wetterslev J, Dahl JB: Local anesthetic infiltration for postoperative pain relief after laparoscopy: a qualitative and quantitative systematic review of intraperitoneal, port-site infiltration and mesosalpinx block. *Anesth Analg*; 2000, 90:899-912.
12. Buck L, Varras MN, Miskry T, Ruston J, Magos A: Intraperitoneal bupivacaine for the reduction of postoperative pain following operative laparoscopy: a pilot study and review of the literature. *J Obstet Gynaecol*; 2004, 24:448-451.
13. Burian M, Geisslinger G: COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. *Pharmacol Ther*; 2005, 107:139-154.
14. Mahabir RC, Peterson BD, Williamson JS, Valnicek SM, Williamson DG, East WE: Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients: part II. 10-day follow-up. *Plast Reconstr Surg;* 2008, 121:638-643.
15. Chen J-Y, Feng I-J, Loh E-W, Wang LK, Lin CC, Tam KW: Analgesic Effects of Locally Administered Ketorolac-Based Analgesics after Breast Surgery: A Meta-Analysis of Randomized Controlled Trials. *Clin J Pain*; Epub ahead of print 14 September 2017.
16. Jabbour-Khoury SI, Dabbous AS, Gerges FJ, Azar MS, Ayoub CM, Khoury GS: Intraperitoneal and intravenous routes for pain relief in laparoscopic cholecystectomy. *JSLS*; 2005, 9:316-321.
17. Khan SA, Khokhar HA, Nasr ARH, Carton E, El-Masry S: Effect of epidural analgesia on bowel function in laparoscopic colorectal surgery: a systematic review and meta-analysis. *Surg Endosc*; 2013, 27:2581-2591.
18. Halabi WJ, Kang CY, Nguyen VQ, Carmichael JC, Mills S, Stamos MJ, Pigazzi A: Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. *JAMA Surg*; 2014, 149:130-136.
19. Jackson SA, Laurence AS, Hill JC: Does post-laparoscopy pain relate to residual carbon dioxide? *Anaesthesia*; 1996, 51:485-487.
20. Wallace DH, Serpell MG, Baxter JN, O'dwyer PJ: Randomized trial of different insufflation pressures for laparoscopic cholecystectomy. *Br J Surg*; 1997, 84:455-458.
21. Mouton WG, Bessell JR, Millard SH, Baxter PS, Maddern GJ: A randomized controlled trial assessing the benefit of humidified insufflation gas during laparoscopic surgery. *Surg Endosc*; 1999, 13:106-108.
22. Berberoğlu M, Dilek ON, Ercan F, Kati I, Ozmen M: The effect of CO2 insufflation rate on the post-laparoscopic shoulder pain. *J Laparoendosc Adv Surg Tech A*; 1998, 8:273-277.
23. Perry CP, Tombrello R: Effect of fluid instillation on postlaparoscopy pain. *J Reprod Med*; 1993, 38:768-770.
24. Wills VL, Hunt DR: Pain after laparoscopic cholecystectomy. *Br J Surg*; 2000, 87:273-284.
25. Balmaceda CM: Evolving guidelines in the use of topical nonsteroidal anti-inflammatory drugs in the treatment of osteoarthritis. *BMC Musculoskelet Disord*; 2014, 15:27.
26. Dong X-D, Svensson P, Cairns BE: The analgesic action of topical diclofenac may be mediated through peripheral NMDA receptor antagonism. *Pain*; 2009, 147:36-45.
27. Elhakim M, Amine H, Kamel S, Saad F: Effects of intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand*; 2000, 44:929-933.
28. Murdoch J, Ramsey G, Day AG, Mcmullen M, Orr E, Phelan R, Jalink D: Intraperitoneal ketorolac for post-cholecystectomy pain: a double-blind randomized-controlled trial. *Can J Anaesth J Can Anesth*; 2016, 63:701-708.