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Original Article

COMPARISON OF PRE-EMPTIVE USE OF DICLOFENAC, KETOROLAC AND TRAMADOL FOR POST-OPERATIVE PAIN IN LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT:

Under treatment of postoperative pain has been the topic of several recent editorials[1]. The prevention, recognition, and management of postoperative pain in adults, as well as in children, have been receiving a great deal of interest. The poor outcome obtained with current regimens is primarily due to the inadequacies of drug administration techniques rather than the qualities of opioids themselves[2].

In this prospective study comparison of preemptive use of diclofenac, ketorolac and tramadol was done for postoperative pain in laparoscopic cholecystectomy.60 patients were divided into three groups. Group A received injection Diclofenac (3mg/kg) 75mg maximum at a time. Group B received injection Ketorolac (30 mg). And group C patients received injection Tramadol (100 mg). All drugs were given intravenous half an hour before induction. Analgesic efficacy was measured in VAS scale. In addition pulse, systolic blood pressure, diastolic blood pressure, mean blood pressure, total pethidine requirement and time of first pethidine requirement were recorded Patients received an increment of 10-20 mg of pethidine when pain score was 3-4.

In this study, total pethidine consumption in group A is 56.5±5.14, in group B is 46.75±4.65 and in group C is 49±5.42. It shows that group B and group C have same analgesic effectiveness and which is better than group A.

On the basis of present prospective clinical study postoperative pain can be managed by preemptive use of diclofenac, ketorolac and tramadol. The analgesic efficacy of ketorolac and tramadol is same and better than diclofenac.

Key Words: Pre-emptive analgesia, Laparoscopic cholecystectomy.

INTRODUCTION:

Under treatment of postoperative pain has been the topic of several recent editorials[1]. The prevention, recognition, and management of postoperative pain in adults, as well as in children, have been receiving a great deal of interest. The poor outcome obtained with current regimens is primarily due to the inadequacies of drug administration techniques rather than the qualities of opioids themselves[2].

The most common method of managing pain following surgery is the use of intramuscular (1M) opioids prescribed on demand basis [3]. Fluctuating blood levels of opioids may result in sedation or other adverse effects when the blood levels are high and inadequate analgesia when the levels are low before the next injection can be given. Another reason for inadequate pain relief by IM opioids is the excessive delay to administer the ordered injection[4]. Excessive concerns about side effects of opioids and addiction also result in the current undertreatment of postsurgical pain[5].

The importance of peripheral and central modulation in nociception has fostered the concept

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of "preemptive analgesia" in patients undergoing surgery. This type of management pharmacologically induces an effective analgesic state prior to the surgical trauma. This may involve infiltration of the wound with local anaesthetic, central neural blockade, or ketamine. Experimental evidence suggests that preemptive analgesia can effectively attenuate peripheral and central sensitization to pain. Although some studies have failed to demonstrate preemptive analgesia in human, other studies have reported significant reductions in postoperative analgesia requirements in patients receiving preemptive analgesia[6] Transmission of pain signals evoked by tissue damage leads to sensitization of the peripheral and central pain pathways. Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce this 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[7].

NSAIDs inhibit the cyclo-oxygenase enzymes, and decrease peripheral central prostaglandin production. In addition to reducing the inflammation that accompanies tissue injury, decreasing prostaglandin production attenuates the response of the peripheral and central components of the nervous system to noxious stimuli. Such a reduction in the response to pain can reduce the peripheral and central sensitization induced by noxious stimuli. These properties would seem to make NSAIDs ideal drugs to use in a pre-emptive fashion, where analgesics are administered prior to a noxious stimulus, such as surgery, with the expectation that reduction in peripheral and central sensitization will lead to a decrease of pain[8]. Tramadol has three fold of mode of action. It binds to and activates the opioid receptors with a 20-fold preference for μ receptor. This action is weak but is that of a full agonist. It also inhibits the neuronal reuptake of norepinephrine, potentiates the release of serotonin and causes descending inhibition of nociception[9]. In laparoscopic surgery there is decreased postoperative pain and consequent smoother recovery than after open operations. Pain after laparoscopy is caused by the stretching of the peritoneum, residual gas, the effect of surgery and the portholes or any skin incisions. Pain is treated optimally with local anaesthetic, paracetamol, NSAIDs and opioids if required[10].

This study was performed to compare the preemptive use of diclofenac, ketorolac and tramadol for postoperative pain in laparoscopic cholecystectomy.

SUBJECTS AND METHODS

Subjects**:**

It is a prospective comparative study of 60 patients scheduled for laparoscopic 1 cholecystectomy under general anesthesia. The purpose of the study was explained to each subject and recruited only after they gave their written consent. In this study patients for laparoscopic cholecystectomy were in ASA grades I&II and the age were in between 18-60 years. Patients who were unwilling to be included in the study, with the H/O allergy to drugs (under study), bleeding diathesis, COPD and lastly the renal disorder were excluded from this study.

Method:

A total of 60 cards, 20 in each group were prepared by another person who was blind about the study. After recruitment every patient was allowed to draw one card and grouped accordingly. Group A: These patients received injection diclofenac. It was given in a dose of 3 mg/kg, up to maximum of 75 mg.

Group B: Patients received injection ketorolac (30mg).

Group C: Patients received injection tramadol (100mg).

All drugs were diluted up to Sm1. After taking approval from the departmental ethical committee and informed consent from each

Patient during preoperative visit 24hours before operation was instructed for 6 hours of fasting and was prescribed tablet Ondansetron (8mg) I hour before operation with sips of water.

In the operation room an intravenous cannula (18G) was inserted and the patient received Ringers lactate solution. Pulse rate, blood pressure, rate of respiration, ECG was recorded before general anesthesia. Then study drug was injected as per group of the patient according to random assignment half an hour before induction. All patients were pre oxygenated/ for 3mins. Induction was done by Thiopental sodium 3-5mg/kg,

suxamethonium 1.5 mg/kg body weight for tracheal intubation and then vecuronium 0.08mg/kg body weight and then incrementally at 0.02mg/kg (when TOF returns at 25%) was used for maintenance of muscle relaxation.

Per operative monitoring was Pulse, Blood pressure oxygen saturation ($SP0_2$), electro cardiogram (ECG), Temperature every hourly for the first six hours, then 2hourly for three readings and then 3hourly for 4 readings.

Pain was evaluated postoperatively using a standard 10cm linear visual analog scale. 0 corresponding no pain and 10 the worst pain possible In addition heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SP02, and ECG were monitored. This recording was performed immediately after operation and then hourly for 6 hours, then 2 hourly for 6 hours, then 3 hourly for 12 hours. The duration of time from the end of operation to the first requirement of analgesic was recorded. When pain score was 3-4, Pethidine 10-20mg I.V. was given. Total consumption of Pethidine in 24 hour was recorded.

RESULTS

Observation of the present study (Table I) was analyzed in the light of comparison among the subject groups (20 patients in each group). All results are expressed as mean ± standard error of mean (SEM) or in frequencies as applicable (Table I). The studied groups became statistically matched for age (p =0.720), weight (p =0.471), duration of surgery (p = 0.671), base line pulse rate (p = 0.121), base line systolic blood pressure (p = 0.939), base line diastolic blood pressure (p = 0.893) as well as base line mean blood pressure (p= 0.900).

There was no significant difference in pulse rate among the three groups. The decrease or increase of systolic blood pressure was not statistically significant. Statistically no significant difference was observed in diastolic blood pressure. The changes of mean blood pressure were not statistically significant. Intensity of pain at different time period was measured using 10 cm visual analogue scale (VAS). The mean-+SEM values of VAS in the POW of group A was 0.65±0.209, group B was 0.45±0.135 and group C was 0.45t0.135; (p = 0.000). (Figure.3) The values are not significant. The time of mean±SEM of 1st rescue dose of pethidine in diclofenac was 1.8±0.11 hour, in ketorolac was 2.2+0.12 hour and in tramadol was 2.3f0.10 hour.

Total pethidine consumption in the present study was measured in mg. The mean±SEM value of the total Pethidine consumption in group A was 56.50±5.14, in group B was 46.75±4.63 and in group C was 49.00±5.42.

Three fourth of the study population experienced no adverse effects. Rest of the patient complains incidence of non-serious adverse effects. No patient terminated the study prematurely because of these adverse events. Some patients of tramadol group complained of nausea & vomiting. Other adverse events such as hangover, urinary retention, itching, and headache were less frequent in all three groups.

Table-I

Demographic data:

	Group A	Groups B	Group C
Age (years)	38.45±192	37 50±1 88	39 60± 1.68
Weight (kg)	65.50±1.05	66.00±0.45	64.75±0.49
Duration (minutes)	70.90+5.08	68.05±6.56	76.00±7.22

Values are expressed as mean ±SEM. between groups analyses were done by ANOVA test. Values are expressed as significant if p<0.05 (CI-95%).

Table-II

Age Distribution:

Age (years)	Group A	Group B	Group C	Total
20-34	5(25%)	7(35%)	3(15%)	15(25%)
35-49	14(70%)	*11(55%)*	14(70%)	39(65%)
50-64	1(5%)	2(10%)	3 (15%)	6(10%)

Values are expressed as frequency. Within parenthesis are percentages over column total.

Table-III

Weight distribution.

Weight(kg)	Group A	Group B	Group C
55-61	3(75%)	0(0%)	l(5%)
62-68	12(60%)	19(95%)	19(95%)
69-75	5(25%)	1(5%)	0(0%)

Values are expressed as frequency. Within parenthesis are percentages over column total.

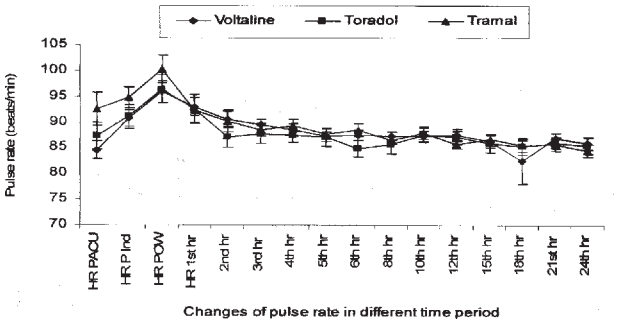

Fig.-1: *Changes of pulse rate in different time period (mean±SEM)*

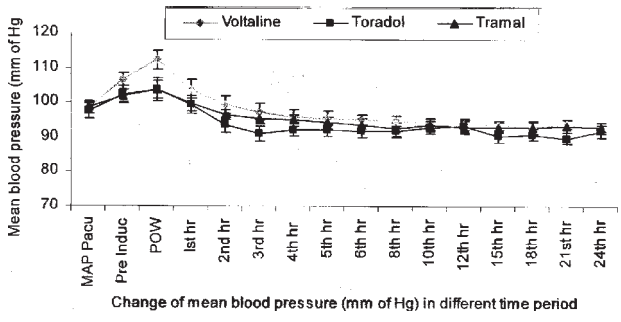

Fig.-2 : *Change of mean blood pressure (mm of Hg) in different time period*

DISCUSSION

Morphine and its derivatives have been extensively used to treat postoperative pain in spite of relatively high incidence of side effects11. The standard practice of injecting intramuscular opioids on demand gives poor result for several reasons. These include difficulty in quantifying pain, widely varying analgesic requirements and varying pharmacokinetics between individuals. The technique of infective IM opioids on demand represents familiar practice, generation of nurses have used this technique and therefore may be safe because of accumulated experience. However, too frequent adequate analgesia is not achieved by this approach [12]. Nevertheless better drugs for relief of postoperative pain are needed[13].

The mean±SEM of pulse rate per minute in group A was 84.55+1.67, in group B was 87.30±2.68 and in group C was 92.55±3.29. There was no significant difference in pulse rate among the three groups. This indicates that analgesia was ensured in three groups: the mean±SEM of systolic blood (SBP), diastolic blood pressure, and mean blood pressure were 110t significant. The mean±SEM of VAS in the POW were not significant. There w[a]s no significant difference in pain score among the three groups. The time of mean+SEM of 1st rescue dose of pethidine in diclofenac was 1.8±0.11 hour. in ketorolac was 2.2±0.12 hour and in tramadol was 2.3-0.10 hour.

The pain intensity was highest in 1st hour in all three groups and gradually declining as time passed which was similar to other study. M. A. Claeys et al., in his study showed that despite diclofenac infusion starting before surgery postoperative pain was present and was similar to that experienced with placebo during the first postoperative hour. This may be either some delay in the onset of effect of diclofenac or limited analgesic capacity of the drugs insufficient to obtund the severity of immediate postoperative pain[14]. In one study of tramadol infusion the pain was according to visual analogue scale between 42 in the 4[th] hour gradually decreasing up to 12 in 24 [1h] hour. But in our study it is different, as pain on tramadol group was 12±2.25 in the 4[th] hour and decline to 5.5±1.35 in 24[t]" hour. The VAS in the 1[st] hour is 12.5-+2.98, but in that study VAS in the 1st was not recorded". The difference was due to

rescue pethidine, as pethidine was given when VAS scale 3-4. There was another study where tramadol and ketorolac was compared for postoperative pain. This study showed that tramadol and ketorolac was similar in analgesic efficacy for postoperative pain[16]. Here preoperatively fentanyl was given 1 µgm/kg. In the postoperative period tramadol 100mg was given intramuscular 6 hourly, ketorolac 30 mg was given intramuscular 6 hourly, and in the control group pethidine 75 mg was given intramuscular 6 hourly. There was another study where tramadol and diclofenac infusion was used for postoperative pain, which showed the same result[17].

In this study, the mean±SEM of total pethidine consumption in group A was 56.5±5.14, in group B is 46.75±4.65 and in group C is 49±5.42. It showed that group B and group C had same analgesic effectiveness and which was better than group A. In another study showed that diclofenac and tramadol were compared for postoperative pain, it showed that analgesic efficacy was similar between these two drugs[18]. Here tramadol group received an initial intravenous bolus of 100 mg just after completion of operation and was followed by infusion of 15mg/hour through an infusion pump. Diclofenac group received an initial loading dose of 0.35 mg/kg, infused in the first 15 minutes followed by infusion of 90 µgm/min. Control group received injection pethidine 2mg/g up to a maximum dose of 100 mg 6 hourly intramuscularly.

Lack of changes in pulse rate, blood pressure and VAS scale in all three groups demonstrate that the analgesia were similar in all three groups. The effect of duration, sex, body weight and ASA grade can be ignored as these data were broadly similar in all groups.

From this study it may be said that both ketorolac and tramadol have same preemptive analgesic effect and which is better than diclofenac in the management of postoperative pain.

CONCLUSION:

On the basis of present prospective clinical study postoperative pain can be managed by preemptive use of diclofenac, ketorolac and tramadol for the 1st 24 hours with little or no supplementation of low dose intravenous pethidine. The analgesic efficacy of ketorolac and tramadol is same and better than diclofenac. There was no significant complication in using the drugs. The drugs are easily available, so they can be used preemptively for postoperative pain.

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