

STUDY OF PREEMPTIVE ANALGESIC EFFECTS OF INTRAVENOUS PARACETAMOL IN REDUCING DOSES OF MORPHINE IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMYAftab Ahmad Khan¹, Shabir Ahmad Sofi², Fayaz Ahmad Munshi³, Mushtaq Ahmad Rather⁴**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: Paracetamol is primarily thought to be a cyclo-oxygenase inhibitor acting through central nervous system. Indirect effects of paracetamol are through serotonergic system as a non-opioid analgesic. We studied intravenous paracetamol 1 gram preoperatively to assess its intraoperative and post-operative analgesic effects, in reducing intraoperative morphine requirements, to reduce the requirement of postoperative analgesia, enable early recovery from anaesthesia and to reduce postoperative nausea and vomiting. One hundred patients from either sex classified in ASA Class I and II scheduled for laparoscopic cholecystectomy were randomly allocated into two groups of 50 patients each. Group I (Study group) received paracetamol 1 gram infusion prior to induction with 50µg/kg morphine diluted with normal saline to a total volume of 5ml. Group II (Control group) received 100µg/kg morphine diluted with normal saline to a total volume of 10ml at induction. We observed that there was significant increase in mean time for rescue analgesia from induction of anaesthesia in Group I (study group) was 11.25±1.827 hours and Group II (Control group) was 6.98±4.568 hours (p value < 0.001). The median value of visual analogue score was lower at all-time points in group I when compared to group II at each interval and it was statistically significant (p value < 0.001). A significant decrease in mean number of administered doses of rescue analgesia during 24 hours was seen in the study group (0.52±0.505) as compared to the control group (1.3±0.463) with a p value of < 0.001. Mean modified Aldrete score in the study group was 9.78±0.465 and in control group it was 8.1±1.15. It was statistically significant p value of <0.001. The mean number episodes of nausea and vomiting in group I were 0.74±0.633 and in group II 0.94±0.652 and was statistically insignificant with p value of 0.361. **CONCLUSION:** Administration of intravenous paracetamol and 50% doses of morphine prior to induction in patients undergoing laparoscopic cholecystectomy ensures effective analgesic intra-operatively as well as postoperatively and was associated with earlier discharge from post anaesthetic care unit when compared with full doses of IV morphine, however above combination was not able to decrease significantly reduction in morphine related adverse effects in these patients.

KEYWORDS: Cholecystectomy, IV Paracetamol, preemptive, morphine.

INTRODUCTION: The results of inadequate pain control after surgery are significant in terms of both physical and physiological responses and can result in long-term complications.

Physiologic responses to injury and stress include pulmonary, cardiovascular, gastrointestinal (GI), and urinary dysfunction, impairment of muscle metabolism and function, and neuroendocrine and metabolic changes. Many of these can be eliminated or reduced with currently analgesic available techniques.^{1,2}

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Preemptive Analgesia: As knowledge of the epidemiology and pathophysiology of postoperative pain has increased, a new analgesic concept has been developed and applied for the prevention of pain whereby analgesic treatment is started prior to trauma and surgical intervention. Within this concept, referred to as preemptive analgesia, it is believed that through application of an analgesic medicine or technique, pain will either subside or be prevented prior to the painful stimulus. Preemptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements, and a decline in morbidity, promoting wellness and shortening the length of hospital stays.^{3,4,5,6}

The nature of pain varies depending on the surgical technique. Following laparotomy, patients complain more of parietal pain (e.g., abdominal pain) whereas after laparoscopic cholecystectomy, patients also report visceral pain.^{7,8} Pain after laparoscopy is multifactorial and different treatments have been proposed to provide pain relief.^{9,10} Preoperative administration of NSAIDs decreases pain, as does opiate consumption after laparoscopic cholecystectomy.^{11,12} In addition to postoperative pain of various types, the most frequent complaints are headache, nausea and vomiting. Postoperative nausea and vomiting (PONV) is one of the main complaints after laparoscopy (40% to 75% of patients) and one of the important factors determining the delay in discharge from a day care facility.^{13,14} It has been seen that intraoperative opioids increase the incidence of PONV,^{15,16} therefore the techniques of analgesia that allow reduction of opioid consumption can contribute to decreasing these symptoms.

MATERIALS AND METHODS: After obtaining approval from institutional ethical committee the present study was conducted in Government SMHS hospital (Which is one of the Associated Hospitals of Government Medical College, Srinagar Kashmir).

This was a prospective, randomized, controlled study undertaken in the patient age group between 18-50 years belonging to physical status ASA I and ASA II of either sex. The criteria for exclusion from the study were:

- Patients allergic to paracetamol or morphine.
- Bleeding diathesis.
- Severe liver insufficiency.
- Severe renal insufficiencies.
- American Society of Anesthesiologists (ASA) III and IV.
- Chronic alcoholism.
- COPD and Asthmatic patients.

Preanaesthetic evaluation was done at least 24 hour prior to surgery.

Visual analogue scale was demonstrated to the patients consenting for the study. No premedication was given to any patient. The patients were advised to remain fasting overnight prior to surgery. On the day of surgery in operating room intravenous line was secured with Ringer lactate solution. The multichannel monitor was attached to the patient and baseline vitals viz. heart rate, non-invasive blood pressure (NIBP), oxygen saturation (SPO₂), electrocardiogram (ECG) and ET_{CO}₂ were recorded. The monitoring was continued intraoperatively at 5 minutes interval till completion of surgery.

The study was conducted on 100 patients who were randomly allocated into two groups by simple random sampling. Each group consisting of 50 patients each.

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Study Group (Consisting of 50 patients) received paracetamol 1gram (100ml) infusion 30 minutes prior to induction over a period of 20 minutes. 50microgram/kg morphine diluted with normal saline to a total volume of 5ml prior to induction.

Control Group (Consisting of 50 patients) received 100microgram/kg morphine diluted with normal saline to a total volume of 10ml prior to induction.

Each patient was induced with injection propofol 1%, 2-2.5mg/kg, muscle relaxation achieved with 0.5mg/kg atracurium for endotracheal intubation and surgical procedure. Maintenance with 50% O₂ and 50% N₂O, isoflurane 0.8-1% with ETCO₂ 35-40mmHg. No more analgesia was given intraoperatively; injection Granisetron 20microgram/kg was injected 15 minutes prior to reversal of anaesthesia.

INTRAOPERATIVE: Vital signs were recorded every 5 minutes during the procedure till completion of the surgery. Neuromuscular block was reversed with neostigmine 2.5mg + glycopyrolate 0.5mg and patient extubated.

POSTOPERATIVE: In the post Anaesthesia care unit (PACU) vital signs were recorded 15 and 30 minutes interval. Pain if any was assessed by visual analogue scale (VAS) 0 to 10 (0 = no pain), 10 = (Most severe pain). If VAS>3 on a scale, rescue analgesia was given as 2-3mg bolus of morphine intravenously. Time for first request for analgesia was recorded. Sedation was assessed by Ramsay Sedation Score.¹⁷ and modified Aldrete score.¹⁸

STATISTICAL ANALYSIS: Metric and non-metric data was expressed as mean + standard deviation (SD) and percentages. Metric data was compared by students 't' test and non-metric by chi square test at 95% CI (Confidence interval) respectively. Software Statistical Package for Social Sciences (SPSS) Version 16.0 and Microsoft Excel were used for data analysis. P value of <0.05 was considered statistically significant.

RESULTS:

1. There was no statistically significant difference among the groups in respect to age, gender, weight, ASA physical status, duration of anaesthesia (p value > 0.05) as depicted in Table 1.

Parameter	Group A	Group B	P-Value
Age (years)	35.46±7.98	38.00±7.756	0.110
Male: Female	17:33	13:37	0.383
Weight (kg)	60.3±6.87	59.2±6.56	0.360
ASA I: ASA II	43:7	44:6	0.766
Duration of Anaesthesia (Minutes.)	42.02±7.36	41.72±9.752	0.172

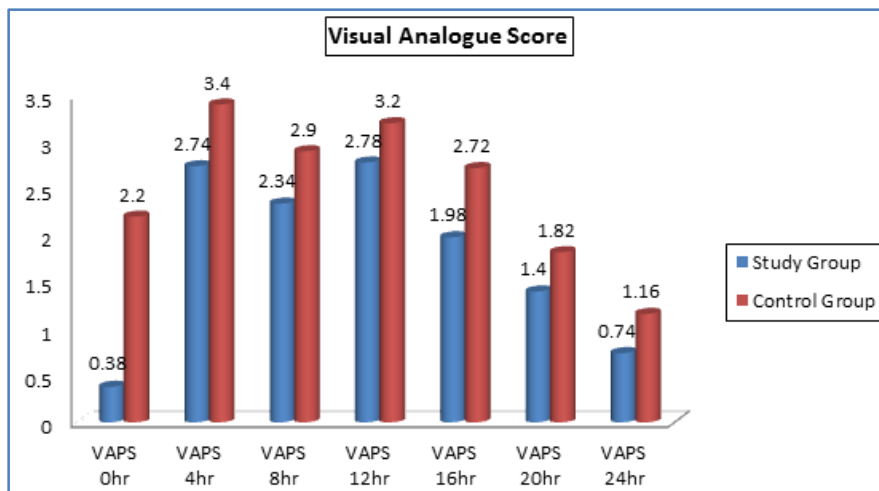
Table 1: Demographic profile of the patients

ASA - American Society of Anesthesiologists.

2. There was no statistically significant difference among the two groups with respect to heart rate, systolic blood pressure and diastolic blood pressure values at the beginning of operation or intraoperatively (p value >0.05).

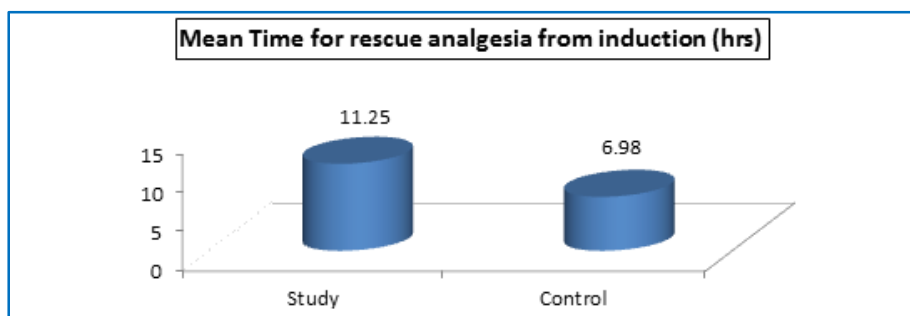
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3. The median value of visual analogue score (VAS) was found significantly lower at all-time points in study group when compared to control group p value of <0.05 (Observation recorded at 4 hours interval).



Graph 1: Showing visual analogue scale at 4 hourly intervals

4. Mean time for rescue analgesia from induction of anaesthesia in the study group was 11.25+1.827 hours and in control group was 6.98+4.568 hours (p value = 0.001).



Graph 2: Showing mean time for rescue analgesia from induction (hours)

5. Modified Aldrete score on arrival to post-anaesthetic care unit (PACU) was higher in study group as compared to control group patients (p value < 0.001).

Modified Aldrete Score	N	Mean	SD	P-value <0.001 (Sig.)
Study	50	9.78	0.465	
Control	50	8.10	1.158	

Table 2: Showing mean modified Aldrete scoring on arrival to post-anaesthetic care unit (PACU)

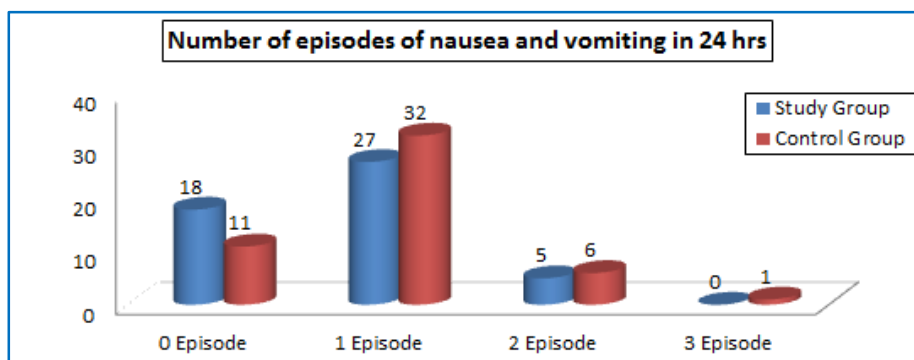
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6. The number of doses administered as rescue analgesic during 24 hours after surgery was statistically significant (p value < 0.001).

Number of Administered Rescue Analgesic Doses during 24 hours in the studied subjects			
Group	Mean	SD	P-value <0.001
Study (0, 1)	0.52	0.505	
Control (1, 2)	1.30	0.463	

Table 3: Showing Number of Administered Rescue Analgesic Doses during 24 hours in the studied subjects

7. The incidence of side effects such as postoperative nausea and vomiting was found statistically not significant in study group when compared to control group (p value = 0.361).



Graph 3: Showing episodes of nausea and vomiting in studied groups

DISCUSSION: Intravenous paracetamol 1 gram preoperatively or intraoperatively provided good post-operative analgesia, with decreased requirements of morphine and reduce side effects.¹⁹

Intravenous paracetamol 1 gram has analgesic activity in moderate to severe post-operative pain similar have shown ketorolac 30 milligram²⁰ diclofenac 75 miligram,²¹ morphine 10 miligram.²² It also demonstrated that Intravenous paracetamol reduce the use of opioid. It reduces the need for the patient's total opioid by 24-46% and increase in patient satisfaction.^{23,24,25,26}

This is the prospective, randomized, controlled study to look at the role of intravenous paracetamol injected 30 minutes before induction of anaesthesia in reducing intraoperative and post-operative morphine requirements in laparoscopic cholecystectomy patients, such that optimum analgesia is achieved with a concomitant reduction in opioid related side effects.

Our study goes in favour of Semih Arici et al (2009),¹⁹ who compared intravenous paracetamol either pre-induction or intra-operatively with control patients who received a placebo, in order to assess postoperative morphine consumption, sedation, pain scores, side effects, patient satisfaction and length of hospital stay in total abdominal hysterectomy patients with laparotomy.

Our study is in agreement with the study of Joaquin Hernandez-Palazon et al (2001),²⁷ who demonstrated the usefulness of propacetamol as an adjunct to PCA morphine in the treatment of postoperative pain after spinal fusion.

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Patients treated with IV injection of 2g propacetamol every 6 hour for 3 days after surgery consumed 46% less morphine than those treated with placebo ($p<0.001$). The pain scores were clinically lower in the propacetamol group measured at two intervals of the study, although visual analog scale pain intensity scores were less than 3 on a scale of 0-10 in both groups. Most patients in the placebo group obtained a greater degree of sedation on postoperative day 3 ($p<0.05$). The incidences of nausea and vomiting, pruritis and urinary retention were similar in both groups.

Our study is comparable with the study conducted by M. Gehling et al (2010),²⁸ who in their study concluded that parecoxib, acetaminophen and their combination reduced postoperative opioid requirement significantly by 50% ($p<0.05$). However, the combination of parecoxib and acetaminophen is not associated with a further reduction in opioid consumption.

Our study is comparable with the study conducted by E. D. Mc Nicol et al (2011),²⁹ who in their study performed a systematic search for single-dose, randomized, controlled clinical trials of propacetamol or intravenous (IV) paracetamol for acute postoperative pain in adults or children. Patients receiving propacetamol or IV paracetamol required 30% less opioid over 4 hour and 16% over 6 hour than those receiving placebo. However, this did not translate to a reduction in opioid-induced adverse events. Similar comparisons between propacetamol or IV paracetamol were neither statistically significant, nor clinically significant. Adverse events occurred at similar rates with propacetamol or IV paracetamol and placebo.

Our study is comparable with the study conducted by Mustafa Arsalan et al (2013),³⁰ who compared intravenous paracetamol either preemptively or postoperatively with control patients who received a placebo, in order to assess postoperative tramadol consumption, pain scores, side effects, patient satisfaction, in laparoscopic cholecystectomy patients. Patients were randomized into three groups; Group I, (Preemptive) received iv paracetamol 1g/100ml 10 min before skin incision, Group II, (Post-operative) received iv paracetamol 1g/100ml at the end of operation, Group III, (Placebo) received saline as placebo. Time to first analgesic requirements was significantly longer in Group I (preemptive paracetamol), and Group II (Post-operative), compared to Group III (placebo) ($P<0.05$).

Time to first analgesic requirement was significantly longer in Group I compared to Group II ($P<0.05$). Total analgesic consumption and postoperative VAS pain scores recorded were significantly lower in Group I and II, compared to Group III. Total analgesic consumption and postoperative VAS pain scores recorded were significantly lower in Group I compared to Group II ($P<0.05$). In conclusion, they study analgesic effect of 1g of paracetamol in patients undergoing laparoscopic cholecystectomy decreased opioid consumption with lower side effects; paracetamol can be safely used in post-operative pain management.

CONCLUSION: Administration of preemptive intravenous paracetamol and 50% dose of morphine prior to induction in patients undergoing laparoscopic cholecystectomy have no negative effects on intraoperative or postoperative hemodynamic parameters, ensure an effective analgesia intraoperatively as well as postoperatively and were associated with earlier discharge from post anesthetic care unit (PACU) when compared with full dose of intravenous morphine. However above combination was not able to decrease significantly the occurrence of adverse effects in these patients.

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AUTHORS:

1. Aftab Ahmad Khan
2. Shabir Ahmad Sofi
3. Fayaz Ahmad Munshi
4. Mushtaq Ahmad Rather

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Anaesthesiology & Critical Care, GMC, Srinagar.
2. Senior Resident, Department of Anaesthesiology & Critical Care, GMC, Srinagar.
3. Associate Professor, Department of Anaesthesiology & Critical Care, GMC, Srinagar.

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4. Senior Resident, Department of Anaesthesiology & Critical Care, GMC, Srinagar.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Mushtaq Ahmad Rather,
Senior Resident,
Department of Anaesthesiology & Critical Care,
GMC, Srinagar-190006.
Email: mushtaqahmad767@gmail.com

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