Academic

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 4, 2011

Research Article

COMPARISON OF EFFICACY OF LORNOXICAM AND DICLOFENAC FOR POSTOPERATIVE PAIN RELIEF IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY

TEENA BANSAL*, ANIL THAKUR, SARLA HOODA*****

Department of Anaesthesiology & Critical Care, Pt. B.D. Sharma University of Health Sciences, Rohtak (Haryana) India.
Email: aggarwalteenu@rediffmail.com

Received: 5 July 2011, Revised and Accepted: 13 Aug 2011

ABSTRACT

Aims & Objectives: The present study was undertaken to compare the analgesic effect of Lornoxicam vis-à-vis diclofenac for postoperative pain relief in patients undergoing abdominal hysterectomy.

Material & Methods: A total of 60 aduts patients having physical status grade I and II according to American Society of Anaesthesiologists (ASA) undergoing abdominal hysterectomy under general anaesthesia were included in the study. Patients were randomly allocated to one of the two groups. Each group consisted of 30 patients.

Group I Patients were administered lornoxicam 8mg intramuscular at the time of closure of the wound and was repeated 12 hourly for the next 48 hours. *Group II* Patients were administered diclofenac 75mg intramuscularly at time of wound closure and was repeated 12 hourly for the next 48 hours. Intravenous morphine was used as rescue analgesia in both groups with patient controlled analgesia (PCA) pump.

Results: Requirement of morphine (rescue analgesia) in lornoxicam group was 50.0 ± 4.74 mg while in the diclofenac group, it was 30.2 ± 3.24 mg during the study period (48 hours). Requirement of morphine in first 24 hours in the lornoxicam group (Group I) was 26.90 ± 3.81mg while in diclofenac group (Group II) it was 24.10 ±3.89 mg, the difference was statistically significant ($p < 0.01$). Requirement of morphine between 24–48 hours was 23.10 ± 4.99 mg in the lornoxicam group, while it was 6.10 ± 2.99 mg in the diclofenac group and the difference was statistically significant ($p <0.001$). The requirement of morphine at 24 to 36 hours in the lornoxicam group was 11.3 ± 3.40mg while in the diclofenac group, it was 3.60 ± 1.99mg ($p<0.001$). The requirement of morphine at 36 to 48 hours was 11.80 ± 3.24 mg, while in the diclofenac group, it was 2.50±1.59 mg ($p<0.001$).

Conclusions: Diclofenac sodium when used in doses of (75 mg 12 hourly) proved to be a better analgesic when compared to lornoxicam (8 mg 12 hourly).

Keywords: DICLOFENAC, Lornoxicam, Morphine, Postoperative pain, Abdominal hysterectomy.

INTRODUCTION

Postoperative pain is invariably associated with any type of surgery. Although the severity of pain is related to type of surgery yet it has been observed that generally 20–40% patients experience pain of moderate intensity and another 50–70% experience severe pain.[1]

There have been many advances in the management of postoperative pain through different modalities like peripheral nerve blocks, epidural local anaesthetics and/or opioids.[2] Opioids have been the mainstay of treatment for postoperative pain but their side effects such as respiratory depression, sedation, constipation, urinary retention and itching limit their use.[3]

Non-steroidal anti-inflammatory drugs (NSAIDS) have recently gained wide spread popularity in postoperative pain management. Almost all NSAIDS have been used for treatment of postoperative pain including non-selective (conventional) cyclo-oxygenase (COX) inhibitors. Their peripheral and central analgesic effect, anti-inflammatory properties and relatively more tolerability than opioids have made them drugs of choice in postoperative analgesia.

Diclofenac (COX-1 & COX-2 inhibitor) is being used conventionally for many years for postoperative pain relief. It is an extremely potent cyclo-oxygenase inhibitor and it is known to accumulate in inflammed tissue where its concentration is maintained much higher than in plasma for many hours. It also has active metabolites that act as analgesic.[4]

Lornoxicam is a relatively new NSAID. It belongs to the oxicam group. Besides its inhibitory effects on COX-1 and COX-2 peripheral receptors, it also increases endogenous dinorphin and beta-endorphin levels promoting central analgesic and anti-inflammatory effects. Lornoxicam (8mg) has been shown to be as effective as morphine (20mg), meperidine (50mg) and tramadol (50mg) in the treatment of postoperative pain.[5,6,7]

Non-steroidal anti-inflammatory drugs although have been in use as one of the treatment modalities for postoperative analgesia but still their differing pharmacology, varying dosing schedule, side effect profile and duration of analgesia make the choice difficult. Further, the availability of newer NSAIDS with better efficacy and side effect profile keep the interest going in the field of postoperative pain management.

There are only a few studies available in literature comparing the postoperative analgesic effect of lornoxicam and diclofenac. Therefore, the present study has been planned to compare the analgesic efficacy of lornoxicam and diclofenac on postoperative pain relief in patients undergoing abdominal hysterectomy in Indian population.

MATERIAL AND METHODS

This prospective randomized study was conducted in the Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma PGIMS Rohtak after obtaining approval from the institutional research/ethical committee. A total of 60 adult patients having physical status grade I & II according to American Society of Anesthesiologists (ASA) undergoing abdominal hysterectomy were included in the study.

Exclusion Criteria

Patients with history of

- Cardiac failure
- Chronic analgesic therapy
- Gastrointestinal bleeding, peptic ulcer, intracerebral bleed
- Known hypersensitivity to NSAIDS and
- Patients with Impaired renal or hepatic function
- In addition patients with bleeding diathesis, pregnancy & morbid obesity were excluded

All patients were visited a day prior to surgery. The general physical as well as systemic examination was carried out. Routine investigations like haemoglobin, bleeding time, clotting time, urine complete examination, blood sugar, chest x-ray, ECG were carried out alongwith blood urea and serum creatinine. A linear visual analogue scale (VAS) on a scale of 0-10 cm (where 0 stands for no pain and 10 for worst possible pain) was explained to each patient and consent to participate in the study was obtained. All patients were premedicated with alprazolam 0.25mg and ranitidine 150mg orally on the night before and two hours prior to surgery.

The patients were then randomly allocated into one of two groups of 30 patients each. Randomization was done by computer generated numbers.

Group I (Lornoxicam Group; n=30): Patients were administered lornoxicam for pain relief in the postoperative period.

Group II (Diclofenac Group; n=30): Patients received diclofenac as an analgesic for pain relief in the postoperative period.

On arrival of patient in the operating room, intravenous line was secured and usual continuous monitoring of non-invasive blood pressure (NIBP), heart rate (HR), electrocardiogram (ECG) and arterial oxygen saturation (SpO_2) was started. A uniform anaesthetic technique was used in all patients. Each patient was given 0.2mg glycopyrrolate intravenously at the induction of anaesthesia. After preoxygenation for 3 minutes anaesthesia was induced with the sleep dose of thiopentone sodium (5-7mgkg^{-1}) and intubation of trachea was facilitated using vecuronium bromide (0.1mgkg^{-1}). Anaesthesia was maintained with 0.5% halothane and 67% nitrous oxide (N_2O) in oxygen (O_2). Intermittent doses of vecuronium bromide as and when required were administered. Intraoperatively analgesia was provided with tramadol 1mgkg^{-1} intravenously at the commencement of surgery in all patients. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 0.05mgkg^{-1} and glycopyrrolate 0.01mgkg^{-1}.

At the start of the closure of wound either lornoxicam 8mg or diclofenac 75mg was administered intramuscularly to the Group I and Group II patients respectively. The respective drug in the same dosage was repeated in both groups 12 hourly for next 48 hours. All patients were kept in postanaesthesia care unit (PACU) during the study period.

Intravenous morphine was used as rescue analgesia in both the groups using patient controlled analgesia (PCA) pump.[8] Patients were made fully aware of the use of PCA pump and were instructed to use it at VAS 4. The PCA pump was set to deliver a 3mg bolus of morphine with a 15 minute lockout interval and a maximum of 24mg over a period of 4 hours. Patients were observed for 48 hours post operatively and the following parameters were recorded.

1. Morphine requirement was recorded at 30 minute interval for initial two hours, then at 2 hour interval for upto 8th hours, at 4 hour interval upto 12th hours, at 6 hour interval upto 24th hours and at 12 hour interval upto 48th hours.
2. Blood urea and serum creatinine were estimated after 48 hours to observe any effect of lornoxicam and diclofenac on renal functions.
3. Side effects like nausea and vomiting, epigastric pain, headache, dizziness, mental confusion, bleeding, allergy or pain at injection site were noted in both the groups.

Statistical Analysis

The different data was statistically analysed. The arithmetic mean and standard deviation were calculated by standard statistical methods and expressed as mean ± 1 S.D. For comparison of data between two groups, unpaired't' test was used.

RESULTS

Mean age of patients in Gp I & II were 44.53 ± 6.03 and 46.97 ± 7.10 years respectively. Duration of surgery in Group I was 100.17 ± 9.95 (minutes), while in Group II it was 99.50 ± 10.03 (minutes). Duration of surgery in the two groups did not show any significant difference statistically.

The requirement of morphine in Lornoxicam Group (Group I) in 48 hours was 50.0 ± 4.74 (mg) while in Group II (Diclofenac group) it was 30.2 ± 3.24 (mg) (Table 1).

Table 1: Showing total dose of Morphine required in Gp 1 & II in 48 hours (MEAN ± S.D.)

Group	Morphine (mg) Mean ± S.D.	't' value
Group I	50 ± 4.74	
Group II	30.2 ± 3.24	15.99 (p<0.001)

These observations reveal that the difference in the dose required in Gp 1 and II was highly significant statistically (p < 0.001).

The requirement of morphine in first 24 hours in Group I was 26.90 ± 3.81 (mg), while in Group II it was 24.10 ± 3.89 (mg), the difference being statistically significant (p < 0.01) (Table 2).

Table 2: Showing morphine requirement in Gp I and Gp II in first 24 hours (MEAN ± S.D.)

Group	Morphine (mg) mean ± S.D.	't' value
Group I	26.90 ± 3.81	
Group II	24.10 ± 3.89	2.81 (p<0.01)

The requirement of morphine in the lornoxicam group was 23.10 ± 4.99 (mg) between 24-48 hours while the requirement of morphine in the diclofenac group was 6.10 ± 2.99 (mg) (Table 3). It was statistically highly significant (p<0.001)

Table 3: Showing morphine requirement in GP I & Gp II between 24 to 48 hours (MEAN ± S.D.)

Group	Morphine (mg) MEAN ± S.D.	't' value
Group I	23.10 ± 4.99	
Group II	6.10 ± 2.99	14.10 (p<0.001)

The difference in requirement of morphine in two groups from 0-6 hours was not significant statistically. When compared from 6-12 hours the difference in morphine requirement was significant (p<0.05). However from 12 to 24 hours, it was comparable in both the groups. At 24–36 hours and at 36–48 hours, the rescue analgesic required was significantly higher in Gp I. Fig. 1 & 2 (Table 4).

Table 4: Showing morphine requirement at different time intervals during the study in Gp I & Gp II (MEAN ± S.D.)

Group	Morphine (mg) at Different time intervals (hrs)mean ± S.D.									
	0-6	t	6-12	t	12-24	t	24-36	t	36-48	t
Group I	14.7± 2.13		6.2 ± 3.69		6.0 ± 3.05		11.3± 3.40		11.80± 3.24	
Group II	14.8± 4.16	0.11 (NS)	4.2 ± 2.79	2.37 (p<0.05)	5.1 ± 2.51	1.25 (NS)	3.60 ± 1.99	10.68 (p<0.001)	2.50±1.59	14.10 (p<0.001)

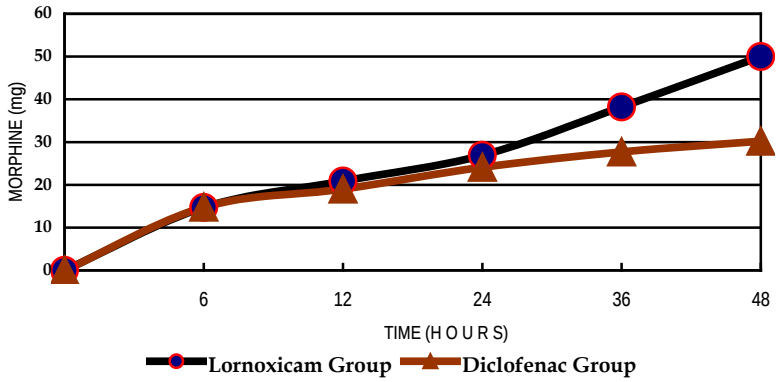

Fig. 1: Mean total morphine requirement at different times

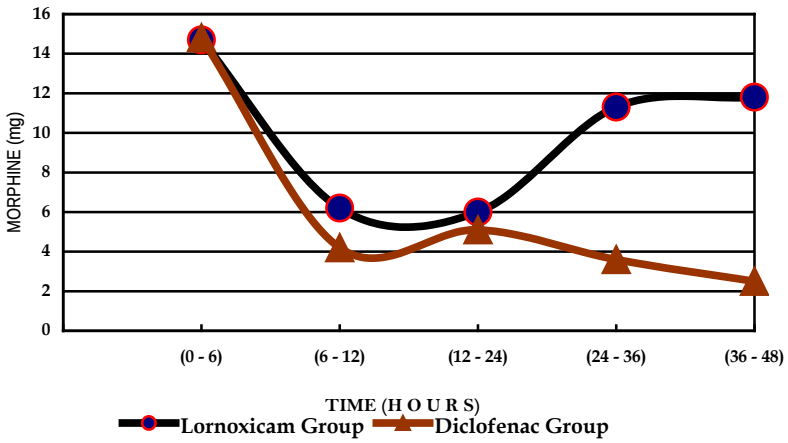

Fig. 2: Mean Morphine requirement at different time intervals

Nearly equal number of patients required the rescue drug during the first 24 hours of the study in both the groups, while between 24-36 hours and 36-48 hours all patients required rescue analgesia in the lornoxicam group. However, 26 patients (86.7 percent) and 23 patients (76.7 percent) required rescue analgesia in the diclofenac group between 24-36 and 36-48 hours respectively (Table 5).

Table 5: Showing Number of patients requiring morphine at different time intervals during the study in Gp I & Gp II

Group	Number of Patients				
	0-6 Hours	6-12 Hours	12-24 Hours	24-36 Hours	36-48 Hours
Group I	30 (100%)	28 (93.3%)	29 (96.7%)	30 (100%)	30 (100%)
Group II	30 (100%)	26 (86.7%)	29 (96.7%)	26 (86.7%)	23 (76.7%)

The parameters of renal functions i.e. blood urea and serum creatinine did not show any significant difference when compared from the basal values to those at 48 hours.

None of the patients in any of the group reported other adverse events like dizziness, headache, mental confusion, bleeding, allergy, pruritis, pain at injection site etc. Therefore both the drugs were fairly well tolerated.

The requirement of rescue analgesia (morphine) was more in the lornoxicam group as compared to the diclofenac group and this requirement was much more in the 2nd half of the study (24 – 48 hours). Also the number of patients requiring rescue analgesia was more in the lornoxicam group as compared to diclofenac group during the 2nd half of the study (100 per cent versus 90 per cent).

DISCUSSION

Postoperative pain causes marked distress and anxiety and is a major factor that affects recovery from anaesthesia and surgery. Despite major improvements in understanding of acute pain pathophysiology over the past decade, approximately 80 percent of patients undergoing surgical procedures experience mild to severe postoperative pain.[9]

Although opioids have been the main stay of managing postoperative pain, their side effects such as respiratory depression, sedation, constipation, urinary retention etc. limit their use.[3] Moreover, many patients experience severe pain despite using intermittent intramuscular opioids.[10,11] On the other hand non-steroidal anti-inflammatory drugs (NSAIDs) have found a wide

spread use in postoperative pain management due to their peripheral and central analgesic effects, anti-inflammatory properties and relatively more tolerability.[12,13] Various studies have suggested that the addition of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce opioid requirements,improve pain relief and reduce respiratory depression.[14,15]

Both diclofenac as well as lornoxicam have been used as analgesic for post operative pain relief in various surgical procedures. These drugs have been used either individually or in combination with others using different rescue drugs in different studies. However, there are only a few studies available in literature where the post operative analgesic effects of these drugs have been compared.

Hodsman et al (1987) studied the morphine sparing effects of diclofenac sodium following abdominal surgery in a randomized double blind placebo controlled study. Immediately following major abdominal surgery and twelve hours later, patients received either placebo or diclofenac 75mg (same dose as in our study) intramuscularly and their morphine requirements administered by a patient controlled system over 24 hours were compared. Morphine consumption in their study was 38.5mg in the diclofenac group.[16]

Whereas, in the present study the requirement of morphine was 24.1 mg in the first 24 hours (Table 2), which is much less as compared to the above mentioned study. The significant difference in the morphine consumption in the Hodsman's study could be attributed to the low VAS score achieved in their patients. The end point in their study was pain relief to the patient's satisfaction (mean VAS < 3), whereas in our study we used a VAS score of 4 as the end point.

Lornoxicam, a new non-steroidal anti-inflammatory analgesic drug of oxicam class has been used as an analgesic both pre-emptively and post operatively in different types of surgical procedures.

Inan et al (2007) studied the efficacy of lornoxicam in post operative analgesia after total knee replacement surgery in a double blind randomized placebo controlled study. The authors used lornoxicam in a dose of 32 mg/48 hours (16 mg intravenously 15 minutes before surgery followed by 8 mg post operatively at 12th and 24th hours) and morphine was used as a rescue drug with patient controlled analgesia device. The authors observed that morphine consumption uptill 48 hours in this study was 34.6±16.32 mg.[17] In the present study however, the morphine requirement in the lornoxicam group was 50.0 ±4.74 mg, which was fairly high (Table 1, Fig. 1). The reduced dose of morphine required in their study could be because they used an additional dose of 2 mg intravenous morphine 30 minutes before extubation. Although the dosage schedule of lornoxicam used is similar in both the studies (32 mg/48 hours) but Inan et al have administered half of this dose 15 minutes before surgery. The too low requirement of rescue analgesia in their study substantiates the role of pre-emptive analgesia as has been observed by Trampitsch et al[18]. They studied the pre-emptive analgesic effect of lornoxicam in patients undergoing gynaecological surgery with varying dosage schedule of lornoxicam and concluded that lornoxicam administered pre-emptively appeared to improve the quality of post operative analgesia and led to reduced consumption of opioid analgesics.

A study similar to present study was conducted by Bahadir et al (2005) who compared the effect of lornoxicam with diclofenac in the pain management after cardiac surgery.[19] Lornoxicam was used in a dose of 8mg intramuscularly every 8 hourly whereas diclofenac was used in a dose of 75 mg intramuscularly every 12 hourly for 48 hours. They showed that efficacy of lornoxicam and diclofenac were similar in providing postoperative pain relief, but in the present the requirement of rescue analgesia (morphine) was significantly more in the lornoxicam group as compared to the diclofenac group. This difference can be explained by the fact that Bahadir et al (2005) used lornoxicam 8mg every 8 hourly whereas in our study we used 8 mg every 12 hours. This might have led to increased requirement of rescue analgesia in lornoxicam group in the present study.

In a study conducted by Sener et al (2008) where although the dose of lornoxicam and diclofenac used for postoperative analgesia was similar in 1st 24 hours to that of the present study (8 mg twice daily vs 75 mg twice daily), but the requirement of rescue analgesia (pethidine) was similar with both the drugs in their study in contrast to ours where the dose of rescue analgesia required was more in lornoxicam group.[20]

We came across only two studies in the literature (described above) which have compared lornoxicam and diclofenac for postoperative pain relief. Bahadir et al in their study concluded that lornoxicam in dose of 24mg/day has equianalgesic potency to that of diclofenac 150mg/day.[19] Whereas Sener et al observed that lornoxicam in dose of 16mg/day was equipotent to 150mg/day diclofenac.[20] In the present study diclofenac (150mg/day) appears to have better analgesic efficacy as compared to 16mg/day lornoxicam.

In the present study the requirement of morphine as rescue analgesic in Group I (Lornoxicam Group) was 50.0 ± 4.74 mg while in Group II (Diclofenac Group) it was 30.2±3.24 mg in 48 hours. The difference was highly significant ($p<0.001$, Table 1, Fig. 1) showing better efficacy of diclofenac.

When the requirement of morphine was analysed during the different time span it was observed that it was almost similar in first 6 hours (Table 4, Fig 1 & 2). With every passing hour, it went on increasing in lornoxicam group. The major bulk of the difference in the requirement of rescue analgesia was in the 2nd half of study i.e. between 24 to 48 hours postoperatively. This could be because diclofenac is known to accumulate in the inflammed tissues where its concentrations are maintained much higher than in plasma for many hours. It also has active metabolites that act as analgesics.[21,22,23]

The present study further revealed that the number of patients requiring rescue analgesia was more for lornoxicam group (n=30) as compared to diclofenac group (n=27) between 24 – 48 hours (100 % Vs. 90%, Table 5). However, all the patients required morphine in first 24 hours in both the groups.

In the present study the renal parameters i.e. blood urea and serum creatinine did not show any significant variation after 48 hours as compared to base line. Since we studied renal functions over a short span of 48 hours, the nephrotoxicity of these drugs cannot be commented in the present study.

NSAIDs are also known to influence haemostasis and coagulation mainly through an effect on platelet aggregation but there were no clinical signs of haemostatic disturbances such as increased post operative bleeding or development of haematoma in our study in either group.

The common side effects of NSAIDs include nausea, vomiting, epigastric pain, headache, dizziness, mental confusion, bleeding, allergy or pruritis and pain at the injection site. In a study by Tarkkila et al, where diclofenac was used as an analgesic; nausea, vomiting and dizziness were observed in 27, 10 and 93 percent patients respectively.[4] However, in the present study we observed nausea and vomiting in 5 patients in each group and epigastric pain in one patient in diclofenac group and no other significant side effects were noted. Therefore, in the present study both the drugs were well tolerated.

From the present study it can be concluded that diclofenac sodium (150mg/day) showed better analgesic efficacy as compared to lornoxicam (16mg/day) for postoperative pain relief in patients undergoing abdominal hysterectomy under general anaesthesia without any significant adverse events. However, long term multi-centric trials with more number of patients are required to address these issues further.

REFERENCES

1. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg 1998;86:1045-50.
2. Vendittoli PA, Makinen P, Drolet P, Lavigne M, Fallaha M, Guertin MC, et al. A multimodal analgesia protocol for total knee arthroplasty. J Bone & Joint surg 2006;88-A(2):282-9.

3. Austrup ML, Korean G. Analgesic agents for the postoperative period: Opioids. Surg Clin North Am 1999;79:253-73.
4. Tarkkila P, Tuominen M, Rosenberg PH. Intravenous ketorolac vs diclofenac for analgesia after maxillofacial surgery. Can J Anaesth 1996;43:216-20.
5. Norholt SE, Sindet-Pedersen S, Larsen U, Bang U, Ingerslev J, Nielsen O, et al. Pain control after dental surgery: a double-blind, randomized trial of lornoxicam versus morphine. Pain 1996;67:335-43.
6. Rosenow DE, Van Krieken F, Stolke D, Kursten FW. Intravenous administration of lornoxicam, a new NSAID and pethidine for postoperative pain. Clin Drug Invest 1996;11:11-9.
7. Ilias W, Jansen M. Pain control after hysterectomy: an observer blind, randomized trial of lornoxicam versus tramadol. Br J Clin Pract 1996; 50:197-202.
8. Macintyre PE. Safety and efficacy of patient controlled analgesia. Br J Anaesth 2001;87(1):36-46.
9. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Post operative pain experience: results from a national survey suggest post operative pain continues to be undermanaged. Anesth Analg 2003; 97:534-40.
10. Nay Man J. Measurement and control of postoperative pain. Annals of the Royal College of Surgeons of England1979;61:419-26.
11. Tamsen A. Comparison of patient-controlled analgesia with constant infusion and intermittent intramuscular regimes. In:Harmer M, Rosen M, Vickers MD. editors. Patient-controlled analgesia. London:Blackwell Scientific Publications 1985; 111-25.
12. Beilin B, Besler H, Mayburd E, Sminov G. Effects of preemptive analgesia on pain and cytokine production in the postoperative period. Anesthesiology 2003;98:151-55.
13. Mc. Crory CR, Sten G, Lindahl GE. Cyclooxygenase inhibition for postoperative analgesia. Anesth Analg 2002;95:169-76.
14. Reasbeck PG, Rice ML, Reasbeck JC. Double-blind controlled trial of indomethacin as an adjunct to narcotic analgesia after major abdominal surgery. Lancet 1982;2:115-8.
15. Gillies GWA, Kenny GNC, Bullingham RES, Mcardle CS. Morphine sparing effect of ketorolac tromethamine, a new parental non-steroidal anti-infalmmatory agent following abdominal surgery. Anaesthesia 1987;42:727-31.
16. Hodsman NBA, Burns J, Blyth A, Kenny GNC, McArdle CS, Rotman H. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia 1987;42:1005-8.
17. Inan N, Ozcan N, Takmaz SA, Ozcan A, Erdogan I, Baltaci B. Efficacy of lornaxicam in postoperative analgesia after total knee replacement surgery. Agri 2007;19(2):38-45.
18. Trampitsch E, Pipam W, Moerti M, Sadjak A, Dorn C, Sittl R et al. Pre emptive randomized double-blind study with lornoxicam in gynecological surgery. Schmerz 2003;17(1):4-10.
19. Bahadir D, Hasan K, Adnan CM, Sitki G, Hakki K, Celalettin K. Comparison of effects of lornoxicam versus diclofenac in pain management after cardiac surgery: A single-blind, randomized, active-controlled study. Current Therapeutic Research 2005;66:107-16.
20. Sener M, Yilmazer C, Yilmaz I, Bozdogan N, Ozer C, Donmez A, et al. Efficacy of lornoxicam for acute postoperative pain relief after septoplasty: a comparision with diclofenac, ketoprofen and dipyrone. J Clin Anesth 2008; 20:103-8.
21. KuEC, Wasvary JM, Cash WD. Diclofenac sodium (GP 45840, Voltaren). A potent inhibitor of prostaglandin systhetase. Biochem Pharmacol 1975; 24:641-3.
22. Fowler PD, Shadforth MF, Crook PR, John VA. Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. Eur J Clin Pharmacol 1983;25:389-94.
23. Menasse R, Hedwall PR, Kraetz J. Pharmacological properties of diclofenac sodium and its metabolites. Scand J Rheumatol 1978;22(Supp):5-16.