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RESEARCH ARTICLE

RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE THE EFFECTS OF TWO ANALGESIC REGIMENS AS PREEMPTIVE ANALGESIA FOR PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY UNDER GENERAL ANAESTHESIA

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Abstract

Background: Preemptive analgesia is a method to provide effective pain relief after the surgery. This study was designed to compare the effects of single analgesic Ketamine intravenous (IV) versus combination of low dose Ketamine and Parecoxib IV as preemptive multimodal analgesia in patients undergoing Laparoscopic Cholecystectomy.

Methods: This was a prospective, randomized, double blind study in 48 patients undergoing laparoscopic cholecystectomy. The study population was divided into two groups. Group I: treatment regimen of Injection (Inj.) Ketamine 0.3mg/kg IV plus Inj. Parecoxib 40mg IV. Group II: treatment regimen of Inj. Ketamine 0.3mg/kg IV plus saline. The treatment was given as single dose pre-operative. Inj. Fentanyl 0.5µg/kg was used as the rescue medication during the surgery and post-opertively. Total (intra-op and post-op) opioid, time for first opioid administration wasdetermined. Pain was assessed using Visual Analyzed Scale(VAS) and wasdetermined at 1 hour (hr.), 2 hr., 4 hr., and every 4 hr. interval till 24 hours after the surgery.

Results: As compared to Group II, Group I patients were administeredsignificantly lower dose of opioid(0.16 ± 0.26 versus 0.37 ± 0.47µg/kg; P= 0.032) during the surgery. Similarly, time to rescue medication post-operativewas significantly more in Group I patients as compared to Group II (68.1 ± 41.1 versus 20.1 ± 16.1 minutes; P <0.001). In post-op, total opioidrequirement was lower in Group I versus Group II patients (7.9 ± 4.1 vs 17.1 ± 6.1 µg/kg; P < 0.001).

Conclusion: Multimodal analgesia regimen using combination of two different groups of analgesics (Ketamine and Parecoxib)was found to be more effective than single analgesic in reducing pain in the post-op laparoscopic cholecystectomy patients.

Introduction:-

Analgesia which is administered to the patient before giving the surgical incision with the aim to reduce post-op analgesic requirement is called the Preemptive analgesia. It can be in the form of IV administration of analgesics regional blocks. The main advantage of the preemptive analgesia is to have reduced analgesic usage during the surgery and to provide patient with a better, pain free post-op period. Multimodal analgesia is another technique to reduce the analgesic requirement of the patient during and after the surgery. In this multimodal approach,

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combination of analgesics are used which are having different mechanism of actions i.e. they are exerting the analgesic effects through different receptors or mechanisms in the body. Aim is to reduce the side effects of one analgesic agent if required to be administered in higher doses. Thus, it provides safe usage of analgesic agents in lower doses. The analgesics used can be administered either through the same route or different. Thus, by combining both the techniques i.e. preemptive as well as multimodal approach, we can provide better management of intra-op and post-op pain. [1,2]Preemptive analgesia actually acts on the central nervous system and reduces the sensitization of it from the painful stimulation during the entire surgical duration.[3]

"Enhanced recovery after surgery"(ERAS) is the term used to denote reduced post-op morbidity, early mobility and provides more comfortability to the patient in terms of pain relief.[4]In our study both multimodal and preemptive are part of this ERAS. There is some discrepancy between the use of terms "multimodal preemptive" and preemptive multimodal". The former term denotes the use of combination of different types of preemptive analgesia while the later term denotescombination of preemptive and multimodal during intra-op and post-op conditions.[5,6]So, ours was a preemptive multimodal analgesia study.

Both of our study drugs have previously been used many times individually to show their effects as preemptive analgesia. Meta-analysis was done previously using clinical trials which showed Ketamine is found to be an effective agent in reducing the use of opioids both intra-op and post-op for pain relief.[7] Ketamine is a well-known drug and has commonly been used previously immense times as an Induction agent, as a sedative, as a preemtpive analgesic, and to provide dissociative anaesthesia.[7]However, there are few studies done previously which show the effect of Ketamine in combination with other drugs to provide preemptive analgesia. For example, combination of Ketamine and dexamethasone was used previously to provide pre-emptive analgesia and to reduce the use of opioids in post-op period in the anorectalsurgery.[7]

Similarly, Parecoxib has also been found to be an effective preemptive analgesic agent in previous studies. It is a selective COX-2 inhibitor and is an effective agent in the moderate to severe post-op pain. Parecoxib combined with para-vertebral block was found to be effective in reducing the post-op opioid dose requirement in the thoracic surgery.[8]

VAS has been found to be effective tool to determine the post-op pain severity in patients. Using, PCA devices pain scoring has been done in many previous studies using the VAS scale.[9]

Although both of our study drugs have been evaluated in many previous studies as individually, however, using these drugs in combination for the preemptive analgesia has not been studied well previously. One study showed the effect of combination of both Ketamine and Parecoxib in laparoscopic uterus removal surgery. It showed the opioid sparing effect in the early post-op period when both Ketamine and Parecoxib were administered immediately before the surgery.[10]Ketamine is a short acting agent while Parecoxib is a relatively long acting analgesic. Therefore, we conducted this study to compare the efficacy of Ketamine alone versus the combination of Ketamine and Parecoxib in pain relief both intra-op and post-op in the randomized, controlled design. Our primary outcomes in this study were time for first opioid requirement, post-op opioid requirement and pain scoring in the post-op period using VAS scoring system.

Methods:-

The requiredInstitutional ethics committee approval and written informed consent were obtained before enrollment of patients. The ethical guidelines were followed as per the Helsinki Declaration of 1975, as revised in 2013. Forty-eight patients were enrolled after meeting the eligibility criteria. It was a prospective, randomized, double-blinded study. Inclusion criteria were patients aged 18-65 years, American society of anaesthesiology(ASA) grade I & II, non-alcoholic, non-smoker, BMI between 18-25 kg/m^2. Exclusion criteria were any major co-morbidity, allergy to study medication, pregnancy or lactating female, any chronic medication usage. Withdrawal criteria were if any patient was not able to complete the study period, or occurrence of any unanticipated adverse event (AE) or serious adverse event (SAE).

After enrollment, patients were randomized into two groups as per the computer generated randomization schedule. Twenty-four patients were enrolled in each group. Group I patients were administered Inj. Ketamine 0.3µg/kg IV and Inj. Parecoxib 40mg IVin 2mL normal saline as preemptive analgesia. Group II patients were administered Inj. Ketamine 0.3µg/kg IV plus 2 mL normal saline IV. Both the study physician and the patient were blinded for the

treatment. The treatment allocation was kept in the sealed envelope and was opened on the day of surgery. All patients were administered pre-medication of Oral Ranitidine 150mg and oral Alprazolam0.25mg on the night before surgery. Patients were taken in the operation theater and standard monitors including electrocardiogram (ECG), non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO_2), end tidal carbon dioxide ($EtCO_2$) were attached. Intravenous access was obtained with 18Gauge IV cannula on non-dominant hand. Patients were administered the study drugs 10 minutes before the induction of anaesthesia. Patients were pre-oxygenated for 3 minutes, and were induced using Inj. Fentanyl 2.0µg/kg IV, InjPropofol 2mg/kg IV. Muscle relaxant used was Inj. Vecuronium 0.1mg/kg. Patients were intubated using standard direct laryngoscopy and airway secured using appropriate size endotracheal tube. Anaesthesia was maintained using Isoflurane, Nitrous oxide and oxygen. Patients were ventilated mechanically keeping the target $EtCO_2$level between 35-40mmHg. For intra-operative analgesia, Inj. Fentanyl 0.5µg/kg IV was used as a rescue medication for pain relief whenever patient's hemodynamic parameters (NIBP or Heart Rate) increased to more than 20% of baseline values. Towards the end of surgery, Inj. Ondansetron 4.0mg IV was administered, and the patients were reversed using Inj. Neostigmine 0.5mg/kg IV and Inj. Glycopyrollate 0.1mg/kg IV. The patients were extubated using standard extubation criteria. Total dose of intra-operative Inj. Fentanyl used was noted. The patients were monitored in the recovery room for 2 hrs.post-surgery and then shifted to Intensive Care Unit.

In Post-op, all study patients were first administered Inj. Fentanyl 0.5µg/kg IV as rescue medication when patient experienced severe pain (VAS more than or equal to 04). Patients were monitored for 24 hrspost-operatively. Severity of pain scores was determinedusing VAS scores at 1 hr.,2 hr., 4 hrs. and then every 4 hrs.till 24 hrs.post-op. Total opioid administered to patient over 24 hrs. period was determined and time to first demand of opioidwas also noted in both groups.

Statistical analysis was done using Statistical package for Social Sciences (SPSS) software version 24.0 (IBM SPSS Inc., NY, USA). Chi-square test was used to analyze categorical data while independent t-test was used to analyze numerical data. P-values of <0.05 was considered statistically significant. Sample size of the study was determined based upon the previous study by Behdad et al,[11]according to which an expected difference of 0.5 between the group means was needed to reject the null hypothesis. The power of the study was kept as 0.8 and Type I error associated with the null hypothesis was kept as 0.05.

Results:-

All forty-eight patients completed the study. No withdrawal or drop outs were noted in our study. Regarding demographic characteristics, there was no significant difference between the two study groups. In group I, there were 3 males and in group II, there were 2 males. Distribution of demographic characteristics are shown in Table 1.

Table 1:- Demographic data of study patients.

Parameter	Group I	Group II	P value
Age (years)	40.2 ± 13.1	40.8 ± 13.9	0.763
Height (m)	1.51 ± 0.48	1.52 ± 0.41	0.814
Weight (kg)	59.1 ± 8.6	59.5 ± 11.4	0.821
BMI (kg/m^2)	24.1 ± 3.6	24.7 ± 4.6	0.718
ASA (I)	19.0	20.0	
ASA (II)	5.0	4.0	

Regarding the intra-op use of opioid (Inj. Fentanyl), there was statistically no significant difference between the two groups (0.31 ± 0.59 µg versus 0.35 ± 0.49 µg; P value = 0.814) in Group I versus (vs) Group II respectively. Group I patients required significantly lower dose of Inj. Fentanyl as rescue medication during the first hour after surgery as compared to Group II patients (0.16 ± 0.26 vs 0.37 ± 0.47 µg; P value= 0.032) (Table 2).

Table 2:- Total Dose of Rescue Medication (Intra-operatively and 1 hour post-surgery).

Parameter	Group I	Group II	P value
Intra-operative Fentanyl (µg)	0.31 ± 0.59	0.35 ± 0.49	0.814
1 hour Post-surgery Fentanyl (µg)	0.16 ± 0.26	0.37 ± 0.47	0.032

Time to first use of rescue medication (Inj. Fentanyl) was significantly more in Group Ias compared to Group II patients (68.1 ± 41.1vs 20.1 ±16.1 minutes; P <0.001) (Table 3). Total Fentanyl administered during 24 hrs. post-op period was also less in Group I as compared to Group II patients (7.9 ± 4.1 vs 17.1 ± 6.1 µg; P < 0.001) (Table 3).

Table 3:- Time to first requirement of rescue medication(Fentanyl) and Total Dose of Fentanyl 24 hours post-surgery.

Parameter	Group I	Group II	P value
Time to first requirement of Fentanyl (min)	68.1 ± 41.1	20.1 ± 16.1	<0.001
Total Dose of Fentanyl in 24 hours post-surgery (µg)	7.9 ± 4.1	17.1 ± 6.1	<0.001

Regarding pain intensity, Group Ipatients showed significantly lower VAS scores as compared to Group II at all study time-points (Table 4).

Table 4:- Intensity of Pain as determined by VAS Score.

Time	Group I	Group II	P value
1 hr	3.2 ± 0.9	4.0 ± 0.8	0.001
2 hr	3.3 ± 0.7	4.4 ± 0.9	0.001
4 hr	3.5 ± 1.0	4.5 ± 1.1	0.002
8 hr	3.7 ± 0.6	4.6 ± 0.7	0.002
12 hr	3.2 ± 0.4	3.8 ± 0.6	0.005
16 hr	2.9 ± 0.7	3.5 ± 0.8	0.001
20 hr	2.5 ± 0.9	3.1 ± 0.8	0.000
24 hr	2.1 ± 0.8	2.5 ± 0.9	0.001

Regarding adverse events, two study patients suffered headache, one had nausea and one patient suffered dizziness. No SAE were noted in our study and there were significantly no differences in the occurrence of AE in our two study groups.

Discussion& Conclusion:-

In this prospective, randomized, double-blind study we found that the preemptive multimodal analgesia using combination therapy of Ketamine and Parecoxib was better than Ketamine alone for pain relief 24 hours post-operatively in patients undergoing laparoscopy cholecystectomy under general anaesthesia. There was significantly less dose of rescue medication administered during 24 hours post-op period, there was significantly prolonged time for first opioid use after surgery and there was significantly lesser pain scores at all study time points 24 hours post-op among patients who were administered combination of Ketamine and Parecoxib as compared to Ketamine alone.

To our knowledge, there was one study only conducted previously comparing the preemptive analgesic effects of Ketamine, Parecoxib and placebo (as single dose) in patients undergoing Laparoscopic uterus surgery. The study, however, did not determine the multimodal effect of using combination therapy for pain relief post-op.[10]Also, in our study, low dose ketamine was used (0.3mg/kg IV) as compared to the previous study which used Inj. Ketamine in the dose of 0.5mg/kg IV. As decrease in the dose results in less side effects and less hemodynamic variations.

Other studies were also reviewed based on multi-modal preemptive analgesia which used Ketamine in combination with other analgesic drugs. One study, which showed the effects of combination of Ketamine (0.15mg/kg) with non-steroidal anti-inflammatory drug Diclofenac (1.0mg/kg) and compared it with the use of Ketamine, Diclofenac and placebo alone among 80 patients undergoing Laparoscopiccholecystectomy. The study showed significant lower pain scores among patients receiving combination therapy than single analgesic alone. Time for rescue medication use was also longer in patients administered the combination therapy as compared to patients receiving single dose alone.[12]The study also showed that Ketamine used alone in very low dose (0.15mg/kg) did not provide preemptive analgesia effect. However, when combined with Diclofenac, the combination showed significant preemptive analgesic effect.

There are varied results on the use of different doses of Ketamine being used as a preemptive analgesia. Singh et al used three doses of Ketamine (1.0, 0.75, 0.5mg/kg IV) as preemptive analgesia among patients undergoing laparoscopic cholecystectomy.[3] They showed that Ketamine has a definitive role as preemptive analgesia in reducing post-op pain. The three doses studied showed varied results in terms of side effects of Ketamine. While dose of 0.5mg/kg did not show any significant effect on hemodynamic parameters, however, dose of 1.0mg/kg resulted in significantly increased blood pressure and heart rate at 0.0 and 0.5 hrs. Ten percent of the patients also suffered from hallucinations among patients administered higher dose (1.0 mg/kg) of ketamine.Thus, dose of 0.5mg/kg was considered optimum to provide preemptive analgesia in patients undergoing laparoscopic surgeries.

Another study showed the effect of Ketamine as preemptive analgesia among patients undergoing surgery for acute appendicitis. The study demonstrated the effect of Ketamine used in dose of 0.5mg/kg as preemptive analgesia when administered within 10 minutes of surgical incision. There was significantly longer time for the first use of rescue medication among patients who received Inj. Ketamine than as compare to patients who received placebo (22.1±7.2 vs 17.1 ±6.9 minutes; p-value =0.03). There was also deceased use of opioids in the 24 hrs. post-op period in the Ketamine group as compared to placebo group (0.7±0.2 vs 2.5±0.6; p-value=0.02).[11]

In contrast to above studies, there was a study conducted by Nistal-Nuno et al which reported no preemptive analgesia effect of Inj. Ketamine when administered in the dose of 0.5mg/kg among patients undergoing colon surgeries.[13] It reported no decrease in the post-op pain among patients administered Ketamine before the surgical incision. Similarly, there were other studies that used Inj. Ketamine in the dose of 0.5mg/kg and did not show preemptive analgesic effect among patients undergoing elective caesarean sections either under spinal or general anaesthesia. They showed Ketamine was not effective in reducing pain scores or opioid requirements during the 24 hours post-op period.[14,15]

There were few limitations in our study. Due to various constraints including time, cost we could not include large patient size in our study. Thus, the result of our study needs to be generalized by including more patient population. Also, pain is a subjective parameter and varies from each patient. More objective parameter needs to be devised for grading pain intensity.

The technique of Multimodal preemptive analgesia using combination of low dose Ketamine (0.3mg/kg) and Parecoxib (40mg) IV was found to be more effective than Ketamine alone for post-op pain relief among patients undergoing Laparoscopic Cholecystectomy under general anaesthesia.

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