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Lornoxicam - a newer oxicam for postoperative pain relief in patients undergoing abdominal hysterectomy

Abdominal histerektomi uygulanan hastalarda postoperatif ağrı tedavisinde yeni bir oksikam-larnoksikam

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Abstract

Aim. The present study evaluated the analgesic effect of lornoxicam- a new thienothiazine derivative of the oxicam class of non-steroidal anti-inflammatory drugs (NSAIDs) for postoperative pain relief in patients undergoing abdominal hysterectomy. **Method.** The study included 50 adult female patients having physical status ASA grade I & II undergoing abdominal hysterectomy under general anaesthesia. Patients were administered lornoxicam 8 mg intramuscular at closure of the wound and were repeated 12 hourly for the next 48 hours. Intravenous morphine was used as rescue analgesia with patient controlled analgesia pump. **Result.** The total mean requirement of morphine was 50.0±4.74 mg during the study period. Mean requirement of morphine in first 24 hours and between 24-48 hours was 37.80±3.81 mg and 12.20±4.99 mg respectively. The mean requirement of morphine at different time intervals during the study i.e. from 0-6 hours was 14.7±2.13 mg, from 6-12 hours was 11.80±3.69 mg and from 12-24 hours, it was 11.30±3.05 mg. The requirement of morphine from 24-36 and 36-48 hours was 6.20±3.40 and 6.0±3.24 mg respectively. **Conclusion.** The requirement of morphine decreased significantly in the second half of the study. The requirement of morphine continued to decrease with each passing hour in the present study. Further, larger trials are needed to establish its efficacy as an analgesic for postoperative pain relief in different surgeries.

Keywords: Lornoxicam, post operative pain, abdominal hysterectomy

Özet

Amaç. Bu çalışmada abdominal histerektomi uygulanan hastalarda postoperatif ağrı tedavisinde nonsteroid antiinflamatuardan oksikam sınıfının yeni bir thienothiazine türevi olan larnoksikamın analjezik etkinliğini değerlendirdik. **Yöntem.** Bu çalışma ASA I-II grubundan genel anestezi altında abdominal histerektomi uygulanan 50 kadın hastayı içermektedir. Tüm hastalara cilt kapanma sırasında 8mg lornoksikam intramuskuler uygulandı ve sonraki 48 saat içinde 12 saatte bir tekrarlandı. Hasta kontrolü analjeziği içinde intravenöz morfin kullanıldı. **Bulgular.** Çalışma periyodu boyunca ortalama total morfin ihtiyacı 50,0±4,74 mg idi. İlk 24 saat için ortalama morfin ihtiyacı 37,80±3,81 mg, 24-48 saat süresince ise 12,20±4,99 mg idi. Çalışma boyunca farklı zamanlarda ortalama morfin ihtiyacı; örneğin 0-6. saat 14,7±2,13 mg, 6-12. saat 11,80±3,69 mg ve 12-24. saat ve 12-24. saat 11,30±3,05 mg idi. 24-36. saat morfin gereksinimi 6,20±3,40 mg ve34-48. saat 6,0±3,24 mg idi. **Sonuç.** Çalışmanın ikinci yarısında morfin ihtiyacı önemli derecede azaldı. Bu çalışmada morfin ihtiyacı her geçen saat azalmaya devam etti. Sonuç olarak farklı cerrahilerde postoperatif ağrı tedavisinde bir analjezik olarak lornoksikam etkinliğini belirlemek için daha geniş çalışmalara ihtiyaç olduğunun kanısındayız.

Anahtar sözcükler: Lornoksikam, post operatif ağrı, abdominal histerektomi

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Introduction

Discovery of non-steroidal anti-inflammatory drugs (NSAIDs) since 1899 led to an important advancement in the management of postoperative pain. These agents have demonstrated effective analgesia in a wide range of postoperative pain states and in some cases comparable to that produced by the opioids. They have been used alone or in combination with opioids for the management of postoperative pain in order to provide better pain relief with fewer side effects [1]. Almost all NSAIDs have been used for treatment of postoperative pain including non-selective (conventional) cyclo-oxygenase (COX-1 & COX-2) inhibitors and selective COX-2 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 [2].

Lornoxicam (chlortenoxicam) is a new thienothiazine derivative of the oxicam class of NSAIDs. Lornoxicam has demonstrated cyclo-oxygenase inhibitory activity approximately 100 times more powerful than that of tenoxicam, along with analgesic activity approximately 10 times greater than that of either tenoxicam or piroxicam. Additionally, and in contrast to other oxicams, lornoxicam has a short plasma half-life of approximately four hours [3, 4]. This may translate into a better tolerability profile for lornoxicam, since NSAIDs with long plasma half-lives have been associated with a higher incidence of adverse effects [5].

Non-steroidal anti-inflammatory drugs have differing pharmacology, varying dosing schedule, side effect profile and duration of analgesia. Further, the availability of newer NSAIDs with better efficacy and fewer side effects keeps the interest going in the field of postoperative pain management. Hence, the present study was conducted to evaluate the analgesic efficacy of lornoxicam on postoperative pain relief in patients undergoing abdominal hysterectomy.

Material and methods

This prospective randomized study was conducted in the Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma PGIMS Rohtak (India) after obtaining approval from the institutional research/ethical committee. A total of 50 adult female 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

- Cardiac failure
- Chronic analgesic therapy
- Gastrointestinal bleeding, peptic ulcer, intracerebral bleed
- Known hypersensitivity to NSAIDS and
- Impaired renal or hepatic function
- Bleeding diathesis, pregnancy & morbid obesity were also not included in the present study

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 and electrocardiography (ECG) were carried out along with 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.

On arrival of patient in the operating room, intravenous line was secured and continuous monitoring of non-invasive blood pressure (NIBP), heart rate (HR), 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 (5-7mg/kg) and intubation of trachea was facilitated using vecuronium bromide (0.1mg/kg). 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 1mg/kg intravenously at the commencement of surgery in all patients. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg.

At the start of the closure of wound, lornoxicam 8mg was administered intramuscularly. The drug in the same dosage was repeated 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 using patient controlled analgesia (PCA) pump (B. Braun,s Perfuser Space PCA infusion pump ,USA) [6]. 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 12^{th} hours, at 6 hour interval upto 24^{th} hours and at 12 hour interval upto 48^{th} hours.
2. Blood urea and serum creatinine were estimated after 48 hours to observe any effect of lornoxicam 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.

Statistical analysis

The different data was statistically analysed using student's t-test. The arithmetic mean and standard deviation were calculated by standard statistical methods and expressed as mean±S.D. (Statistical analyses were performed with SPSS 16 software)

Observations

The study included 50 adult female patients having physical status grade I & II according to American Society of Anaesthesiologists (ASA) scheduled for abdominal hysterectomy. Mean age of patients was 44.53±6.03 years. Mean weight of patients was 54.93±8.40 kg. The mean duration of surgery was 100.17±9.95 minutes. The total mean requirement of rescue analgesic (morphine) in 48 hours was 50±4.74 mg. The mean requirement of morphine in the first 24 hours and between 24 to 48 hours was 37.80±3.81 and 12.20±4.99 mg respectively (Table 1). The mean requirement of morphine at different time intervals during the study i.e. from 0-6 hours was 14.7±2.13 mg, from 6-12 hours it was 11.80±3.69 mg and from 12-24 hours it was 11.30±3.05 mg. The requirement of morphine from 24-36 and 36-48 hours was 6.20±3.40 and 6.0±3.24 mg respectively (Table 2, Figure 1). All patients required morphine in the first 24 hours and between 24 to 48 hours. However the requirement of morphine decreased significantly in the second half of study ($p<0.001$).

The drug was fairly well tolerated. Five patients reported nausea which was relieved after administering ondansetron. None of the patients reported adverse events like dizziness, headache, mental confusion, bleeding, allergy, pruritis or pain at injection site etc. 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.

Table 1. Morphine requirement during study (Mean±SD).

Duration	Morphine (mg) Mean±SD	
First 24 hours	37.80±3.81	P<0.001
24 to 48 hours (2nd 24 hours)	12.20±4.99	
Total 48 hours	50.00+4.74	

Table 2. Morphine requirement at different time intervals (Mean ± SD).

Morphine (mg) at different time intervals (HRS) Mean+SD								
0-6 hours	6-12 hours	0-6 vs 6-12	12-24 hours	6-12 vs 12-24	24-36 hours	12-24 vs 24-36	36-48 hours	24-36 vs 36-48
14.7 ±2.13	11.8 ±3.69	P<0.1	11.3±3.05	N.S.	6.2±3.40	P<0.01	6.0±3.24	N.S.
***N.S.**=Not significant								

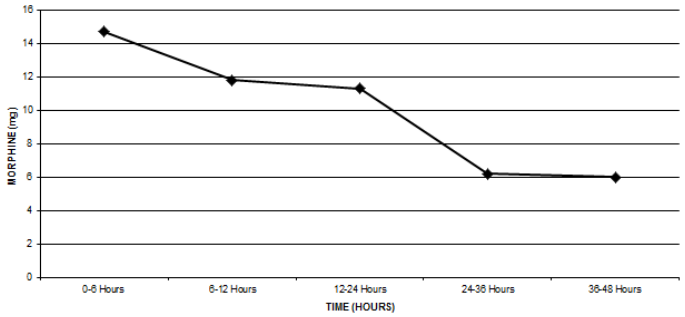

Figure 1. Mean morphine requirement at different time intervals.

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 patho-physiology over the past decade, approximately 80 percent of patients undergoing surgical procedures experience mild to severe postoperative pain [7].

Although opioids have been the mainstay of managing postoperative pain, their side effects such as respiratory depression, sedation, constipation, urinary retention etc. limit their use [8]. Moreover, many patients experience severe pain despite using intermittent intramuscular opioids [9, 10]. On the other hand 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 [11, 12]. Various studies have suggested that the addition of NSAIDs may reduce opioid requirements, improve pain relief and reduce respiratory depression [13, 14].

The present study included 50 adult patients who underwent abdominal hysterectomy under general anaesthesia. The primary end point of this study was the dose of rescue analgesia (morphine) required in 48 hours postoperatively to keep VAS < 4. In the present study the mean requirement of morphine in total 48 hour duration was 50±4.74 mg. The mean requirement of morphine in first 24 hours and between 24 to 48 hours was 37.80±3.81 and 12.20±4.99 mg respectively (Table 1). The requirement of morphine continued to decrease with each passing hour (Table 2) in the present study.

Lornoxicam is a relatively new NSAID. It belongs to the oxicam group [15]. 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. Its analgesic potency in animal pain models exceeds that of tenoxicam and piroxicam by approximately 12 and 3 fold respectively; whereas it is 4 to

6 fold more potent as compared to indomethacin and diclofenac [3]. Intravenous lornoxicam (8mg) has been shown to be as effective as morphine (20mg), pethidine (50mg) and tramadol (50mg) in the treatment of postoperative pain [16-18]. After intramuscular injection maximum plasma concentrations are achieved after approximately 20-25 minutes. Clonazepam and diazepam inhibit metabolism of lornoxicam. It does not interact with ranitidine and antacids [19, 20]. Concomitant administration of lornoxicam and anticoagulants or platelet aggregation inhibitors may prolong the bleeding time. It may increase the hypoglycemic effect of sulphonylureas and decrease the efficacy of diuretics and angiotensin converting enzyme (ACE) inhibitors.

Lornoxicam has been used in several trials for postoperative pain relief after various types of surgical procedures. Ilias and Jansen M [18] studied pain relief after hysterectomy in an observer blind randomized trial of lornoxicam versus tramadol. The study included 78 female patients aged 20-65 years. After surgery lornoxicam was given as intravenous injection in a dose of 4 mg and 8 mg while tramadol was given in a dose of 50 mg. The study concluded that intravenous lornoxicam at a dose of 8mg was superior to placebo and at least as effective as intravenous tramadol 50 mg in relieving moderate to intolerable post hysterectomy pain. Furthermore, lornoxicam seemed to possess a more favourable tolerability profile than tramadol.

Sapolya et al. [21] investigated the analgesic effects of lornoxicam after total abdominal hysterectomy in a randomized placebo controlled double blind study. Fifty patients were randomized to receive either oral placebo or lornoxicam 8mg an hour before surgery. All patients received patient controlled analgesia with tramadol. The authors concluded that a single oral dose of lornoxicam given preoperatively enhanced the analgesic effect of tramadol, decreasing tramadol consumption and side effect and shortened the length of hospitalization.

Kemal et al. [22] compared the analgesic effect of tramadol, tramadol-metamizol and tramadol-lornoxicam administered by intravenous PCA in 60 adult female patients undergoing lower abdominal surgery. The authors concluded that tramadol-metamizol and tramadol-lornoxicam combinations administered by intravenous PCA provided efficient post operative analgesia with lesser side effects.

Lornoxicam has also been compared to other NSAIDs in addition to its comparison to opioid analgesics. Sener et al. [23] in a prospective, randomized, placebo controlled, double blind study compared the efficacy of lornoxicam with diclofenac, ketoprofen and dipyrone for relief of acute postoperative pain in patients undergoing septoplasty. Patients were divided into five groups depending upon the drug used. The drugs were used intramuscularly. They used lornoxicam (8mg twice daily), diclofenac (75mg twice daily), ketoprofen (100mg twice daily), dipyrone (1g thrice daily) and placebo (twice daily). Intramuscular pethidine 1mg/kg^{-} was used as rescue analgesia. Pethidine requirement was found to be significantly higher in the placebo group. However, there was no significant difference among the remaining four groups.

İnan et al. [24] 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 PCA device. The authors observed that morphine consumption up till 48 hours in this study was 34.6±16.32 mg. In our study however, the morphine requirement was 50.0±4.74 mg, which was fairly high. 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 İnan et al. [24] have administered half of this dose 15 minutes before surgery. The lesser requirement of rescue analgesia in their study substantiates the role of pre- emptive analgesia as has been

observed by Trampitsch et al. [25], who 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.

Therefore the observation of the present study is in agreement with various studies carried out for observing the post operative analgesic effect of Lornoxicam. The requirement of rescue analgesic i.e. morphine continued to decrease with each passing hour in the present study and almost one third dose of morphine was required in the 2nd 24 hours as compared to the first 24 hours. However, further studies with more number of patients are required to authenticate the present observations.

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