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Comparison of Intramuscular Lornoxicam and Diclofenac Sodium for Pre-Emptive Analgesia in Patients Undergoing Open Cholecystectomy.

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ABSTRACT

The present study was undertaken to study and compare the efficacy of lornoxicam and diclofenac sodium for pre-emptive analgesia in open cholecystectomy patients. A total of 90 adult patients having physical status grade I and II according to American Society of Anaesthesiologists (ASA) undergoing open cholecystectomy under general anaesthesia were included in the study. Patients were randomly allocated to one of the three groups. Each group consisted of 30 patients. Group I Patients were administered Inj. Normal Saline 2ml (placebo) intramuscular 30-45 minutes prior to induction of anaesthesia. *Group II* Patients were administered diclofenac 75mg intramuscularly 30-45 minutes prior to induction of anaesthesia. . *Group III* Patients were administered lornoxicam 8mg intramuscularly 30-45 minutes prior to induction of anaesthesia. Rescue analgesia was given in the form of Inj. Butorphanol 0.025 kg^{-1} intravenously.The pain intensity scores were significantly lower in and pain relief scores were significantly better in Group-II (diclofenac) and Group-III (lornoxicam) as compared to Group-I (placebo) but there was no difference in pain scores between Group-II and Group-III.Pain relief scores were significantly higher in Group-II (diclofenac) and Group-III (lornoxicam) as compared to Group-I (placebo) but there was no difference in pain relief scores between Group-II and Group-III. Time to demand for the first dose of rescue analgesic i.e. butorphanol was significantly ($p<0.01$) longer in Group-II (501.40± 56.11 minutes) and Group-III (504.43±63.22 minutes) as compared to placebo Group-I (234.47±41.47 minutes) but there was no difference in the time to demand for first dose of rescue analgesic between Group-II (diclofenac) and Group-III (lornoxicam). Therefore cumulative 24 hours analgesic requirements were comparable in all the three groups. Hence it is apparent that both the study drugs have no effect on twenty four hour analgesic requirements when given pre-emptively. Postoperative nausea and vomiting (PONV) were the main side effects observed during study period. The incidence of side effects was significantly lower in Group-III (lornoxicam) as compared to Group-I (placebo) and Group-II (diclofenac). Both lornoxicam and diclofenac have significant pre-emptive analgesic effect, are equally effective but lornoxicam is associated with significantly lower incidence of side effects (PONV). Therefore lornoxicam is a better drug than diclofenac when used pre-emptively in open cholecystectomy.

Keywords: Diclofenac, Lornoxicam, Pre-emptive analgesia, Open Cholecystectomy.

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INTRODUCTION

Pre-emptive analgesia is a recent concept for the management of postoperative pain and it implies that the analgesic should be given before the painful stimulus is applied [1]. Pre-emptive analgesia is defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from injuries. Earlier definitions that have been used in various clinical trials had limitations. Pre-emptive analgesia has been defined as: 1) antinociceptive treatment starting before surgery; or 2) antinociceptive treatment that prevents central sensitization. It is important to consider the definition used in a clinical trial for determining the effectiveness of pre-emptive analgesia. Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce central sensitization. Owing to this 'protective' effect on the nociceptive system, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Theoretically, immediate postoperative pain may be reduced and the development of chronic pain may be prevented [2].

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.

Both diclofenac and lornoxicam have similar pharmacokinetics on intramuscular injection with similar peak plasma levels in 25- 30 minutes. Some studies have indicated that lornoxicam has a better tolerability profile and fewer side effects. Therefore, we studied the efficacy of intramuscular lornoxicam as pre-emptive analgesic and compared it with diclofenac in patients undergoing open cholecystectomy. Effects on the postoperative analgesic requirements and side effects were studied.

MATERIAL AND METHODS

This comparative study was conducted in 90 patients of either sex, belonging to ASA physical status grade I and II, between the ages of 20-50 yrs, weighing between 40-70 kg who underwent elective open cholecystectomy under general anaesthesia in Indira Gandhi Medical College and Associated Hospitals, Shimla. Informed consent was taken from these patients. The hospital ethical committee was informed about the procedure to be undertaken and the risk involved to these patients. These patients were divided into three groups of 30 each using a random chart and drugs were given intramuscularly in a double blinded manner.

Group I: All the 30 patients in this group were given Inj. Normal saline 2 ml (placebo) *im 30*–45 minutes prior to induction of anaesthesia.

Group II: All the 30 patients in this group were given Inj. Diclofenac 75 mg *im* 30-45 minutes prior to induction of anaesthesia.

Group III: All the 30 patients in this group were given Inj. Lornoxicam 8 mg *im* 30-45 minutes prior to induction of anaesthesia.

Exclusion Criteria: The following classes of patients were excluded from the study

- Pregnant and lactating female patients.
- Hypersensitivity to NSAIDs.
- H/O peptic ulcer, upper GI disease, ulcerative colitis, smoking, concurrent steroids, alcohol abuse etc.
- H/O bleeding tendencies, cirrhosis and esophageal varices.
- Chronic uncontrolled systemic diseases e.g. diabetes mellitus, hypertension, asthma, collagen disorders etc.
- Use of any analgesic for chronic pain.

All the eligible patients were examined thoroughly one day before surgery and were explained the Four Point scale for pain intensity and Five Point scale for pain relief to record pain and subjective sensations.

All the patients were premedicated with alprazolam 0.5 mg orally the night before surgery and 0.25 mg orally two hours preoperatively. Tab. pantoprazole 40 mg was given orally two hours preoperatively. Intravenous line was started one hour prior to induction of anaesthesia in preoperative room and Inj. Normal saline 2 ml (placebo) *im* 30- 45 min prior to induction of anaesthesia in Group I patients , Inj. Diclofenac 75 mg *im*in Group II patients and Inj. Lornoxicam 8 mg *im* in Group III patients was given. On the operation table, patient was attached to GE DatexOhmeda S/5 monitor (Datex Inc. Finland) for monitoring of continuous heart rate, ECG lead- II, noninvasive blood pressure (NIBP) and pulse oximetry. Pre-induction values of all these parameters were recorded. Capnography was started after intubation of the patient.All the patients were given Inj. ondansetron 4mg *iv*slowly at the time of induction as a prophylaxis against postoperative nausea and vomiting.

The patients were induced with propofol 2mg kg^{-1}*iv* and orotracheal intubation was facilitated with succinylcholine 1.5 mg kg^{-1}*iv*. Anaesthesia was maintained with 66% N_2O in oxygen, halothane 0.5%-0.8% and atracurium 0.5 mg kg^{-1} along with intermittent positive pressure ventilation on Ohmeda 7000 anaesthesia ventilator to maintain normocarbia. Intra-operative analgesia was provided by pentazocine 0.5 mg kg^{-1}*iv*. Residual neuromuscular blockade was reversed with Neostigmine 0.05 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1} *iv*. After successful reversal patients were extubated.

Postoperatively the following parameters were recorded: - 1.) Pain intensity and pain relief scores for first 24 hours i.e. at 0, 2, 4, 6, 8, 12, 16, 20 & 24 hours. 2.) Vitals for 24 hours. 3.) Side effects, if any. 4.) Total analgesic requirement in first 24 hours. Time to first demand of rescue analgesic was noted. All the patients were observed for any untoward side effects like nausea, vomiting, sedation, restlessness etc. If analgesia was inadequate and the pain intensity ≥ 2, then rescue medication was given in the form of injection butorphanol 0.025mg kg^{-1}*iv*.

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. The data obtained were compiled and analysed statistically by using student's t test and chi-square test.

RESULTS

Demographic features of patients in both the groups were comparable with regards to age and body weight. The mean age of patients was 38.70 $\pm$ 5.72 years in Group-I, 37.50 $\pm$ 6.65 years in Group-II and 38.07 $\pm$ 7.02 years in Group-III. The mean weight of patients was 54.27 $\pm$ 9.25 kg in Group-I, 52.80 $\pm$ 7.66 kg in Group-II and 56.37 $\pm$ 9.56 kg in Group-III. The difference in the mean age and weight of the patients in the three groups was statistically insignificant ($p>0.05$).

Baseline parameters-Mean Pulse rate was 82.10 $\pm$ 4.53 per minute in Group-I, 81.23 $\pm$ 8.00 per minute in Group-II and 83.93 $\pm$ 8.05 per minute in Group-III respectively. Mean systolic blood pressure was 128.33 $\pm$ 4.84 mmHg in Group-I (placebo), 129.77 $\pm$ 7.39 mmHg in Group-II (diclofenac) and 129.10±8.47 in Group-III (lornoxicam). The mean diastolic blood pressure was 82.33 $\pm$ 5.59 mmHg in Group-I, 82.23 $\pm$ 7.10 mmHg in Group-II and 83.43 $\pm$ 4.23 mmHg in Group-III. The mean blood pressure was 97.67 ± 4.19 mmHg in Group I, 98.10 $\pm$ 6.63 mmHg in Group-II and 98.90 $\pm$ 7.52 mmHg in Group-III. The difference in baseline hemodynamic parameters between Group-I, Group-II and Group-III was statistically insignificant.

The pain intensity scores were recorded at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours postoperatively. The scores were significantly higher in Group-I (placebo) as compared to Group-II (diclofenac) at 0, 4, 12, 16, 20 & 24 hours. Whereas pain intensity scores at 6 and 8 hours postoperatively were significantly lower in Group-I as compared to Group-II. As compared to Group-III (lornoxicam) the pain intensity scores of Group-I (placebo) were higher at 0, 4, 12, 16 & 20 hours postoperatively and lower at 6 and 8 hours which was found to be statistically significant ($p<0.05$). Lower pain intensity scores at 6 and 8 hours in the placebo group coincided with administration of rescue analgesic. The pain intensity scores of Group-III were significantly ($p<0.01$) higher as compared to Group-II at 24 hours postoperatively.

Pain relief scores were recorded at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours postoperatively in all the three groups. As compared to Group-II (diclofenac) the pain relief scores of Group-I (placebo) were significantly lower at 0, 2, 4,12, 16, 20 & 24 hours postoperatively and higher at 6 and 8 hours postoperatively. This better quality of pain relief in the placebo group at 6 and 8 hours coincided with the dose of rescue analgesic. The pain relief scores of Group I (placebo) were significantly lower than Group-III (lornoxicam) at 0, 2, 4, 12, 16 & 20 hours postoperatively and significantly higher than Group-III at 6 and 8 hours postoperatively. The pain relief scores of Group-II as compared to Group-III were significantly lower at 6 hours and significantly higher at 24 hours postoperatively.

Pulse rate**,** systolic, diastolic and mean blood pressure was recorded at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours postoperatively.

The mean pulse rate was significantly higher in Group-I at 4 hours postoperatively and significantly lower at 6, 8, 12 and 16 hours postoperatively as compared to Group-II. The pulse rate in Group-I was significantly ($p<0.05$) higher than Group-III at 2 and 4 hours postoperatively and was significantly ($p<0.01$) lower than Group-III at 8 hours postoperatively. The pulse rate in Group-II was significantly ($p<0.05$) higher than Group-III at 2, 16 and 24 hours postoperatively. At all other times during study period the pulse rate of the three study groups was comparable.

Mean systolic BP between Group-I and III was statistically significant at 0 and 4 hours postoperatively. The difference in mean systolic BP between Group-II and III was statistically significant at 6, 8 and 24 hours postoperatively. Diastolic BP of Group-I was higher than Group-III at 2 and 4 hours postoperatively which was found to be statistically significant ($p<0.01$).At 6 hours postoperatively the diastolic BP of Group-II was higher than Group-III which was statistically significant ($p<0.05$). During all other study period the diastolic BP was comparable in all the three study groups. The mean BP of Group-I was higher than mean BP of Group-III at 2 and 4 hours postoperatively which was found to be statistically significant ($p<0.01$). The mean BP of Group-II was higher than Group-III at 4 and 6 hours postoperatively and it was statistically significant. Except on these occasions the mean BP was comparable in all the three study groups during whole period.

Mean time to the demand for rescue analgesic was 234.47 $\pm$41.47 minutes in Group-I, 501.40 $\pm$56.11 in Group-II and 504.43 $\pm$63.22 in Group-III. The difference in the mean time to demand rescue analgesic in Group-I and II, and in Group-I and III was statistically significant. The difference in Group-II and III was statistically insignificant.

In Group-I (placebo) out of 30 patients 29 patients required only one dose of rescue analgesic (butorphanol 0.025mg kg^{-1}*iv*) whereas 1 patient demanded two doses of rescue analgesic. In Group-II (diclofenac) all the 30 patients required only one dose of rescue analgesic (butorphanol 0.025mg kg^{-1}*iv*). In Group-III (lornoxicam) also all the 30 patients required only one dose of rescue analgesic (butorphanol 0.025mg kg^{-1}*iv*). The results of all the three study groups were comparable with regard to total analgesic requirement in 24 hours.

Postoperative nausea and vomiting (PONV) were the main side effects observed during study period. In Group I (placebo) out of 30 patients 5 patients developed PONV (4 patients developed nausea & 1 patient developed vomiting) during the study period. The incidence of side effects in Group-I came out to be 16.66 %. In Group-II (diclofenac) out of 30 patients 4 patients reported PONV (1 patient reported nausea and 3 patients reported vomiting) making an incidence of side effects to be 13.33 %. Whereas in Group-III (lornoxicam) only 2 patients developed PONV (1 patient developed nausea and 1 patient developed vomiting) with an overall incidence of side effects of 6.66 %. Thus it was observed that the incidence of side effects was significantly lower in Group-III (lornoxicam) as compared to Group-I (placebo) and Group-II (diclofenac) as shown in Table I and Fig.I .No other side effects like increased bleeding, asthma or allergic reactions were seen in any of the groups. Overall incidence of side effects i.e. PONV was 12.22%.

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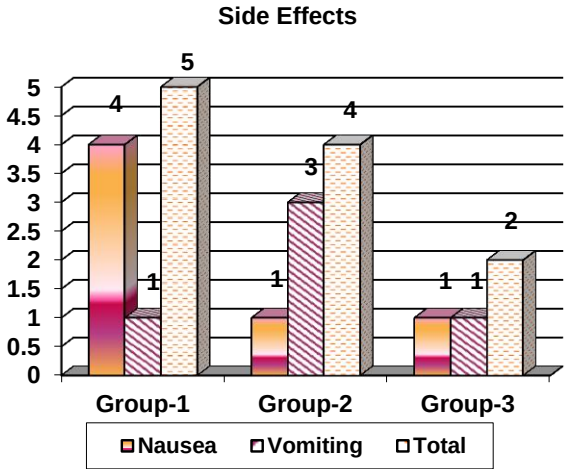
Table. I Side Effects

Side Effects	Group					
	I		II		III	
	No.	%age	No.	%age	No.	%age
Nausea	4	13.33%	1	3.33 %	1	3.33 %
Vomiting	1	3.33 %	3	10%	1	3.33 %
Total	5	16.66%	4	13.33%	2	6.66 %

Fig. I: Side Effects



DISCUSSION

The concept that pain should be anticipated and pre-empted with analgesic techniques targeted at the periphery sensory inflow in nerves and cells in the central nervous system is in existence for a long time. This concept of pre-emptive analgesia has received renewed interest in the recent past. In the past, number of studies has been conducted to understand the pre-emptive effect by preoperative administration of local anesthetic by local infiltration, nerve blocks or by using regional techniques. Studies have been conducted using various drugs either alone or in combination to assess the value of pre-emptive analgesia in the management of acute postoperative pain.

Buggy DJ et al [3] reported pre-emptive analgesic effect of diclofenac in a randomized double blind study on 40 healthy female patients, undergoing laparoscopic tubal ligation. The treatment group had lower pain and a longer latent period until the request for first dose of morphine. Pre-emptive effect has been described as delayed onset of pain or lesser severity of pain (lower pain scores) and decreased requirement of analgesic in postoperative period or all of these.

Gong ZY et al [4] reported that lornoxicam provides an alternative to morphine and tramadol for the treatment of postoperative pain after hysterectomy, when given preoperatively. Statistically significant equivalence of lornoxicam, morphine and tramadol was shown by TOTPAR (total pain relief) and SPID (summed pain intensity difference) values respectively. However lornoxicam caused fewer adverse events than morphine and tramadol (10.0% vs. 26.7% and 17.2% of patients respectively). Based on a series of cases, Ovechkin AM et al [5] recommended preoperative lornoxicam in combination with local anaesthetics to reduce postoperative pain and inflammatory responses. Inanoglu K et al [6] conducted a study to know the

analgesic efficacy of preoperative versus postoperative lornoxicam in varicocele repair and they concluded that intravenous lornoxicam administered before surgery has a better analgesic effect for varicocelectomy than when administered postoperatively. Trampitsch et al [7] suggested that lornoxicam administered pre-emptively improved the quality of postoperative analgesia and opioid consumption in patients undergoing gynaecological operations. Our study correlates with these studies in proving that lornoxicam used preoperatively provides better postoperative pain relief when compared to placebo and is equally efficacious when compared to diclofenac. However in our study 24 hour analgesic requirements did not differ in all the three groups. All patients (except one patient in placebo group who required 2 doses) required only one dose of the rescue analgesic i.e. butorphanol 0.025mg kg^{-1}*iv.*

In our study the time to demand for first rescue analgesic was compared in all the three groups. It was found in our study that lornoxicam increased the duration of demand of analgesia significantly when compared with placebo but it was similar to diclofenac group. This finding contradicts a variety of other studies in which lornoxicam was found to be more effective than other conventional analgesics.

Petrova VV et al [8] in their study of 140 patients undergoing oncologic surgeries studied the analgesic effects of lornoxicam, comparing it to ketorolac (60–90 mg) and ketoprofen (200-320 mg). It was found that lornoxicam was superior to even the highest doses of other agents in this study with respect to duration for the demand of rescue analgesic. Also it was associated with lesser consumption of rescue analgesic buprenorphine. The results of this study were comparable with that of ours.

Karamen S et al [9] studied the effects of preoperative intramuscular lornoxicam (8 mg) and compared with ketoprofen (100 mg) in patients undergoing abdominal hysterectomy. It was found in their study that both reduced morphine consumption and lornoxicam was found to be better than ketoprofen. Isik B et al [10] conducted a prospective, double blind, randomized study to assess the efficacy and adverse effects of preoperatively administered lornoxicam versus tramadol in adults, for post-tonsillectomy pain. They concluded that preoperative 8 mg lornoxicam was more effective than 50 mg tramadol with respect to early postoperative tonsillectomy pain in adult patients, and side effects i.e. nausea-vomiting, bleeding and postoperative haemorrhage values were similar between the two groups. Papadima A et al [11] conducted a prospective, randomized, double-blind, placebo-controlled trial comparing the efficacy of lornoxicam versus parecoxib for the management of pain after laparoscopic cholecystectomy. They concluded that parecoxib 40 mg *iv*and lornoxicam 8 mg *iv* were equi-analgesic and both were more efficacious than placebo for the management of pain after laparoscopic cholecystectomy. In our study we monitored pain intensity scores, pain relief scores, time to demand for rescue analgesic during 24 hours and found both lornoxicam and diclofenac equally effective, however incidence of side effects was higher with diclofenac.

Likar R et al [12] in a multi-centre trial reported that lornoxicam is well tolerated in most clinical trials, especially with regard to GI side effects. Safety and efficacy of lornoxicam was comparable to standard analgesic treatment of the respective centre. However, the incidence of serious adverse events or adverse drug reactions was lower in the lornoxicam group than in the standard analgesic treatment group. Gong ZY et al [13]also reported that lornoxicam had fewer adverse events when given preoperatively for pain relief after hysterectomy as compared to morphine and tramadol. Our study correlates with these studies as we also found that incidence of side effects was significantly less in the patients who received lornoxicam (6.66%) as compared to patients who received diclofenac (13.33%) or placebo (16.66%).

With the foregone part of discussion it is evident that both diclofenac sodium and lornoxicam have been compared with either opioid or other NSAID analgesics. There are fewer studies having compared lornoxicam directly with diclofenac sodium. However there is abundance of studies especially of lornoxicam having been compared with almost all other NSAIDs. Despite the claims of very high efficacy of lornoxicam on the basis of *in-vitro*[14,15] experimental studies, efficacy of pharmacological doses of lornoxicam is comparable with conventional NSAIDs including diclofenac sodium. Our study convincingly supports this evidence.

Time for the demand of first and the only dose of analgesic i.e. butorphanol was prolonged by similar duration in treatment groups of our study. Until the administration of rescue analgesic i.e. butorphanol, pain scores were significantly higher in placebo group. These findings support the pre-emptive effect of both lornoxicam and diclofenac sodium.

So far as reduction in cumulative requirement for postoperative analgesia is concerned, unlike most other studies we did not observe any reduction in postoperative analgesic requirement. This decreased requirement of analgesia in all groups could be because long duration of action of our rescue analgesic i.e. butorphanol. Use of a short acting opioid preferably given as small incremental doses through PCA could have reflected the post-operative analgesic requirement more precisely.

CONCLUSION

Based on the above observations we conclude that both lornoxicam and diclofenac have significant pre-emptive analgesic effect, are equally effective but lornoxicam is associated with significantly lower incidence of side effects (PONV). Therefore lornoxicam is a better drug than diclofenac when used pre-emptively in open cholecystectomy.

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