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Pre-emptive analgesia with diclofenac in combination with ketamine in patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Background: Laparoscopic cholecystectomy is a minimally invasive surgery which most often is associated with post-operative pain. Pre-emptive administration of ketamine and diclofenac in combination reduces post-operative pain. **Aims and Objectives:** In patients undergoing laparoscopic cholecystectomy, the aim of this study was to evaluate the efficacy of preemptively administered ketamine and diclofenac and their combination on post-operative pain. **Materials and Methods:** A total of 90 patients, with American Society of Anesthesiologists physical grading I and II, were recruited for the study. Patients were allocated randomly into the following groups: Group I was administered 100 mL isotonic saline intravenous (IV) 20 min before the induction of anesthesia and 0.15 mg/kg ketamine IV diluted in 5-mL isotonic saline before skin incision; Group II received diclofenac in the dose of 1 mg/kg diluted in 100-mL isotonic saline IV 20 min before the induction of anesthesia and 5-mL isotonic saline IV before skin incision; Group III was administered a combination of diclofenac 1 mg/kg diluted in 100-mL isotonic saline IV 20 min before the induction of anesthesia and 0.15 mg/kg ketamine diluted in 5-mL isotonic saline IV before skin incision. Time for rescue analgesia, post-operative Visual Analog Scale score, hemodynamic changes, and adverse effects were evaluated. **Results:** Post-operative analgesia was longer in Group III as compared to Group II and Group I at 2, 4, and 6 h ($P < 0.05$). The mean time to receive rescue analgesia was significantly higher in Group III (6.950 ± 0.6208) and Group II (5.633 ± 0.7184) as compared to Group I (2.833 ± 0.6205). Significantly higher heart rate and blood pressure were noted in Group I as compared to Group II and Group III at 2, 4, and 6 h postoperatively. **Conclusion:** Administration of ketamine and diclofenac preemptively in the patients undergoing laparoscopic cholecystectomy has a definitive role in providing post-operative analgesia without any adverse side effects whereas ketamine alone when given preemptively did not produce any benefit in post-operative pain relief.

Key words: Ketamine; Diclofenac; Laparoscopic cholecystectomy; Pre-emptive; Post-operative analgesia

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INTRODUCTION

IASP defined pain as "An unpleasant sensory and emotional experience associated with, or resembling that is associated with, actual or potential tissue damage.[1]

In surgical procedures, incisions and tissue manipulation lead to pain receptor sensitization, resulting in significant pain and hemodynamic changes postoperatively. If this post-surgical pain is left uncontrolled, it can escalate patient morbidity and mortality rates. Therefore, effective management of post-surgical pain is vital.[2]

Laparoscopic cholecystectomy, a minimally invasive procedure known for its advantages of less post-operative pain compared to traditional open surgery, still

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presents with challenges regarding post-operative pain management.[3] Insufflation of carbon dioxide into the abdominal cavity leads to peritoneal stretching which results in post-operative pain and discomfort.[4-6] Pre-emptive analgesia is a proactive approach that involves administering analgesic interventions before the onset of a painful stimulus.[7]

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been investigated for its potential role in pre-emptive analgesia. Its unique mechanism of antagonizing NMDA receptors plays a crucial role in preventing central sensitization. Ketamine may prevent the establishment of persistent pain states and also reduce the need for opioids.[8,9]

Diclofenac, a non-selective cyclooxygenase inhibitor, decreases the synthesis of prostaglandins, the chemicals responsible for the development of pain and inflammation associated with tissue injury.[10-12]

Aims and objectives

The aim of this study was to compare the efficacy of pre-emptive ketamine and diclofenac and their combination in reducing post-operative pain.

Primary objective

To evaluate the differences in the pain intensities among the three groups based on Visual Analog Scale (VAS) score and time for rescue analgesia (TRA) administration.

Secondary objective

To evaluate the post-operative hemodynamic parameters and the number of patients who experienced the side effects including post-operative nausea and vomiting, headache, dizziness, and sedation.

MATERIALS AND METHODS

Following the approval from the Institutional Ethics Committee with approval certificate no. "115/IEC-GRMC/2022, this prospective randomized study was conducted at G.R. Medical College and JAH group of hospitals from 2022 to 2024.

Inclusion criteria

The patient gave consent to participate in the study and was scheduled for laparoscopic cholecystectomy.

- Age between 17 and 80 years
- American Society of Anesthesiologists (ASA) physical grade I and II
- Gender both male and female.

Exclusion criteria

- ASA grade III and IV
- Uncooperative patients or those not able to understand pain assessment test
- Pregnant and lactating women
- History of any significant pulmonary, cardiovascular, neurological, hepatorenal, psychiatric, or metabolic diseases
- Bleeding diathesis and history of any previous allergy to the study drug.

Sample size

90.

Formula used:

$$n=\frac{2\left(S_1^{\ 2}-S_2^{\ 2}\right)\times\left(Z1_{-\pm/2}+Z_{1-^2}\right)^2}{\overline{x}_2-\overline{x}_1}$$

where,

S – Standard deviation, $Z_{1-ß}$ – standard normal variate for power 80% power (0.84).

x_2-x_1 – Effect size (difference between two mean values), $Z_{1-\alpha/2}$ – level of significance (1.96). The sample size was calculated using G*Power 3.1.9.7 software.

The input parameters

Effect size – 0.4 (Large, according to Cohen).

(Previous research by Nasek-Adam et al., 2012 revealed significant differences in the VAS score for pain between the groups, therefore, a large effect size is considered for sample size calculation).

α probability error – 0.05, Power (1-β error probability) – 0.90.

Number of groups – three.

Output parameters

Critical f – 3.109, Sample size – 84.

The minimum required sample size was 84. Therefore, 90 subjects (more than the minimum required) were included in the study. Total patients were divided into three groups, each group had 30 patients.

- Group I – Patients received 100-mL isotonic saline intravenous (IV) 20 min before the induction of anesthesia and 0.15 mg/kg ketamine IV diluted in 5-mL isotonic saline before skin incision
- Group II – Patients received diclofenac 1 mg/kg diluted in 100-mL isotonic saline IV 20 min before the induction of anesthesia and 5-mL isotonic saline IV before skin incision
- Group III – Patients received a combination of

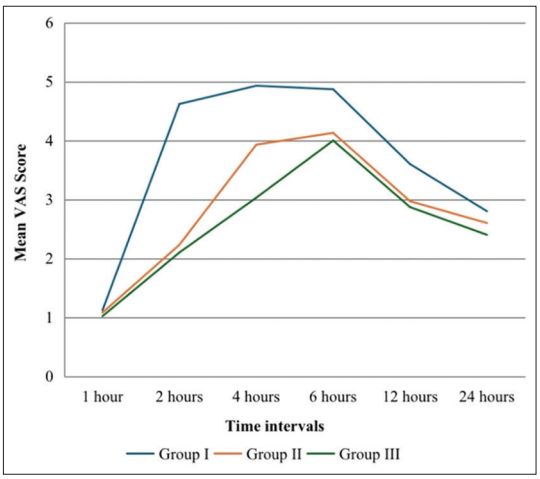

Figure 1: Comparison of post-operative Visual Analog Scale score among the three groups

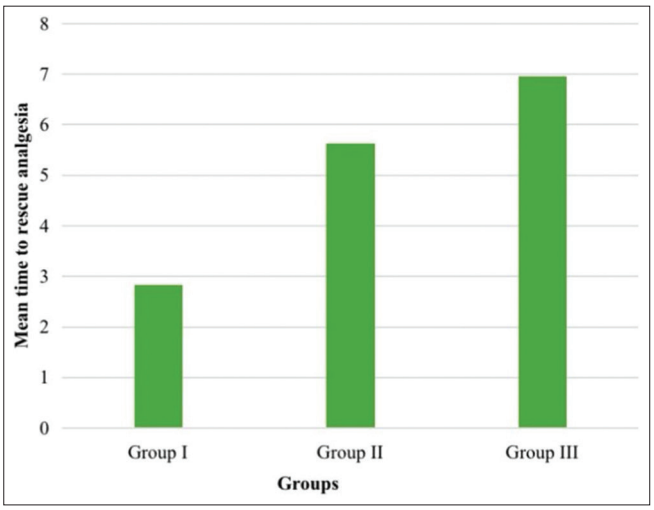

Figure 2: Time to rescue analgesia

diclofenac 1 mg/kg diluted in 100-mL isotonic saline IV 20 min before the induction of anesthesia and 0.15 mg/kg ketamine diluted in 5-mL isotonic saline IV before skin incision.

Patients planned for laparoscopic cholecystectomy were kept on overnight fasting. Written and informed consent were taken, after pre-operative assessment, patients were taken in the operating theater, and routine monitors including an electrocardiogram, pulse oximeter (SpO_2), and non-invasive blood pressure were attached. An IV cannula (18G or 20G) was secured, and patients were administered the study drugs as per following:

Patients were pre-medicated with 0.2 mg IV glycopyrrolate and 1 mg IV midazolam. General anesthesia induction involved pre-oxygenation with 100% oxygen, 0.5 mg/kg IV pentazocine, and 2 mg/kg IV propofol, followed by 2 mg/kg IV succinylcholine to facilitate tracheal intubation after 1 min using an appropriately sized cuffed endotracheal tube connected to the anesthesia machine (Drager Fabius GS) breathing circuit. Anesthesia was maintained with a mixture of nitrous oxide and oxygen, along with the inhalation of isoflurane (0.8–1%) in oxygen and the muscle relaxant atracurium, administered based on body weight for loading (0.25 mg/kg) and maintenance (0.1 mg/kg) doses. Ventilation was controlled to maintain normocapnia with $ETCO_2$ between 35 and 45 mmHg.

After the procedure, patients were fully reversed with 0.05 mg/kg neostigmine and 0.01 mg/kg glycopyrrolate, extubated, and oxygenated for 10 min. Hemodynamic variables were recorded after induction, intubation, and at 15, 30, 60, 90, and 120 min. Postoperatively, patients were monitored, and hemodynamic variables and side effects were recorded at 1, 2, 4, 6, 12, and 24 h. Rescue analgesia with 100 mg IV Tramadol was given when the patient reported pain and VAS score was recorded above the value of 4, and the TRA was noted for all groups.

Statistical method

The data were organized in a suitable spreadsheet format and analyzed using the statistical package for the Social Sciences, version 20.0. Where $P<0.05$ was considered statistically significant, a $P>0.05$ was considered statistically insignificant, and a $P<0.01$ was considered highly significant. One-way analysis of variance test to assess the significance of differences in hemodynamic variables across the three groups.

RESULTS

As shown in Table 1, age, sex, and weight were comparable between the groups, $P>0.05$ which was statistically insignificant.

The study found no significant differences in demographic parameters or ASA grading among the three groups, with a higher proportion of male patients in all groups. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), arterial pressure, and SpO_2 showed no statistically significant differences among the groups at all-time intervals preoperatively ($P>0.05$).

As show in Figure 1 and Table 2, all groups reported no pain at 1 and 2 h postoperatively, but group III (diclofenac+ketamine) experienced significantly lower pain scores at 4 and 6 h compared to groups I and II, indicating superior and prolonged analgesic effects.

As per Figure 2 and Table 3, the time to receive rescue analgesia was longest in group III and shortest in group I,

Table 1: Demographic profile (mean±SD) associated with the groups

Demographic parameters	Group I	Group II	Group III	P-value
Age	42.47±11.48	42.30±11.34	44.67±7.95	0.617
Sex				
Male	16 (53.3)	19 (63.3)	14 (46.7)	0.688
Female	14 (46.7)	11 (36.7)	16 (53.3)	
Weight	62.97±9.77	60.90±10.47	66.43±6.39	0.274
Duration of surgery	104.33±12.51	105.00±12.59	101.33±12.523	0.490

Table 2: The time for post-operative VAS score was more in Group I as compared to Group II and Group III at 2, 4, and 6 h

Time intervals	Group I	Group II	Group III	P-value
1 h	1.12±0.01	1.08±0.76	1.02±0.78	0.2929
2 h	4.62±0.06	2.23±0.66	2.10±0.76	<0.001
4 h	4.93±0.83	3.93±0.58	3.03±0.25	0.0131
6 h	4.87±0.95	4.13±0.38	4.00±0.17	0.0411
12 h	3.60±0.62	2.97±0.31	2.87±0.57	0.1374
24 h	2.80±0.66	2.60±0.00	2.40±0.56	0.6648

VAS: Visual Analog Scale

Table 3: The time for rescue analgesia

Time to rescue analgesia	Mean	Standard deviation	P-value
Group I	2.833	0.6205	<0.001
Group II	5.633	0.7184	
Group III	6.950	0.6208	

showing significant differences among the groups. There was notable HR variability and differences in blood pressure in the early post-operative period, which normalized by 12 and 24 h.

Despite variations in mean arterial pressure (MAP), all groups maintained adequate oxygen saturation without adverse respiratory effects, indicating good tolerance across all regimens.

DISCUSSION

Laparoscopic cholecystectomy has become the widely accepted method for treating gallbladder disease. General anesthesia with muscle relaxation, tracheal intubation, and intermittent positive pressure ventilation is the preferred approach for abdominal surgeries.[13-15]

Pre-emptive analgesia using synergistic and additive drugs aims to provide effective pain relief while minimizing side effects.[16] In this study, we evaluated the use of low-dose pre-emptive ketamine, in combination with diclofenac. This combination aims to reduce the stress response to surgery and anesthesia, decrease post-operative opioid consumption, and improve patient recovery.

Our study involved 90 patients of ASA grade I and II, who were divided into three groups of 30 each to assess the efficacy of IV low-dose ketamine in combination with diclofenac when administered preemptively for intraoperative and post-operative analgesia. All three groups were examined for the hemodynamic parameters, VAS score, TRA, and the adverse effects following surgery in the post-operative period.

The demographic characteristics were similar across the study groups, as shown in Table 1. HR, SBP, DBP, and MAP were monitored at various stages during the surgery, including baseline, induction, and at 15, 30, 60, 90, and 120 min. There were no significant differences (P>0.05) in intraoperative HR, SBP, DBP, MAP, and SpO_2 among the groups, consistent with the findings of Kwok et al.,[17] Jan et al.,[18] Sen et al.,[12] and Reza et al.[19] Post-operative hemodynamics, including HR, SBP, DBP, MAP, and SpO_2, were recorded in all three groups at 1, 2, 4, 6, 12, and 24 h after surgery.

When comparing HRs among the three groups, we observed a significant increase in HR in Group I (96.03±14.81 at 4 h and 112.77±9.21 at 6 h) compared to Group II (77.03±8.00 and 80.00±4.84) and Group III (76.40±11.76 and 79.43±7.73) during the post-operative period (P<0.001). This is consistent with Singh et al.[3] However, Nistal-Nuño et al.,[20] found no significant differences in HRs among different groups when evaluating hemodynamic parameters.

In Table 4 we measured SBP and DBP at several post-operative intervals: 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h. We found that at 2 h, 4 h, and 6 h, Group I had significantly higher SBP and DBP compared to Groups II and III (P<0.001). These findings align with Nistal-Nuño et al.[20] Similarly, Singh et al.[3] found higher SBP and DBP in the placebo group compared to those receiving ketamine, especially within the first 1.5 h post-surgery. The elevated blood pressure in Group I at 2 h, 4 h, and 6 h is likely due to inadequate pain control, as reflected by higher VAS scores during these periods.

We noted a significant increase in MAP at 4 and 6 h postoperatively, with Group I showing higher MAP values (93.07±5.15 and 93.07±6.48) compared to Group II (80.07±6.51 and 81.03±6.95) and Group III (78.03±6.14 and 73.03±9.45). While the difference at 4 h was near

Table 4: SBP and DBP of the post-operative period

Time interval	Groups (SBP and DBP)			P-value
	Group I Mean±SD	Group II Mean±SD	Group III Mean±SD	
1 h	122.57±6.8, 70.53±9.22	119.77±8.33, 68.97±7.06	118.77±8.33, 69.57±7.06	P>0.05
2 h	117.93±7.56, 77.53±8.93	108.83±8.5, 79.90±13.06	107.67±8.5, 66.07±7.49	P>0.05
4 h	140.57±8.76, 70.33±10.98	116.67±11.54, 63.37±6.47	105.47±10.04, 65.77±7.51	P<0.001
6 h	119.07±10.04, 81.07±8.46	108.33±9.27, 68.33±7.12	105.47±10.04, 65.77±7.51	P<0.001
12 h	104.70±9.26, 65.97±8.46	107.33±9.27, 66.77±6.54	108.33±9.27, 66.77±6.54	P>0.05
24 h	106.87±8.04, 65.90±6.13	108.57±8.41, 68.10±4.32	106.57±8.41, 68.10±4.32	P>0.05

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

significance (P=0.067), it was significant at 6 h (P<0.001). These results are consistent with Helmy et al.[21]

In our study, the TRA was significantly longer in Group III (6.95±0.62) compared to Group I (2.83±0.62) and Group II (5.63±0.71) (P<0.05), indicating notable differences among the groups during the post-operative period. These results are consistent with Nesek-Adam et al.[11] In contrast, ketamine alone did not show a pre-emptive effect. Patel et al.[22] observed that patients receiving paracetamol had a longer time to require rescue analgesia compared to those receiving diclofenac. In addition, Singh et al.[23] found that combining ketamine with parecoxib was more effective than using a single analgesic for post-operative pain relief.

We assessed pain levels in the three groups at various times post-surgery using the VAS. At 2 h, Group III had a significantly lower mean VAS score (2.10±0.76) compared to Group II (2.23±0.66) and Group I (4.62±0.06) (P<0.001). At 4 and 6 h, Group I had higher pain scores (4.93±0.83 and 4.87±0.68) compared to Group III (3.23±0.25 and 4.00±0.47) and Group II (3.93±0.58 and 4.03±0.47), respectively. These findings were in concordance with those of Solanki et al., Nesek-Adam et al.,[11] and Solanki et al.,[25] also found that combining ketamine with diclofenac improved post-operative pain relief, whereas ketamine alone did not. In contrast, Buggy et al.[24] found that pre-emptive diclofenac and ketamine did not enhance post-operative pain control.

Side effects observed in our study included nausea, vomiting, and headache, which were experienced by 26.7%, 16.7%, and 23.3% of patients, respectively. Sedation was reported in 36.7% of Group I, and dizziness affected 26.7% of patients in Group III. According to Nesek-Adam et al.,[11] adverse effects were similar across different groups, with minimal need for rescue medication due to nausea and vomiting. Nistal-Nuño et al.[20] also found that nausea, urinary retention, and vomiting occurred in both the ketamine and control groups, with no significant differences between them.

Limitations of our study

In our study, we used VAS score which is based on subjective findings of patients and can be influenced by patient perception of pain. Incorporating objective methods of assessing pain could have yielded a better evaluation of analgesic efficacy.

CONCLUSION

Our study revealed that administering a combination of low-dose ketamine and diclofenac sodium preemptively enhanced post-operative pain relief following laparoscopic cholecystectomy. Ketamine alone at a dosage of 0.15 mg/kg did not produce a pre-emptive analgesic effect. A low-dose ketamine and diclofenac were devoid of any adverse side effects and hemodynamic changes.

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VS- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation and submission of the article, design of the study, statistical analysis, and interpretation; **SG-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **DSG-** Review manuscript; **NE-** Review manuscript; **GV-** Review manuscript.

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