WOUND INFILTRATION WITH KETOROLAC VERSUS LIDOCAINE AFTER ABDOMINAL HYSTERECTOMY: PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND STUDY

Marwa M. Mowafi[1], Marwa AK. Elbeialy[1] and Amr A. Riad[2]

Abstract

Background: Ketorolac (a non-steroidal anti-inflammatory drug) could be a safe and effective alternative to local anesthetics for wound infiltration. The goal of this study was to compare between ketorolac and lidocaine for wound infiltration to provide postoperative analgesia after total abdominal hysterectomy (TAH).

Materials and Methods: Eighty female patients of American Society of Anesthesiologists (ASA) I-II scheduled for TAH were randomly distributed into 2 groups: Group K (n = 40) received wound infiltration with ketorolac 30 mg in 20 ml saline and Group L (n = 40) their wound was infiltrated with 20 ml of 1% lidocaine at the end of surgery. A standard general anesthesia technique was used in all patients. The time for first analgesia requirement, pain scores, the opioid consumption and patient satisfaction in the first 24 h postoperatively were compared between both groups.

Results: Ketorolac group experienced a longer postoperative pain free period. Total opioid consumption and pain scores were significantly less in the ketorolac group as compared to lidocaine group while satisfaction of patients was higher in the ketorolac group.

Conclusion: Ketorolac was superior to provide postoperative analgesia in patients undergoing TAH with more patient satisfaction when compared to lidocaine.

Keywords: ketorolac, lidocaine, wound infiltration, postoperative analgesia, hysterectomy.

Introduction

Acute post-operative pain management for total abdominal hysterectomy (TAH) has received special attention over the last years[1-3]. It continues to be challenging and often contributes to patient anxiety and dissatisfaction if inadequately treated[4,5]. Wound infiltration is considered a method for postoperative analgesia that is commonly used alone or as part of multiple regimen for perioperative pain management. It is an easy and effective mean of excellent pain control for diverse types of surgeries as it helps to reduce opioid consumption and its associated adverse reactions such as respiratory depression, puritus, nausea and vomiting and urinary retention[6].

Lidocaine is a widely used amide local anesthetic for wound infiltration due to its rapid onset

1 MD, Department of Anesthesiology, Intensive care and Pain Management, Faculty of Medicine, Ain-Shams University, Cairo, Egypt.

2 MD, Department of Obstetrics and Gynecology Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Corresponding Author: Dr. Marwa Ahmed Khairy Elbeialy, Department of Anaesthesiology, Intensive care and Pain Management, Faculty of Medicine, Ain-Shams University, Abbassia, Postal code: 11591, Cairo, Egypt. Tel: +20 1006518802. E-mail: mar_khairy@yahoo.com

Conflict of Interest: the authors declare no conflict of interest.

and low cardiotoxicity. It was first introduced into clinical practice since 1943[7]. It leads to pain relief, has anti-hyperalgesic[8] and anti-inflammatory effects[9]. It is known to have intermediate duration of action[10].

Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) which acts by suppression of formation of prostaglandins, is said to have pain relieving properties comparable with opioids like morphine[11-14]. Recent studies showed that its local application could be a safe route for provision of analgesia while reducing the possibility of systemic effects[15,16].

The aim of the current study is to compare wound infiltration with ketorolac versus lidocaine for postoperative analgesia in TAH operation in regard their efficacies and their adverse effects.

Materials and Methods

The study is a randomized, double-blind and prospective study and that was conducted in gynecology and obstetrics hospital at Ain-Shams University. After approval of the study protocol by the Ethical Research Committee at Ain Shams University and obtaining informed consents, eighty females of age 20-60 years and ASA physical status I and II planned for elective TAH were included. Patients with the following criteria were excluded from the study: ASA physical status more than II, body mass index (BMI) >35 kg/m^2, previous abdominal surgeries, malignancy, individuals with chronic pain, a history of severe systemic disease, a pre-existing neurological or psychiatric illness, known to be addict on alcohol or drugs or known allergy to the study drugs. All operations were done by the same surgical team.

Comprehensive preoperative evaluation was done for all patients on the day before the operation. Randomization was done by computer-generated random numbers and concealed by sealed envelope technique. The patients were randomly distributed into one of the following groups:

- Group L (n = 40): wound infiltration with 20 ml of 1% lidocaine (Lidocaine Hydrochloride; Lidocaine HCL 50 mg/5 ml produced by Pharco B International for Pharco Pharmaceuticals, Alexandria, Egypt).
- Group K (n = 40): wound infiltration with ketorolac (Adolor; Ketorolac tromethamine 30 mg/2 ml produced by Pharco B International for Pharco Pharmaceuticals, Alexandria, Egypt) 30 mg in 20 ml saline.

The person who prepared the study drugs was blinded to the study protocol and did not participate in data recording.

In the operating room, insertion of a peripheral IV cannula was done and ringer's lactate solution infusion was started. Patients were premedicated using 0.05-0.1 mg/kg midazolam, 50 mg ranitdine, and 0.1 mg/kg ondansetron administered intravenously. Patients were monitored using electrocardiogram (ECG), non-invasive automated arterial blood pressure, pulse oximetry and capnography.

After preoxygenation, fentanyl 2 µg/kg was administered slowly IV then induction of general anesthesia took place with propofol 2 mg/kg. Intubation was done by administration of atracurium 0.5 mg/kg, and maintenance of anesthesia was achieved by isoflurane 1.25% in oxygen adjusted as clinically required. The patients were mechanically ventilated by intermittent positive pressure ventilation to keep normocapnia.

Mean arterial pressure (MAP) and heart rate (HR) were maintained within 20% of their value before surgery. Hypotension (MAP 20% below its basal level) was treated with fluid bolus of ringer lactate or ephedrine 6 mg IV boluses if needed. If bradycardia (HR less than 60 beats/min) occurred, atropine 0.5 mg IV was given.

Before skin closure, the subcutaneous tissue and skin all around the wound were infiltrated by 20 ml of 1% Lidocaine in Group L and 20 ml of saline with 30 mg ketorolac in Group K then closure of the skin was done.

At the end of operation, neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were given to reverse neuromuscular blockade. The trachea was extubated on fulfilling the standard criteria. The patients were transferred to the postanesthesia care unit then to ward after meeting the discharge criteria, where they were observed by an anesthesiologist who was blinded for the group assignment for 24 h. Pain score was done by

visual analog scale (VAS) (0 = no pain, while 10 cm = worst possible pain). Pain score was recorded just after extubation (taken as 0 h) and after 1, 2, 4, 6, 12, 18 and 24 h later. Patients were instructed about the VAS score before the operation.

Postoperative analgesia was provided with IV pethidine 50 mg to both groups when the VAS score is ≥4. The time for the first analgesic requirement (Rescue analgesia time) and the total opioid consumption were recorded. The total duration of study was 24 h from the time of extubation.

The patients were also inspected for analgesia satisfaction using five-point Likert score in the ward by an anesthetist blind to the study where (1: excellent, 2: very good, 3: good, 4: fair, 5: poor). The incidence of postoperative complications related to the study drugs was recorded.

Our primary outcome was the time for first analgesia requirement while secondary outcomes were the patient's pain score, the total analgesic consumption and the incidence of occurrence of postoperative complications related to the study drugs.

Using PASS II for sample size calculation, and according to the results of previous studies[17,18] a sample size of 37 patients per group to achieve 80% power to detect three hours difference as regarding time to first analgesic requirement between both groups with estimated group standard deviations of 4.0 hours and with (alpha) level 0.05 was needed. Forty patients per group were included to compensate for any drop outs.

Statistical analysis was performed using a standard SPSS software package version 17 (Chicago, IL). Parametric data are provided as mean ± SD and between group differences were compared using the Student's *t*-test. Non-parametric data are provided as median (IQR) and compared using Mann Whitney test. Categorical data were analyzed using the χ^2 test and are presented in the form of number (%). P <0.05 is considered statistically significant.

Results

Demographic data (age, weight, BMI and ASA physical status) and length of operation showed no statistically significant differences between the two groups (Table 1).

Table 1
Demographic data and Length of operation

	Group L (n = 40)	**Group K (n = 40)**	**p-value**
Age (yrs)	42.85 ± 5.2	41.6 ± 5.9	0.317
Weight (kg)	89.98 ± 4	91.83 ± 7.2	0.12
BMI (kg/m2)	30.78 ± 2	31.1 ± 1.9	0.07
ASA I/II	33/17	28/22	0.371
Length of operation (min)	125.3 ± 11.2	127.3 ± 6.6	0.981

Data are presented as mean ± SD or numbers

In regard to the time to first analgesic request, there was a significant difference in the keteroloac group when compared to the lidocaine group as patients in the ketroloac group experienced longer pain free period (Table 2). Total analgesic consumption in the first twenty four hours was significantly lower in the ketorolac group as compared to the lidocaine group (Table 3).

Table 2
Rescue analgesia time

	Group L (n = 40)	**Group K (n = 40)**	**p-value**
Rescue analgesia time (h)	3.83 ± 0.77	8.73 ± 0.808	<0.001

Data are presented as Mean ± SD

Table 3
Total opioid Consumption

	Group L (n = 40)	**Group K (n = 40)**	**p-value**
Total dose of pethidine (mg/24 h)	110 ± 34.5	60.78 ± 25	<0.001

Data are presented as Mean ± SD

Pain scores were significantly lower in the ketorolac group in comparison with lidocaine group at 2, 4 and 6 hours postoperatively; there was no significant difference immediately postoperatively, at 12, 18 and 24 hrs postoperatively (Figure 1).

In regard to patient satisfaction, there were significantly higher numbers of patients with excellent satisfaction in the ketorolac group (70%) when compared to lidocaine group (30%) (Table 4).

Fig. 1

Postoperative pain scores; VAS; Visual Analog Scale. The middle black solid line represents the median, the upper and lower margins of each box represent the interquartile range (IQR), and whiskers represent maximum and minimum values. (*) indicates significant statistical difference

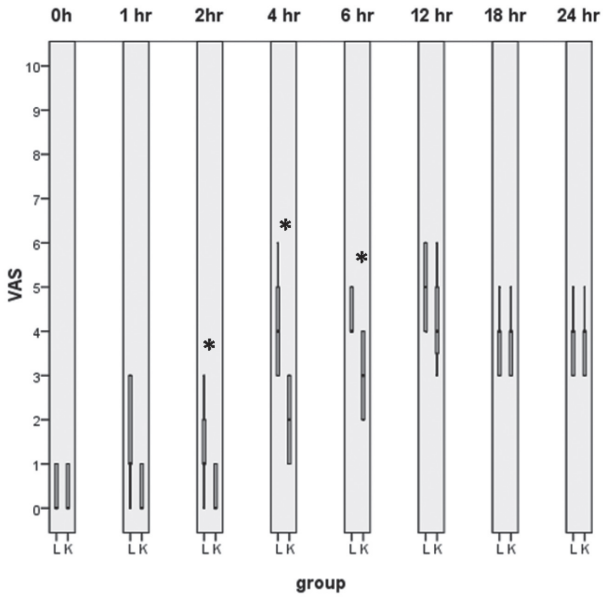

Table 4

Patient satisfaction in first 24 h

	Group L (n = 40)	Group K (n = 40)	p-value
Excellent	12(30%)	28(70%)	0.011
Very good	20(50%)	8(20%)	
Good	6(15%)	4(10%)	
Fair	2(5%)	0(0%)	
Poor	0(0%)	0(0%)	

Data are presented as number (%)

There was no local or systemic complications to the used drugs observed in both groups.

Discussion

This study demonstrated that wound infiltration with ketorolac was superior in providing postoperative analgesia in patients undergoing TAH with more patient satisfaction when compared to infiltration with lidocaine.

Numerous studies have shown that wound infiltration with local anesthetics with or without additives is considered a simple and less costly modality for providing effective analgesia for many types of surgical procedures without any major adverse effects; moreover, it decreases the possibility of local anesthetic toxicity[6] Furthermore, it had been shown to significantly decrease opioid consumption with their deleterious effects on recovery of patients and sometimes wound infiltration may be used as single method for postoperative analgesia[19,20].

Local anesthetics act directly by blocking pain transmission across A-delta and C-type nerves through their attachment to the fast sodium channels within the neuronal axons, thus prevention of propagation of action potential[21]. Also their action may be attributed to their antinflammotry properties as it has been shown that they suppress inflammatory mediators release from neutrophils, inhibit their adhesion to endothelium, decrease oxygen free radicals synthesis, and formation of edema. This local inflammation process contributes to pain by sensitizing nociceptive receptors[22-24] However, a recent study showed that wound infiltration with bupivacaine following cesarean section (CS) indicated that IL-10 decrease and substance P marked excess in wound exudates warrants the need for further trials[25] We used lidocaine because it has been the commonly used amide local anesthetic, safe with less systemic side effect[26]. In a study conducted by Navali et al, they concluded that post-incisional wound infiltration with lidocaine 1% showed better results in decreasing pain after CS when compared to placebo and reduced the number of postoperative rescue analgesic doses. In addition, the place of post–incisional lidocaine wound infiltration either subcutaneous, intramuscular, or subcutaneous plus intramuscular infiltration was not clinically important factor in pain relief after CS[27].

In a study by Sedek and Kassab comparing wound infiltration with lidocaine 1% versus bupivacaine 0.25% for pain relief after cesarean section, their results showed no significant difference in VAS nor in total pethidine consumption (the drug used as rescue analgesic in their study) in 24 h. Also, patients in both groups showed significant prolonged pain free interval when compared to the control group which received no infiltration[28].

Wound infiltration with nonsteroidal anti-inflammatory drugs (NSAIDs) had not been widely

studied, however, in most of these studies that compared wound infiltration of NSAIDs versus placebo or no treatment demonstrated a significant improvement in postoperative pain control[29]. Prostaglandins are considered one of the local chemical mediators released in response to surgical trauma that leads to sensitization of the nociceptors of the peripheral nerve endings[30]. NSAIDs reduce their production by inhibition of cyclo-oxygenase enzyme and thus, decrease sensitization and leads to reduction in postoperative pain[31].

Ketorolac is a NSAID derived from arachidonic acid that interferes with the synthesis of inflammatory and pain mediators; it inhibits both types of cyclo-oxygenase (COX) enzymes (COX1 and COX2)[32]. Ketorolac has been shown to be effective when administered locally for postburn hyperalgesia in healthy volunteers[33], in patients undergoing elective hand surgery[34], mastectomy[35], infiltration prior to gynecologic surgical procedures[36], herniorrhaphy[37], intraarticular administration after knee arthroscopic surgery[38], or intravenous regional anesthesia[39,40]. To our knowledge, there are no studies comparing ketorolac to lidocaine in total abdominal hysterectomy.

It has been reported that infiltrating the wound with 30 mg ketorolac is better than intramuscularly administered 60 mg ketorolac and it was as effective as infiltration of 20 ml bupivacaine 0.25%[37]. So ketorolac can be a safe alternative as it carries no systemic side effects with similar efficacy when compared to bupivacaine. The choice of ketorolac dose in our study(30 mg) was based on recommended doses in the literature; however, in the United Kingdom the dose had been decreased to 10 mg[34].

The current study showed that pain scores were comparable in the first hour in ketorolac and lidocaine groups postoperatively but they were significantly less at 2, 3 and 6 hours in the ketorolac group. Other studies showed similar results[34,35,37]; they reported that wound infiltration with ketorolac can significantly lower pain scores in comparison to groups received placebo or no treatment. However, in a study done by Akhtar and colleagues, they concluded that wound infiltration with bupivacaine 0.25% was better compared to ketorolac 60 mg for postoperative analgesia regarding pain relief onset and duration of action[18].

In another study by Reuben and Duprat[34], a significant difference was seen in the time to first analgesic request as pain-free interval was prolonged up to five hours in the group that received wound infiltration in comparison to group that received no treatment. Also, the total analgesics consumption in the first twenty-four hours was recorded in the same study, and there was a significant reduction (51%) in the group that received wound infiltration in comparison to the group that received no treatment[34]. This is similar to the findings of the current study where the rescue analgesia time was prolonged significantly in the ketorolac group in comparison to the lidocaine group with pain free period up to 9 hours and the total opioid consumption in the first twenty-four hours was significantly lower. There was higher patient satisfaction in ketorolac group as 70% of patients in this group reported that the analgesic modality was excellent.

In previous studies, evidence confirmed the safety of ketorolac infiltration with no occurrence of petichae and hematomas on injection. There was no evidence of local or systemic complications to the used drugs in the current study.

Limitations of this study were that it was conducted only for the first 24 h of the postoperative period. Also we didn't study the effect of the used drugs on the rate of wound infection and time to discharge from hospital.

Conclusion

Our study revealed that usage of ketorolac for wound infiltration was a safe and effective way for immediate postoperative pain relief with more patient satisfaction when compared to lidocaine for patients undergoing TAH.

References

1. Ahmed A, Latif N, Khan R: Post-operative analgesia for major abdominal surgery and its effectiveness in a tertiary care hospital. *J Anaesthesiol Clin Pharmacol*; 2013, 29:472-7.
2. Ng A, Swami A, Smith G, Davidson AC, Emembolu J: The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine after total abdominal hysterectomy. Anesth Analg; 2002, 95:158-62.
3. Stanley G, Appadu B, Mead M, Rowbotham DJ: Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynecological surgery. *Br J Anaesth*; 1996, 76:484-6.
4. White PF, Kehlet H: Improving postoperative pain management: What are the unresolved issues? *Anesthesiology*; 2010, 112:220-5.
5. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*; 2003, 97:534-40.
6. Scott NB: Wound infiltration for surgery. *Anesthesia*; 2010, 65 (Suppl 1):67-75.
7. Achar S, Kundu S: Principles of office anesthesia: Part I. Infiltrative anesthesia. *Am Fam Physician*; 2002, 66:91-4.
8. Koppert W, Ostermeier N, Sittl R, Weidner C, Schmelz M: Low-dose lidocaine reduces secondary hyperalgesia by a central mode of action. *Pain*; 2008, 5:217-24.
9. Kawamata M, Takahashi T, Kozuka Y, Nawa Y, Nishikawa K, Narimatsu E, et al: Experimental incision-induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia. *Pain*; 2002, 100:77-89.
10. Mclure HA, Rubin AP: Review of local anaesthetic agents. *Minerva Anestesiol*; 2005, 71:59-74.
11. Brown CR, Mazzulla JP, Mok MS, Nussdorf RT, Rubin, PD, Schwesinger WH: Comparison of repeat doses of intramuscular ketorolac tromethamine and morphine sulfate for analgesia after major surgery. *Pharmacotherapy*; 1990, 10:45S-50S.
12. Yee JP, Koshiver JE, Allbon C, Brown CR: Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. *Pharmacotherapy*; 1986, 6:253-61.
13. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D: Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. *Clinical Pharmacology and Therapeutics*; 1987, 41:556-61.
14. Furst DE, Ulrich RW, Prakash S: *Basic & clinical pharmacology*, Katzung BG, Masters SB and Trevor AJ Ch.36. McGraw-Hill education, New York, 2012.
15. Greer IA: Effects of ketorolac tromethamine on hemostasis. *Pharmacotherapy*; 1990, 10:71S.
16. 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. *Plast Reconstr Surg*; 2004, 114:1910.
17. Mansour Ghenaee M, Rahmani S, Jafarabadi M: Local lidocaine 2% in postoperative pain management in cesarean delivery. *J Family Reprod Health*; 2015, 9:19-21.
18. Akhtar MI, Saleem M, Zaheer J: Wound infiltration with Bupivacaine versus Ketorolac for postoperative pain relief in minor to moderate surgeries. *J Pak Med Assoc*; 2009, 59:385-8.
19. Leblanc KA, Bellanger D, Rhynes VK, Hausmann M: Evaluation of continuous infusion of 0.5% bupivacaine by elastomeric pump for postoperative pain management after open inguinal hernia repair. *J Am CollSurg*; 2005, 200:198-202.
20. Sidiropoulou T, Buonomo O, Fabbi E, Silvi MB, Kostopanagiotou G, Sabato AF, Dauri M: A prospective comparison of continuous wound infiltration with ropivacaine versus single-injection paravertebral block after modified radical mastectomy. *Anesth Analg*; 2008, 106:997-1001.
21. Whiteman A, Bajaj S, Hasan M: Novel techniques of local anesthetic infiltration. *Contin Educ Anaesth Crit Care Pain*; 2011, 11:167-71.
22. Cassuto J, Sinclair R, Bonderovic M: Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiol Scand*; 2006, 50:265-82.
23. Hollmann MW, Durieux ME: Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology*; 2000, 93:858-75.
24. Hahnenkamp K, Theilmeier G, Van Aken HK, Hoenemann CW: The effects of local anesthetics on perioperative coagulation, inflammation, and microcirculation. *AnesthAnalg*; 2002, 94:1441-7.
25. Carvalho B, Clark DJ, Yeomans DC, Angst MS: Continuous subcutaneous instillation of bupivacaine compared to saline reduces interleukin 10 and increases substance P in surgical wounds after cesarean delivery. *Anesth Analg*; 2010, 111:1452-9.
26. Golzari SEJ, Soleimanpour H, Mahmoodpoor A, Saeid Safari S, Ala A: Lidocaine and Pain Management in the Emergency Department: A Review Article. *Anesth Pain Med*; 2014, 4:e15444.
27. Navali N, Fouladi RF, Nikpour MA: A comparison of post-incisional subcutaneous, intramuscular, and subcutaneous plus intramuscular infiltrations of lidocaine in post-caesarean section pain control. *SAJOG*; 2013, 19:8-12.
28. Sedek AA, Kassab FA: Study of the effectiveness of local anesthetic wound infiltration in post cesarean section pain relief. *Al-Azhar Assiut Medical Journal*; 2015, 13:152-62.
29. Romsing J, Moiniche S, Ostergaard D, Dahl JB: Local Infiltration with NSAIDs for postoperative analgesia: Evidence for a peripheral analgesic action. *Acta Anaesthesiol Scand*; 2000, 44/6:672-83.
30. Raja SN, Meyer RA, Campbell JN: Peripheral mechanisms of somatic pain. *Anesthesiology*; 1988, 68:571-90.
31. Koch-Weser J: Nonsteroidal antiinflammatory drugs. *NEJM*; 1980, 302:1179-85.
32. Jankovic RJ, Visnjic MM, Milic DJ, Stojanovic MP, Djordjevic DR, Pavlovic MS: Does the addition of ketorolac and dexamethasone to lidocaine intravenous regional anesthesia improve postoperative analgesia and tourniquet tolerance for ambulatory hand surgery? *Minerva Anestesiol*; 2008, 74:521-7.
33. Lundell JC, Silverman DG, Brull SJ, O'connor TZ, Kitahata LM, Collins JG, Lamotte R: Reduction of postburn hyperalgesia after local injection of ketorolac in healthy volunteers. *Anesthesiology*; 1996, 84:502-9.
34. Reuben SS, Duprat KM: Comparison of wound infiltration with ketorolac versus intravenous regional anesthesia with ketorolac for postoperative analgesia following ambulatory hand surgery. *Reg Anesth*; 1996, 21:565-8.
35. Bosek V, Cox CE: Comparison of analgesic effect of locally and systemically administered ketorolac in mastectomy patients. *Ann Surg Oncol*; 1996, 3:62-6.
36. Richman G, Maurer P, Williams M, Torjman M, Dunton C, Seltzer

J: Does pre-incision local wound infiltration with bupivacaine and ketorolac decrease postoperative pain and opioid analgesic requirements following gynecological surgery? *Anesthesiology*; 1994, 81:A958.

37. Ben-David B, Katz E, Gaitini L, Goldik Z: Comparison of IM and local infiltration of ketorolac with and without local anaesthetic. *Br J Anaesth*; 1995, 75:409-12.
38. Reuben SS, Pohlman M, Duprat KM: Intraarticular bupivacaine and ketorolac for postoperative analgesia following arthroscopic knee surgery. *Anesthesiology*; 1994, 81:A957.
39. Reuben SS, Steinberg RB, Kreitzer JM, Duprat KM: Intravenous regional anesthesia using lidocaine and ketorolac. *Anesth Analg*; 1995, 81:110-3.
40. Vanos DN, Ramamurthy S, Hoffman J: Intravenous regional block using ketorolac: preliminary results in the treatment of reflex sympathetic dystrophy. *Anesth Analg*; 1992, 74:139-41.