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Original Article

Anaesthesia Section

A Comparative Study of Ketorolac with Lornoxicam as Pre-emptive Analgesics in Patients Who were Undergoing Elective Abdominal Surgery under General Anaesthesia

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ABSTRACT

Introduction: NSAIDs and opioids are the drugs which are commonly used in the post-operative pain management. The purpose of the present study was to determine the pre-emptive analgesic effects of lornoxicam, and ketorolac and the reduction in the opioid consumption post operatively.

Materials and Methods: Ninety patients of ASA class I-II, who were undergoing abdominal surgeries under general anaesthesia, were assigned in a randomized manner into three groups. Group K received a single IV injection of Ketorolac 30 mg (1ml), Group L received a single IV injection of lornoxicam 8mg (1ml) and Group P received IV saline (1ml) 1 hour before surgery.

Results: The post-operative pain scores were evaluated at 2, 4, 8, 12 and 24 hours by using a Visual Analogue Scale (VAS). The time taken to administer the first dose of rescue analgesic was significantly delayed in the Groups K and L as compared to Group P (291 min for gp K, 302 min for gp L as compared to P of 107 min, $p<0.001$). The pain scores between the Groups K and L were significantly lower as compared to those in Group P at 2,4, 8 ,12 and 24 hours. The twenty four hour analgesic consumption was significantly lower in Groups K and L as compared to that in Group P ($p<0.05$). The 24 hr total opioid consumption was 47 % and 54 % less in the lornoxicam and the ketorolac groups as compared to that in the placebo group. The degree of satisfaction with the post-operative pain management was excellent in 15 % and 40 % of the patients in Groups K and L respectively. Nausea and vomiting were seen more in Group P due to increased tramadol consumption.

Conclusion: Lornoxicam decreased the VAS score and the need for opioids as compared to ketorolac, by its pre-emptive administration. It was found to be an equally effective analgesic like ketorolac in abdominal surgeries.

Key Words: Pre-emptive analgesia, Abdominal surgeries, Lornoxicam, Ketorolac, Tramadol

INTRODUCTION

Pain relief during the post-operative period is usually inadequate, and the conventional approaches do not take into account the underlying mechanism. A new approach which provides adequate relief from pain during the post-operative period is the administration of an analgesic agent, either an opioid or an NSAID before the surgery. This concept is called pre-emptive analgesia, wherein the development of pain in the post-operative period is prevented. Pre-operatively administered analgesics prevent the nociceptive sensation which is generated during surgery due to the sensitizing of the central neurons in the spinal cord [1]. Thus, it prevents the post-operative pain from getting established, which is difficult to treat. Opioids are the gold standard for the post-operative pain management and they are commonly used but they are associated with respiratory depression, sedation, cardiovascular instability, nausea, and vomiting. NSAIDs lack these adverse effects and are used as alternatives to the opioids. Ketorolac is one of the NSAIDs which are commonly used for pre-emptive analgesia [1]. Lornoxicam is a newer oxicam class NSAID with a potent analgesic and anti-inflammatory activity, which is available as oral and parental formulations [2]. Hence, this study was aimed at determining the efficacy and safety of lornoxicam and ketorolac as pre-emptive analgesics in patients who were undergoing elective abdominal surgeries.

MATERIALS AND METHODS

This was a randomized, single dose, double blind, placebo controlled, comparative study. Patients who were aged between 20 to 50 years, of either sex, of ASA (American Society of Anaesthesiologists) grade 1 and 2, who were undergoing elective open abdominal surgery under general anaesthesia, were enrolled.

The patients who had received analgesic drugs within 2 weeks of surgery, those who were taking anti-platelet drugs (drug interaction), those who had a history of alcohol abuse, allergy to NSAIDs and gastric ulcer, pregnant women, children and those with hepatic, renal and cardiac impairment were excluded from the study. The institutional ethical clearance was obtained and informed consent was taken from all the patients.

Preoperative Examination

The routine pre-anaesthetic examinations and investigations of all the patients were done on the previous day of the surgery. All the patients received tab. alprazolam 0.25 mg and ranitidine 150 mg, the night before the operation. The patients were randomized to

3 groups of 30 patients each. The randomization was done by random numbers table into 3 groups.

- Group K received a single IV injection of Ketorolac 30 mg (1ml),
- Group L received a single IV injection of Lornoxicam 8mg (1ml) and
- Group P was taken as the control and it received IV saline (1ml).

The test drugs were administered approximately one hour before the induction of the anaesthesia. The patients were explained about how to describe the pain intensity on a visual analog scale (VAS) of 0 to 10.

Anaesthetic Technique

The patients in the 3 groups were pre-medicated with injection glycopyrrolate 0.2 mg IV, 15 minutes before the induction of the anaesthesia. All the patients were pre-oxygenated for 3 minutes with 100% oxygen. Fentanyl 2µg/kg was administered to all the patients before the induction and it was continued to be administered intra-operatively. The patients were induced with thiopentone sodium (4-7mg/kg, 2.5%), followed by injection suxamethonium chloride 2mg/kg, to facilitate endotracheal intubation. After adequate relaxation, laryngoscopy was performed and the intubation was done.

The anaesthesia was maintained with nitrous oxide, oxygen and isoflurane. Injection vecuronium was used as muscle relaxant. Injection neostigmine and injection glycopyrrolate were used for the reversal of the neuromuscular blockade. The patients were administered a rescue medication, injection tramadol 2mg/kg post-operatively, when the VAS score was more than 3.

The primary measurement of the efficacy was the pain intensity score which was measured on a Visual Analog Scale from 0 (no pain) to 10 (severe pain) at 2, 4, 8, 12 and 24 hours. The total VAS score at the end of 24 hours was assessed to compare the analgesic efficacy of these drugs. The above parameters were assessed by a trained nurse observer who was unaware of the study medication. Neither the patient nor the observer knew which drug was administered to them.

The analgesic duration, which is the duration of the analgesia between the time of the end of the surgery and the time of the first rescue dose of analgesia which was given, was noted. In addition, the total amount of the rescue medication which was given was noted. Adverse effects like nausea and vomiting were observed and ondansetron was administered to the patients who complained of vomiting.

The patient's satisfaction (global efficacy) was assessed at the 24th hour by patients on a 4-point Likert's scale, in which

1. Poor
2. Fair
3. Good and
4. Excellent

The patients were withdrawn from the study if the tramadol requirement was more than 3 doses during the first 4 hours, if they demanded analgesia more than 2 times during the 2 hours period following the initial 4hours or if they consumed the total daily dose allowance before the end of the 24 hours observation period.

Statistical and Analysis Methods

The sample size was determined by power analysis with power of 0.95 and it was found to be 30 in each group. The demographic data which was obtained was analyzed by using descriptive statistics which was expressed as mean ± standard deviation. For comparing the continuous variables such as weight, age, duration of the surgery and the time for the first analgesia, the ANOVA test was performed. The VAS pain scores were analyzed by using ANOVA and the Bonferroni adjustment was used for comparing the intragroup VAS values. The total analgesic consumption of the groups was compared by using the Kruskal Wallis test and between the groups, it was compared by the Mann-Whitney U-test. The sex, ASA grade, patient satisfaction (global efficacy score) between the groups and the incidence of the side effects were analyzed by using the Chi square test. A probability (p) value of <0.05 was considered as statistically significant. The statistical analysis was performed by using SPSS, version16.0 (SPSS Inc, Chicago, IL, April 2008).

RESULTS

There were no significant differences between the groups with regards to the demographic variables (age, gender, weight and ASA physical status) or the mean duration of the surgery in minutes [Table/Fig-1]. The most common abdominal operations included acute appendectomy, cholecystectomy, hernia repair, hysterectomy and laprotomy.

The changes in the post-operative VAS pain scores are shown in [Table/Fig-2]. The VAS pain scores which were recorded at 2, 4, 8, 12 and 24 hrs after the operation were higher in Group P, as compared to those in Groups K and L (p=0.0001).

The pain scores were significantly lower in the lornoxicam group as compared to those in the placebo group at 2, 4, 8, 12 and 24 hrs (*p*=0.0001). The pain scores were significantly lower in the ketorolac group at 2, 4, 12 and 24 hrs as compared to those in the placebo group. There was no difference in the pain score between the ketorolac and the lornoxicam groups (p>0.05).

Groups	Group K (n=30)	Group L (n=30)	Group P (n=30)	P value
Gender (M/F)	15/15	16/14	19/11	0.410
Age (year)	38.60 ± 14.38 (20-60)	39 ± 12.99 (20-60)	37.85 ± 14.61 (20-68)	0.966
Weight (kg)	54.45 ± 7.10 (35 - 64)	53.75 ± 8.75 (37-70)	56.60 ± 11.38 (44 - 100)	0.600
ASA (I/II)	17/13	15/15	19/11	0.435
Duration of surgery (min)	110.50 ± 52.53 (45-270)	127.50 ± 51.61 (60-270)	121.75 ± 58.85 (60-300)	0.606

[Table/Fig-1]: Demographic characteristics and duration of surgery
Values in parenthesis indicates the range.

VAS	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs
Group K	3# (2-6)	3# (2-6)	4.5*# (2-7)	3# (2-6)	3 # (2-5)
Group L	2# (2-4)	2.5*# (2-6)	4*# (2-6)	3*# (2-6)	2 # (2-5)
Group P	6 (3-9)	6 (2-8)	5.5 (3-8)	6 (2-9)	4 (2-9)
ANOVA P value	0.0001#	0.0001#	0.0001#	0.0001#	0.0001#

[Table/Fig-2]: Post-operative VAS values [Median (min-max)].
*Significant as compared to 2 hrs in each group. Group K - p = 0.004 at 8 hours as compared to 2 hours. Group L - p = 0.033, 0.0001 & 0.005 at 4, 8 and 12 hours as compared to 2 hours.
p=0.0001- Group K and Group L significant as compared to placebo at 2,4, 8, 12 and 24 hours.

	Group K	Group L	Group P	p
Time for first tramadol administration (min)	291.25 ± 100.34* (140-480)	302.75 ± 92.57* (75-420)	107.50 ± 50.71 (30-290)	0.0001
Analgesic consumption (mg)	194.20 ± 81.45* (50-360) 53%	170.40 ± 65.20* (88-288) 46%	365.70 ± 182.18 (128-1000)	0.0001
Number of patients requiring tramadol (percentage)	29 (97%)	30 (100%)	30 (100%)	

[Table/Fig-3]: Analgesic required and postoperative analgesic requirements [Mean ± SD, (min-max)].
*p<0.05: compared to Group P.

	Group K	Group L	Group P	P
1 Poor	–	–	65	0.0001 *
2 satisfactory/adequate	35	15	35	
3 very good	50	45	–	
4 excellent	15	40	–	

[Table/Fig-4]: Patient satisfaction [percentage].
*significant as compared to placebo

Within the groups, the pain scores at 8 hours were significantly lower (p=0.004) as compared to those at 2 hours in the ketorolac group, whereas in the lornoxicam group, the pain scores were lower at 4, 8 and 12 hours as compared to those at 2 hours (p =0.033, 0.0001 and 0.005 respectively).

There was a significant difference with respect to the first analgesic requirement time between the three groups. The time for the first analgesic requirement was longer in the lornoxicam (302.75 ± 92.57 min) and the ketorolac groups (291.25 ± 100.34 min) as compared to that in the placebo group (107.50 ± 50.71 min) (p=0.0001) [Table/Fig-3]. The amount of analgesic consumption was significant between the groups and it was less in the ketorolac (47%) and the lornoxicam (54%) groups as compared to that in the placebo group (p=0.0001). There was no statistical difference in the analgesic consumption between the lornoxicam and the ketorolac groups. Tramadol was used in all the patients who received placebo and lornoxicam and in 96.6% of the patients who received ketorolac [Table/Fig-3].

The degree of satisfaction with the post-operative pain management was excellent in 15 % and 40% of the patients who received ketorolac and lornoxicam (p=0.0001) respectively [Table/Fig-4].

The most frequent side effects in both the groups were nausea and vomiting and their incidence was significantly higher in the placebo group as compared to those in Group L (p<0.05).

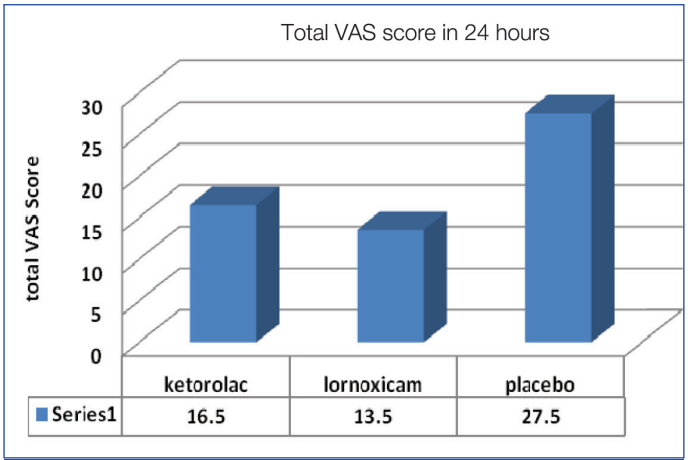
DISCUSSION

Based on the mechanism pain can be divided into nociceptive, inflammatory and neurogenic pain. Nociceptive pain is often regarded as the key feature of the acute post-operative pain, the most common form of the acute pain symptoms. However, in addition to the incisional damage to the skin and various other tissues, the nociceptive barrage during surgery is followed by a protracted inflammatory state which is mediated by prostaglandins in the post-operative period. The transmission of the pain signals which are evoked by tissue damage during surgery leads to the sensitization of the peripheral and the central pain pathways. The only way to prevent the sensitization of the nociceptive system is to block completely any pain signal which originates from the surgical wound from the time of the incision until the final wound healing [3, 4]. Thus, the concept of pre-emptive analgesia was postulated.

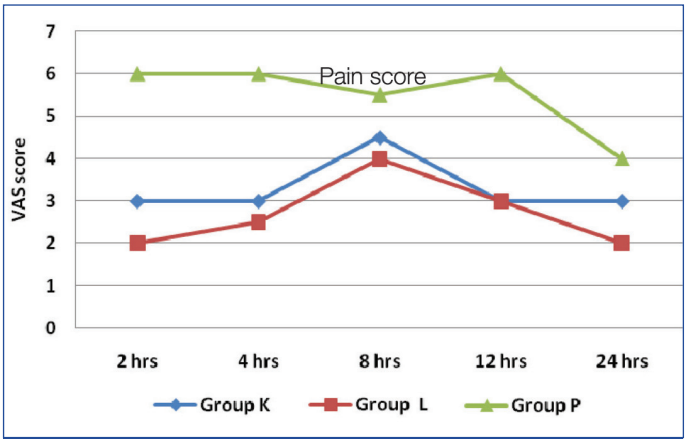
The present study demonstrated that that pre-emptive administration of the test drugs produced a significant decrease in the VAS score at 2,4, 8 hours and 24 hours, which was suggestive of the effectiveness of the analgesic drugs as compared to the placebo. [Table/Fig-3]. The findings of this study confirmed those of other studies, wherein the VAS score was significant at 12 and 24 hours in the active comparator groups (lumiracoxib, rofecoxib) as compared to placebo till 30 hours [Table/Fig-5] [5, 6]. The surgical damage produced the upregulation of PGE_2, IL-6 and IL-8 in CSF and the surgical sites (upto 25 to 30 hours), that amplified the post-operative pain because of hyperalgesia [6]. Hence, it can be explained that the pre-operative administration of NSAIDs decreased the PGE_2 and the IL-6 in the CSF and the surgical sites upto 30 hours, which was correlated with a decreased VAS score [7].

The 24 hours total opioid consumption was 47% and 53.5% less in the lornoxicam and the ketorolac groups as compared to that in the placebo group and the time for the first tramadol administration for the pain was more in the lornoxicam and the ketorolac groups. This indicated that NSAIDs had an opioid sparing effect and that they could be used for pre-emptive analgesia. The advantages of reducing the narcotic usage were evident as the patients were more alert and cooperative and as they could ambulate more rapidly. Besides their analgesic effects, the anti-inflammatory properties of NSAIDs decrease the inflammatory mediators in the post-operative period, thus contributing significantly to the recovery of the patients as compared to opioids in the post-operative period.

Lornoxicam has been successfully used in the prevention and treatment of post-operative pain [8,9]. Lornoxicam provides an alternative to morphine and tramadol for the treatment of post-operative pain, with fewer adverse events after hysterectomy [10]. Lornoxicam suppresses the inflammatory mediators like the prostagland in production at the time of the surgical trauma. Ketorolac, as a pre-emptive analgesia for laporoscopic surgeries, has been demonstrated to reduce the need for narcotic medication in the post-operative period [11]. Previous studies have established the pre-emptive analgesic effects at a dose of 8mg for lornoxicam and at a dose of 30mg for ketorolac [12,13]. The pre-operative administration of lornoxicam 8 mg had a greater analgesic efficacy in the prevention of the post-operative pain than its post-operative administration in male patients who were undergoing varicocelectomy [Table/Fig-6] [14]. Intravenous ketorolac, as pre-emptive analgesia, had a longer pain free time interval and the request for the first analgesic supplement was made after 90 minutes as compared to a shorter interval of 60 minutes in the intramuscular diclofenac sodium group, in laparoscopic surgeries [15]. Thus, pre-emptively, its administration improved the quality of the post-operative analgesia. Intravenous lornoxicam 8 mg was found to be equianalgesic to 20 mg of morphine, 50 mg of pethidine and 50 mg of tramadol [16]. The objective data from the present study revealed that the analgesic consumption was lower and that the



[Table/Fig-5]: Total VAS score in 24 hours



[Table/Fig-6]: VAS score in post operative period
Group K - Ketoraolac, group L- Lornoxicam and group P - Placebo

time for first tramadol use was more in the lornoxicam than in the ketorolac group, even though it was insignificant.

The total VAS score was less in Group L as compared to that in Group K. The quality of the post-operative analgesia was excellent in 40% of the patients in the lornoxicam group as compared to 15% in the ketorolac group. This indicated that lornoxicam had an advantage over ketorolac. Studies have shown that lornoxicam releases endogenous dynorphin and beta endorphin in the spinal cord, thus providing a central analgesic effect apart from the anti-inflammatory, peripheral analgesic action through prostaglandin synthesis inhibition at the site of the surgery [16].

Lornoxicam has a time-to-peak effect of approximately 20–30 min and an elimination half-time of 3–5 h in healthy young volunteers [17]. The 5′-hydroxy metabolite has a mean terminal elimination t 1⁄2 of about 11 hours with a range of 6 to 24 hours for a single 4mg dose, and a range of 8.5 to 9 hours after a parenteral single or twice daily doses [18].

The biological activity of Ketorolac tromethamine is associated with the S-form. The peak analgesic effect of Ketorolac tromethamine occurs within 2 to 3 hours. The half-life of the Ketorolac S-enantiomer was approximately 2.5 hours as compared to the 5 hours of the R-enantiomer. The half-life for the racemate has been reported to lie within the range of 5 to 6 hours. Whereas the major metabolites of ketorolac are glucuronide conjugate , which may also be formed in the kidney, and p-hydroxy ketorolac. Neither metabolite has a significant analgesic activity [19].

The most frequent side effects were nausea and vomiting in the placebo group. Visceral and pelvic pains were the frequent causes of the post-operative nausea and vomiting. Studies reported the improvement of the nausea after the treatment of the pain [20].The reason for a high incidence of nausea and vomiting in Group P may be visceral and pelvic pains and a higher consumption of opioids in the post-operative period. Hypotension can be caused by opioid use. NSAIDs are known for their tendency to cause bleeding, as a result of the inhibition of cyclooxygenase and thereby, platelet aggregation. But a meta-analysis of 1368 patients who were undergoing tonsillectomy reported that the incidence of the post-operative bleeding was not affected by the NSAID consumption [21]. In the present study, none of the patients had significant post-operative bleeding in the lornoxicam and the ketorolac groups.

Another aspect was the outcomes like the shorter time in physical therapy and the early mobility and rehabilitation which were seen in patients who received NSAIDs pre-emptively. This could be because of the decreased VAS score in those groups, which was correlated with a decrease in PGE_2 and IL-6 at the site of the operation [7].

Thus, pre-emptive analgesia may prevent the nociceptive input which is generated during surgery via the sensitizing central neurons. Owing to this 'protective' effect on the nociceptive system, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment which is initiated after the surgery. It has been suggested that pre-emptive analgesia may reduce the risk of developing chronic post-operative pain [1]. In a study on patients who were undergoing limb amputation, who were allocated pre and intra-operative epidural blockade or an intra-operative blockade alone, the occurrence of phantom limb pain for the subsequent 12 months was assessed. The results showed a significant reduction in the phantom limb pain 6 months post-operatively in the pre- and the intra-operative groups [1].

Post-operative lornoxicam should also be compared to pre-emptive lornoxicam to unlock its true pre-emptive analgesic effect. The follow up of the patients should have been made beyond 24 hours in order to assess the effect of the pre-emptive analgesics, the post-operative recovery, and the early rehabilitation.

CONCLUSION

Lornoxicam and ketorolac are useful pre-emptive analgesics which are used for the post-operative pain, especially in patients who undergo abdominal surgeries and have a significant opioid sparing effect. This minimises the related adverse effects of the opioids and at the same time, improves the quality of the post-operative analgesia. Lornoxicam appears to be better than the ketorolac analgesic, as was seen by a lesser VAS score, a better quality of analgesia and less tramadol requirement which were related to its use. Hence, lornoxicam is an equally effective a pre emptive analgesic as compared to ketorolac.

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