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Original Article

A Prospective Randomized Double-blind Controlled Study Comparing Intravenous Paracetamol Plus Fentanyl and Intravenous Fentanyl Alone for Post-operative Analgesia for Laparoscopic Cholecystectomy

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Abstract

Background: Acute pain after laparoscopic cholecystectomy is complex in nature which shows individual variation in intensity and duration; therefore, adequate pain control is mainstay during post-operative period. This study compares the effect of intravenous (IV) paracetamol plus IV fentanyl and fentanyl alone for analgesic efficacy, intraoperative hemodynamic, opioids sparing effects, and opioid-related side effects after laparoscopic cholecystectomy.

Aim of the Study: The aim of the study was to determine the efficacy of IV paracetamol for post-operative analgesia in patients undergoing elective laparoscopic cholecystectomy under general anesthesia and to compare the occurrence of opioid-sparing effects in patients receiving IV fentanyl plus IV paracetamol and IV fentanyl alone postoperatively.

Materials and Methods: A total of 60 patients undergoing laparoscopic cholecystectomy were randomized into two groups. In Group A, IV paracetamol 1 g (100 mL) was administered 10 min before induction. Group B served as a control group and received saline normal saline 100 mL. Both groups received fentanyl during induction. Intraoperative hemodynamic such as heart rate, mean arterial pressure, and intraoperative fentanyl consumption was measured and recorded. The post-operative pain relief was evaluated by a visual analog scale (VAS) score, consumption of fentanyl as rescue analgesia, and sedation scores, the incidence of post-operative nausea and vomiting (PONV) and pruritus was measured in the post-operative period.

Observations and Results: The mean VAS score in immediate and 1 h after surgery was less in the group receiving IV paracetamol (3.03 ± 0.41* vs. 3.53 ± 1.04; 3.13 ± 0.57* vs. 3.90 ± 1.21); the fentanyl consumption intraoperatively was less in the paracetamol group (41.50 ± 32.40* vs. 84.66 ± 32.32*), overall intraoperative hemodynamic was stable in paracetamol group. The time requirement of the first dose of rescue analgesic in the post-operative period was also significantly prolonged in the group receiving IV paracetamol (5.84 ± 4.44 *vs. 1.83 ± 1.09). The sedation scores at 1^{st}, 6^{th}, and 12^{th} h were less in paracetamol group (1.43 ± 0.67* vs. 1.83 ± 0.64; 1.20 ± 0.40* vs. 1.56 ± 0.72; and 1.10 ± 0.30* vs. 1.43 ± 0.50). There was no difference in the incidence of PONV and pruritus in the two groups.

Conclusion: The use of IV paracetamol 1 g for preemptive analgesia as an adjunct to IV fentanyl in patients undergoing laparoscopic cholecystectomy had better intraoperative hemodynamic parameters, good quality postoperative analgesia, reduced consumption of fentanyl doses, and lesser sedation in post-operative period.

Key words: Intravenous paracetamol, Laparoscopic cholecystectomy, Post-operative pain, Post-operative analgesia

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INTRODUCTION

Surgical pain is a form of acute pain that occurs in response to tissue damage caused by the surgical act, and it is the expression of autonomic responses, that can produce an unpleasant and unwanted sensory-emotional experience. Recent data suggest that at least 30–40% of all surgical

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patients do experience moderate or severe postoperative pain.[1,2] Acute pain after laparoscopic cholecystectomy is complex in nature. Pain after laparoscopy is caused by the stretching of the peritoneum, residual gas, the effect of surgery and skin incisions. The pain pattern does not resemble pain after other laparoscopic procedures; hence, the analgesic treatment required after laparoscopic cholecystectomy might be different or multimodal. Thus, effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge.[3] In laparoscopic cholecystectomy, overall pain is of three different types mainly clinically divided as: Incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (presumably referred visceral pain). Characteristically, there is a high inter-individual variability in intensity and duration in such types of pain. It has been observed in many studies that pain is most intense on the day of surgery and the following day and subsequently declines to low levels within 3–4 days. However, severe pain is found in approximately 13% of patients throughout the 1st week after laparoscopic cholecystectomy.[4] Hence, this could be one of the reasons for a prolonged duration of stay in the hospital postoperatively. It is found in 17–41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery.[5] Different combinations of drugs are available for optimal pain management which include local anesthetics, nonsteroidal anti-inflammatory drugs, opioids, and paracetamol. Opioids are very commonly used in the management of moderate to severe post-operative pain extensive use of opioids is associated with a variety of perioperative side effects, such as ventilatory depression, drowsiness and sedation, post-operative nausea and vomiting (PONV), pruritus, urinary retention, ileus, and constipation that can delay hospital discharge.[6] Intraoperative use of large bolus doses or continuous infusions of potent opioid analgesics may actually increase post-operative pain as a result of their rapid elimination and/or the development of acute tolerance.[7] To avoid the adverse effects of the individual drug at high doses an adjunctive drug may be used. Recent evidence suggests that the reduction in these adverse effects may be best achieved using a combination of protocols involving both central and peripheral acting drugs.[8] Recently launched intravenous (IV) paracetamol is commonly used for preemptive analgesia during various operative procedures. The aim of providing preemptive analgesia with IV paracetamol before a painful stimulus is to prevent central sensitization caused by painful stimulus and consequently to decrease the need for post-operative analgesia.[9] The analgesic effects of acetaminophen are mediated in the central nervous system by inhibiting the synthesis of prostaglandins. Its IV administration provides rapid and predictable therapeutic plasma concentration. Initiation of treatment with centrally acting acetaminophen shortly before or during laparoscopic cholecystectomy is optimal.[10] The opioids sparing effects of acetaminophen are in the range of 20–30%. Recent data from routine use of acetaminophen suggested hastened and higher quality of recovery along with less use of opioids in cholecystectomy.[11] The concept of multimodal "opioid-sparing" analgesic techniques (so-called balanced analgesia) was introduced more than 15 years ago, with the aim of improving analgesia by combining analgesics that have additive or synergistic effects. It involves the use of smaller doses of opioids in combination with non-opioid analgesic drugs (e.g., local anesthetics, ketamine, acetaminophen, and nonsteroidal anti-inflammatory drugs) to prevent pain after surgery. Thus, the present study is done to evaluate the analgesic efficacy of IV paracetamol in patients undergoing laparoscopic cholecystectomy.

Aim of the Study

The aim of the study was to determine the efficacy of IV paracetamol for post-operative analgesia in patients undergoing elective laparoscopic cholecystectomy under general anesthesia and to compare the occurrence of opioid-sparing effects in patients receiving IV fentanyl plus IV paracetamol and IV fentanyl alone postoperatively.

Type of Study

This was a progressive randomized double-blind controlled study.

Period of Study

This study was from May 2012 to May 2013.

Institute of Study

This study was conducted in the Department of Anaesthesiology, C.S.I Holdsworth Memorial Hospital, Mysuru.

MATERIALS AND METHODS

The present study was conducted in the Department of Anaesthesiology, CSI Holdsworth Memorial Hospital, Mysuru - 21. The study was undertaken after obtaining Ethical Committee Clearance as well as informed consent from all patients. 60 patients, scheduled for elective laparoscopic cholecystectomy belonging to ASA Class I and II were included in the study.

Inclusion Criteria

The following criteria were included in the study:

1. Patients aged between 18 and 65 years.
2. Patients with ASA Grades I and II.

3. Patients scheduled for elective laparoscopic cholecystectomy under general anesthesia.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with known hypersensitivity to paracetamol, fentanyl.
2. Patients with abnormal coagulation profile.
3. Patients with hepatic or renal insufficiency.
4. Laparoscopic cholecystectomy converted to open cholecystectomy intraoperatively.

Randomization

Based on the computer-generated randomization numbers, patients were randomly divided into two groups with 30 patients in each group. Group A (n = 30, paracetamol + fentanyl group) received 100 mL of paracetamol IV (1 g) 10 min before induction. Group B (n = 30, fentanyl alone group) received 100 mL of normal saline 10 min before induction. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anesthetic procedure. The routine blood investigations were followed and thorough pre-anesthetic evaluation was done on the evening before surgery. All patients included in the study were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bedtime the previous night before surgery. They were kept nil orally 10 pm onward on the previous night. The investigators involved in the study did not know about the content of the 100 mL bottle as the preparation of the study drug was done by an anesthesiologist not involved with the observations made for the study. Patients were explained about the study but did not know which drug was used. On arrival of the patient in the operating room, two IV lines were secured, one 20 G IV cannula in right hand for the infusion and another 18 G IV cannula in left hand for IV fluids and drug administration. 500 mL of crystalloids (ringer lactate) was started. Monitors, electrocardiography, non-invasive blood pressure, pulse oximeter, and $ETCO_2$ were attached. HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were monitored before, during and after the surgery. End-tidal carbon dioxide was monitored intraoperatively and kept between 30 and 35 mmHg depending on different stages of laparoscopy. The study drug paracetamol 100 mL (1 g) given to Group A as single dose IV over 10 min just before induction. The Group B patients served as control were given 100 mL normal saline over 10 min just before induction. After the preoxygenation for 3 min, patients in both the groups were induced with injection fentanyl 2 μg/kg, injection propofol 2 mg/kg, and injection rocuronium 0.6 mg/kg. Laryngoscopy and endotracheal intubation were done and lungs were mechanically ventilated. Anesthesia was maintained with O_2 in N_2O (66%:33%), isoflurane 1% and intermittent bolus dose of rocuronium. Fentanyl was repeated in a dose of 1 μg/kg intraoperatively if both HR and MAP increased >15–20% from baseline despite maintaining adequate depth of anesthesia. The intraoperative hemodynamic monitoring such as SBP, DBP, MAP, and HR was done after induction of the patient in every 15 min interval. Moreover, intraoperative requirement of injection fentanyl was noted and recorded. (1) Heart rate [HR] in beats per minute (bpm), (2) SBP in mmHg, (3) DBP in mmHg, and (4) MAP in mmHg. The above cardiovascular parameters were monitored in the following time intervals: (1) Baseline parameter recording, (2) at the time of induction, (3) at the time of intubation, (4) during insufflations of CO_2 (pneumoperitoneum [PNP]), (5) every 15 min after PNP, and (6) deflation of PNP and after extubation. After surgery patients were reversed with injection glycopyrrolate 0.01 mg/kg and injection neostigmine 0.05 mg/kg and the patients were extubated and transferred to postanesthesia care unit. Post-operative pain was assessed using visual analog scale (VAS: 0 - "no pain" and 10 - "worst pain ever") and the posto-perative rescue analgesia was provided with injection fentanyl 0.5 μg/kg when VAS score exceeded 3. The degree of sedation was determined by RAMSAY sedation score ranging from 1 to 6 score. The VAS score is assessed at an interval of 1, 2, 4, 6, 12, and 24 h after surgery similarly sedation score assessed at an interval of 1, 2, 4, 6, and 12 h. The total fentanyl consumption at these times for both the group was recorded. The time of first dose of rescue analgesia was recorded. The incidence of PONV and Pruritus was also observed in post-operative period and treated accordingly. Sample size calculation: The number of participants required in each study group, m, was calculated using the formula as below:

$$\mathrm{m} = \frac{2 \times [Z(1-\alpha/2) + Z(1-\beta)]^2}{\Delta^2}$$

Where Z (1-α/2) and Z (1-β) represent percentage points of the normal distribution for statistical significance level and power, respectively, and Δ represents the standardized difference (i.e., the treatment difference divided by its standard deviation).

$$\text{The standardised difference } \Delta = \frac{p1 - p2}{\sqrt{p \times (1-p)}}$$

Where

$$p = \frac{(p1 + p2)}{2}$$

In our study, p_1 = 0.80 (or 80%), p_2 = 0.40 (or 40%), and so, $p = \frac{0.8 + 0.4}{2} = 0.6$

Hence, $\Delta = \frac{0.8 - 0.4}{\sqrt{0.6 \times (1 - 0.6)}} = 0.82$

Using the values for a significance level of 5%, Z (1-α/2) = 1.96, and a power of 80%, Z (1-β) = 0.8416,

$$m = \frac{2 \times [1.96 + 0.8]^2}{(0.82)^2} = 23$$

From the above calculations, the sample size was taken as 23. Hence, it was decided to study 30 patients in each group. Statistical method applied: Frequencies: The frequencies procedure provides statistics and graphical displays that are useful for describing many types of variables. For a frequency report and bar chart, the distinct values arranged in ascending or descending order, or by their frequencies. The frequencies report can be suppressed when a variable has many distinct values. The charts labeled with frequencies (the default) or percentages.

Descriptives

The descriptives procedure displays univariate summary statistics for several variables in a single table and calculates standardized values (z scores). Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which you select the variables (the default). When z scores are saved, they are added to the data in the Data Editor and are available for charts, data listings, and analyses. When variables are recorded in different units (for example, gross domestic product per capita and percentage literate), a z-score transformation places variables on a common scale for easier visual comparison.

Paired-samples *t*-test

The paired-samples *t*-test procedure compares the means of two variables for a single group. The procedure computes the differences between the values of the two variables for each case and tests whether the average differs from 0.

Table 1: Demographic data showing mean age, DOS, and weight of patient

Characteristics	Group A	Group B	*P* value
Age (years)	43.93±12.90	43.87±11.94	0.984
Weight (kg)	70.47±9.9	68.57±7.9	0.415
Duration of surgery (min)	111±13.98	114±12.20	0.380

DOS: Duration of surgery

One-way ANOVA

The one-way ANOVA procedure produces a one-way analysis of variance for a quantitative dependent variable by a single factor (independent) variable. Analysis of variance is used to test the hypothesis that several means are equal. This technique is an extension of the two-sample *t*-test.

OBSERVATIONS AND RESULTS

The mean age of the patients observed was 43.93 ± 12.90 in Group A and 43.87 ± 11.94 in Group B with *P* value 0.984 (not significant statistically). The mean weight in Group A was 70.47 ± 9.9 and 68.57 ± 7.9 in Group B with *P* value of 0.415 (not significant). The duration of surgery (DOS) in Group A was 111 ± 13.98 and 114 ± 12.20 min in Group B [Table 1 and Figure 1].

In Group B (*n* = 30, control), the basal mean HR was 82.20 ± 12.58. 10 min after bolus drug administration, at induction the mean HR was 76.47 ± 10.61 which is statistically significant (*P* = 0.001). 15 min after PNP and subsequently the mean HR was significantly high compared to basal value (*P* = 0.028). The mean HR after deflation of abdomen was not statistically significant compared to basal value (*P* = 0.277) and soon after extubation mean HR remained significantly high compared to basal value (*P* = 0.003) [Table 2].

In Group A (paracetamol), the basal mean HR was 78.43 ± 14.30. The mean HR after induction and PNP was statistically insignificant compared to basal HR. After extubation HR was 85.33 ± 7.28 which was statistically significant (*P* = 0.008). In our study, we found the mean HR in paracetamol group with different stages of laparoscopy was maintained with basal HR intraoperatively [Table 3].

The mean HR in control Group(B) after PNP and subsequently at 30, 45, 75, 90, and 105 min and after

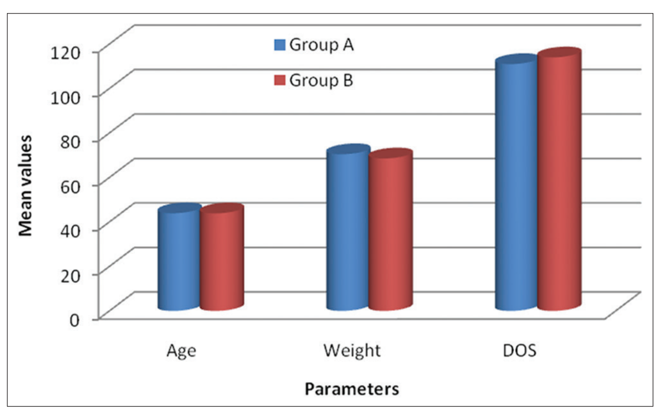

Figure 1: Mean age, duration of surgery, and weight of patient

Table 2: Intraoperative comparison of mean HR/min changes in response to laryngoscopy and intubation and PNP in control Group (B) compared to basal HR

Time interval	HR /min	*P* value
Basal (M1)	82.20±12.58	
At induction (M2)	76.47±10.61	0.001
Intubation (M3)	79.70±10.09	0.238
PNP (M4)	81.47±11.29	0.695
15 min after PNP (M5)	87.63±10.62	0.028
30 min after PNP (M6)	85.67±9.37	0.167
45 min after PNP (M7)	82.67±9.49	0.835
60 min after PNP (M8)	81.03±7.36	0.617
75 min after PNP (M9)	81.73±7.29	0.847
90 min after PNP (M10)	81.29±7.11	0.464
105 min after PNP (M11)	83.00±8.61	0.195
After abdomen deflation (M12)	84.73±6.98	0.277
After extubation (N1)	88.67±5.57	0.003

HR: Heart rate, PNP: Pneumoperitoneum

Table 3: Intraoperative comparison of mean HR/min changes in response to laryngoscopy and intubation and PNP in paracetamol Group (A) compared to basal HR

Time interval	HR /min	*P* value
Basal (M1)	78.43±14.30	
At induction (M2)	76.23±11.67	0.085
Intubation (M3)	81.57±10.02	0.085
PNP (M4)	80.20±9.65	0.362
15 min after PNP (M5)	83.47±9.64	0.045
30 min after PNP (M6)	80.50±10.93	0.524
45 min after PNP (M7)	77.33±9.20	0.660
60 min after PNP (M8)	78.17±9.69	0.907
75 min after PNP (M9)	76.50±8.90	0.362
90 min after PNP (M10)	74.86±8.78	0.223
105 min after PNP (M11)	76.38±8.30	0.608
After abdomen deflation (M12)	80.87±7.31	0.358
After extubation (N1)	85.33±7.28	0.008

HR: Heart rate, PNP: Pneumoperitoneum

Table 4: The intergroup comparison of mean HR/min changes in response to laryngoscopy and intubation and PNP between control Group (B) and paracetamol (A) Group

Time interval	Group A	Group B	*P* value
Basal (M1)	78.43±14.30	82.20±12.58	0.283
At induction (M2)	76.23±11.67	76.47±10.61	0.936
Intubation (M3)	81.57±10.02	79.70±10.09	0.475
PNP (M4)	80.20±9.65	81.47±11.29	0.642
15 min after PNP (M5)	83.47±9.64	87.63±10.62	0.117
30 min after PNP (M6)	80.50±10.93	85.67±9.37	0.054
45 min after PNP (M7)	77.33±9.20	82.67±9.49	0.031
60 min after PNP (M8)	78.17±9.69	81.03±7.36	0.202
75 min after PNP (M9)	76.50±8.90	81.73±7.29	0.016
90 min after PNP (M10)	74.86±8.78	81.29±7.11	0.010
105 min after PNP (M11)	76.38±8.30	83.00±8.61	0.012
After abdomen deflation (M12)	80.87±7.31	84.73±6.98	0.041
After extubation (N1)	85.33±7.28	88.67±5.57	0.051

HR: Heart rate, PNP: Pneumoperitoneum

Table 5: Intraoperative comparison of MAP in mmHg changes in response to laryngoscopy and intubation and PNP in control Group (B) compared to basal MAP

Time interval	MAP (mmHg)	*P* value
Basal (M1)	93.67±10.41	
At induction (M2)	85.97±10.19	0.000
Intubation (M3)	90.37±7.94	0.074
PNP (M4)	93.77±9.28	0.965
15 min after PNP (M5)	101.67±9.65	0.000
30 min after PNP (M6)	99.20±8.66	0.019
45 min after PNP (M7)	95.07±6.01	0.462
60 min after PNP (M8)	93.57±5.62	0.961
75 min after PNP (M9)	92.80±5.53	0.671
90 min after PNP (M10)	93.13±5.18	0.739
105 min after PNP (M11)	95.25±7.70	0.593
After abdomen deflation (M12)	95.60±6.81	0.327
After extubation (N1)	101.07±5.74	0.000

MPA: Mean arterial pressure, PNP: Pneumoperitoneum

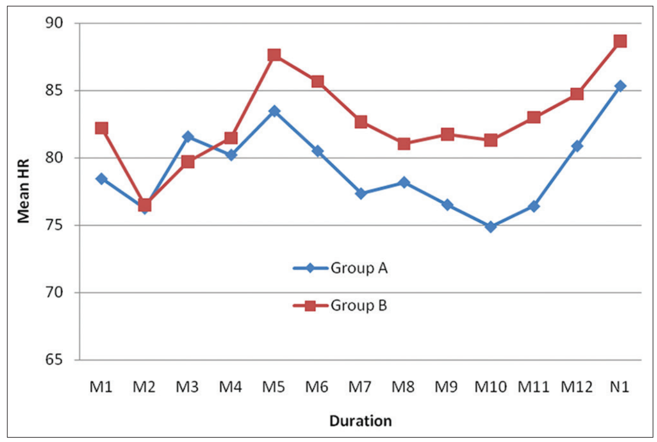

Figure 2: The intergroup comparison of mean heart rate (HR/min) changes in response to laryngoscopy and intubation and pneumoperitoneum between control Group (B) and paracetamol (A) Group

extubation was increased compared to basal value and mean HR of paracetamol Group (A), which was statistically significant ($P < 0.05$) [Table 4].

In control Group (B) the MAP compared to basal MAP, at induction was 85.97 ± 10.19 ($P = 0.000$); however, 15 min after PNP and after extubation the MAP was high 101.67 ± 9.65 and 101.07 ± 5.74, respectively, which was statistically significant ($P = 0.000$) [Table 5 and Figure 2].

In paracetamol group, there was no statistically significant change in MAP compared to basal MAP intraoperatively, except the MAP at induction is 89.07 ± 12.10 ($P = 0.000$) and 75 min after PNP is 89.03 ± 7.35 ($P = 0.026$) which was statistically significant [Table 6].

In control Group (B), the MAP was increased compared to paracetamol Group (A) intraoperatively, and it

Table 6: Intraoperative comparison of MAP in mmHg changes in response to laryngoscopy and intubation and PNP in paracetamol Group (A) compared to basal MAP

Time interval	MAP (mmHg)	*P* value
Basal (M1)	94.43±10.86	
At induction (M2)	89.07±12.10	0.000
Intubation (M3)	94.13±11.30	0.845
PNP (M4)	94.03±10.83	0.827
15 min after PNP (M5)	97.53±11.28	0.172
30 min after PNP (M6)	95.67±15.40	0.689
45 min after PNP (M7)	90.80±11.00	0.158
60 min after PNP (M8)	91.50±10.30	0.280
75 min after PNP (M9)	89.03±7.35	0.026
90 min after PNP (M10)	88.52±7.58	0.062
105 min after PNP (M11)	88.95±7.73	0.074
After abdomen deflation (M12)	91.33±6.53	0.211
After extubation (N1)	95.80±6.35	0.551

MPA: Mean arterial pressure, PNP: Pneumoperitoneum

Table 7: The intergroup comparison of mean MAP in mmHg changes in response to laryngoscopy and intubation and PNP between control (B) group and paracetamol (A) group

Time interval	Group A	Group B	*P* value
Basal (M1)	94.43	93.67±10.41	0.781
At induction (M2)	89.07	85.97±10.19	0.288
Intubation (M3)	94.13	90.37±7.94	0.141
PNP (M4)	94.03	93.77±9.28	0.919
15 min after PNP (M5)	97.53	101.67±9.65	0.133
30 min after PNP (M6)	95.67	99.20±8.66	0.278
45 min after PNP (M7)	90.80	95.07±6.01	0.067
60 min after PNP (M8)	91.50	93.57±5.62	0.339
75 min after PNP (M9)	89.03	92.80±5.53	0.029
90 min after PNP (M10)	88.52	93.13±5.18	0.021
105 min after PNP (M11)	88.95	95.25±7.70	0.009
After abdomen deflation (M12)	91.33	95.60±6.81	0.016
After extubation (N1)	95.80	101.07±5.74	0.001

MPA: Mean arterial pressure, PNP: Pneumoperitoneum

Table 8: Requirement of intraoperative dose of IV fentanyl in both groups

Intra-operative dose	Group A	Group B	*P* value
Intraoperative dose Mean (mcg)	41.50±32.40	84.66±32.32	0.000

was statistically significant after 60 min of PNP and subsequently until after extubation ($P < 0.05$). However, in paracetamol group, there was no significant variation in MAP compared to basal MAP [Table 7 and Figure 3].

We found the intraoperative requirement of a mean dose of IV fentanyl was 41.50 ± 32.40 in paracetamol Group (A) and 84.66 ± 32.32 in control Group (B) which is statistically significant ($P = 0.000$) [Table 8 and Figure 4].

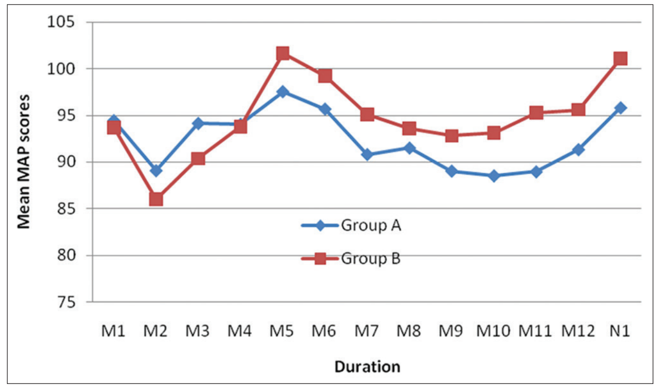

Figure 3: The intergroup comparison of mean arterial blood pressure (MAP in mmHg) changes in response to laryngoscopy and intubation and pneumoperitoneum between control (B) Group and paracetamol (A) Group

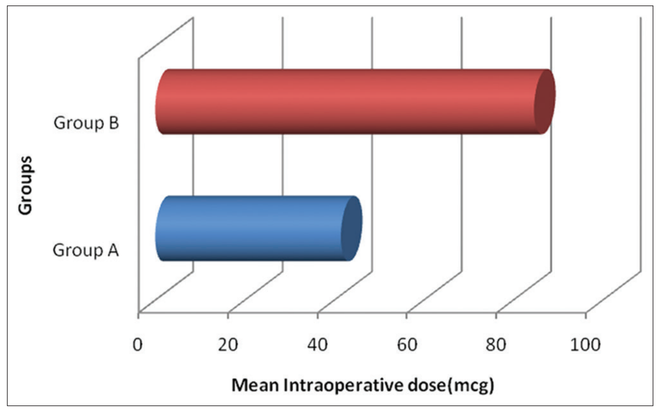

Figure 4: Requirement of intraoperative dose of IV fentanyl in both groups

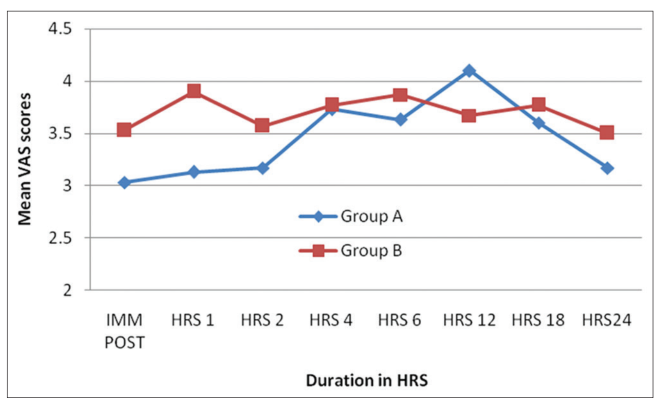

Figure 5: Comparison of visual analog scale score at different hours postoperatively between control and paracetamol group. IMM POST - immediate post-operative, HRS - hours, and VAS - visual analog scale

The mean VAS score immediate postoperatively and after 1 h was lower in the paracetamol group with statistically significant $P = 0.018$ and $P = 0.003$, respectively [Table 9 and Figure 5].

The Ramsay sedation score in paracetamol group was less as compared to control group at 1 h ($P = 0.023$), 6 h

Table 9: Comparison of VAS scores at different hours postoperatively between control and paracetamol group

VAS score	Group A	Group B	*P* value
Immediate postoperative	3.03±0.41	3.53±1.04	0.018
1 HR	3.13±0.57	3.90±1.21	0.003
2 HR	3.17±0.59	3.57±1.00	0.066
4 HR	3.73±1.08	3.77±1.16	0.909
6 HR	3.63±1.15	3.87±1.22	0.452
12 HR	4.10±1.34	3.67±0.95	0.157
18 HR	3.60±0.89	3.77±0.85	0.464
24 HR	3.17±0.46	3.50±0.93	0.086

HR: Heart rate, VAS: Visual analog scale

Table 10: Comparison of Ramsay sedation score at different hours postoperatively between control (B) and paracetamol (A) group

Ramsay sedation score	Group A	Group B	*P* value
1 HR	1.433±0.678	1.833±0.647	0.023
2 HR	1.500±0.572	1.566±0.568	0.652
4 HR	1.700±0.702	1.500±0.682	0.268
6 HR	1.200±0.406	1.566±0.727	0.019
12 HR	1.100±0.305	1.433±0.504	0.003

Table 11: Requirement of first dose of rescue analgesia in both groups

Requirement of dose	Group A	Group B	*P* value
First dose - rescue analgesia			
Received	26	24	0.000
Not received	4	6	
Mean (hours)	5.84±4.44	1.83±1.09	

Table 12: Frequency (number of doses) of rescue analgesia

NO of doses	Group A	Group B	*P* value
Frequency -rescue analgesia			
Mean	1.81±1.0	2.80±0.55	0.000

(*P* = 0.019), and at 12 h (*P* = 0.003) postoperatively which was statistically significant [Table 10 and Figure 6].

The requirement of the first dose of rescue analgesia in Group (B) was in early hours postoperatively as compared to paracetamol Group (A). The mean hours was 5.83 in Group A and 1.83 in Group B which was statistically highly significant (*P* = 0.000). The 4 patient out of (*n* = 30) did not require rescue analgesia (13.3%) in Group A whereas 6 patient out of (*n* = 30) did not required rescue analgesia (20%) in Group B [Table 11 and Figure 7].

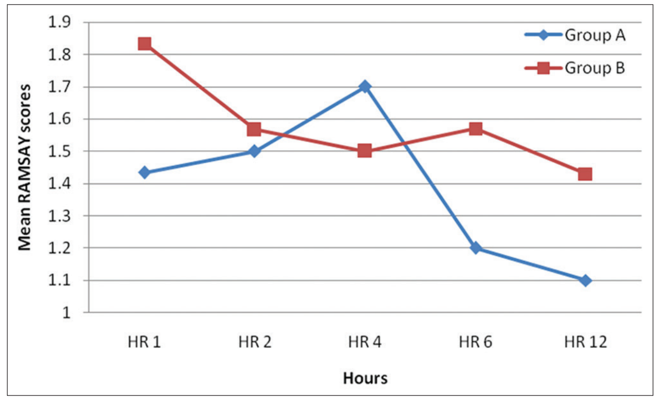

Figure 6: Comparison of Ramsay sedation score at different hours postoperatively between control (B) and paracetamol (A) Group

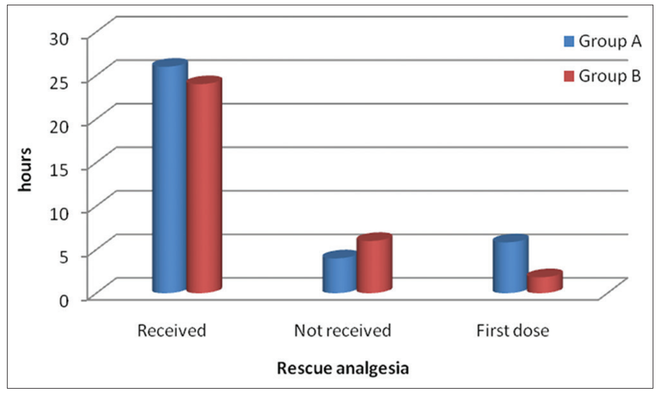

Figure 7: Requirement of first dose of rescue analgesia in both groups

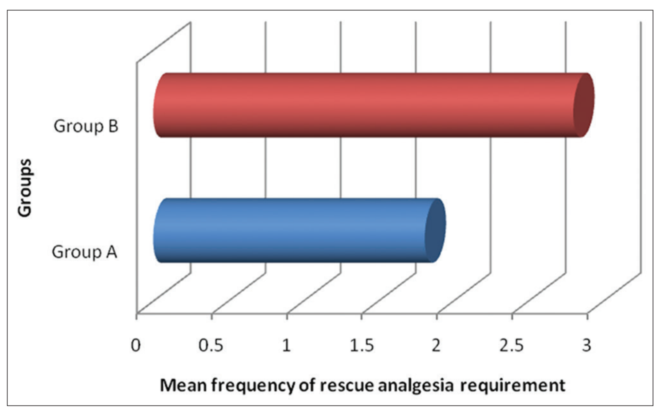

Figure 8: Frequency of rescue analgesia

The mean frequency (no of doses) of rescue analgesia in paracetamol Group (A) was lower as compared to control Group (B) which was 1.81 ± 1.00 and 2.80 ± 0.55, respectively, and was statistically highly significant with *P* = 0.000 [Table 12 and Figure 8].

There was no significant difference found in the incidence of PONV and pruritus in both groups [Tables 13 and 14].

Table 13: Incidence of PONV between control (B) and Paracetamol group (A)

PONV	Group A *n* (%)	Group B *n* (%)
1 h		
No	28 (93.3)	27 (90)
Yes	2 (6.7)	3 (10)
2 h		
No	28 (93.3)	30 (100
Yes	2 (6.7)	0 (0.0)
4 h		
No	30 (100)	28 (93.3)
Yes	0 (0.0)	2 (6.7)
6 h		
No	29 (96.7)	30 (100)
Yes	1 (3.3)	0 (0.0)
12 h		
No	29 (96.7)	30 (100)
Yes	1 (3.3)	0 (0.0)
18 h		
No	30 (100)	30 (100)
Yes	0 (0.0)	0 (0.0)

PONV: Post-operative nausea and vomiting

Table 14: Incidence of pruritus

Symptom	Group A (%)	Group B (%)	*P* value
Pruritus			
No	29 (96.7)	28 (93.3)	0.554
Yes	1 (3.3)	2 (6.7)	

DISCUSSION

The overall pain after laparoscopic cholecystectomy shows individual variation in intensity and duration. Adequate pain control is the mainstay during the post-operative period. Poor pain control may lead to short-term or long-term complications. The complications such as atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, and myocardial ischemia are related to inadequate pain control.[12] The present study was conducted in the Department of Anaesthesiology, CSI Holdsworth Memorial Hospital, Mysuru - 21 during the period of May 2012–May 2013. The study population consisted of 60 patients divided randomly by using computer-generated randomization numbers into two groups with 30 patients in each group. Both the groups were comparable, and there was no statistically significant difference with regard to mean age, weight, and DOS. In this study, efforts have been taken to evaluate the efficacy of IV Paracetamol for post-operative analgesia. Opioids are most commonly used as post-operative analgesics, but the side effects of opioids such as PONV, sedation, and respiratory depression are frequently encountered. Recent studies show opioid-sparing effect of IV paracetamol; therefore, we studied the effects of IV paracetamol.

Table 15: Studies showing different doses of paracetamol with opioids

Author and year	Dose of paracetamol	Opioids used
Arici. S[17] 2009	1 g 30 min before induction (Group I) and 1 gm before skin closure (Group II)	Morphine
Memis *et al*.[19] 2010	1 g every 6 hourly	Meperidine
Altun *et al*.[20] 2010	1 g - Group I 2 g - Group II	Tramadol
Chaudhury *et al*.[21] 2011	1 g paracetamol just before induction	Fentanyl
Present study	1 g paracetamol 10 min before induction	Fentanyl

Table 16: Intraoperative hemodynamic observation

Author and year	Observation
Semih *et al*.[13] 2009	No intraoperative and post-operative change in hemodynamic
Turan *et al*.[14] 2012	No intra-operative change in MAP, HR
Present study	Intraoperative hemodynamic MAP, HR was stable with paracetamol group

Dose of Paracetamol

In this study, we used single dose IV paracetamol (1 g) as a preemptive analgesic 10 min before induction. Various studies used paracetamol dose of 1 g or 2 g for comparison with different opioids [Table 15].

Intraoperative Hemodynamics

In laparoscopic cholecystectomy intraoperative hemodynamic alteration is known to occur due to PNP and pain. In this study, we used 1 g (100 mL) IV paracetamol 10 min before induction as a part of the multimodal analgesic regime. Intraoperatively we assessed heart rate, MAP during induction, intubation, PNP, and every 15 min subsequently until extubation. We found there was a significant change in heart rate and MAP with fentanyl group, however, with paracetamol hemodynamic were stable. However, there was no significant change found in intraoperative hemodynamics with paracetamol in studies done by Semih *et al.*[13] and Turan *et al.*[14] [Table 16].

Fentanyl Requirement

In this study, as we found there was a significant change in HR and MAP in control Group (B) compared to paracetamol Group (A) from the baseline value; hence, the requirement of fentanyl was more in control group. It may be due to the short-acting nature of fentanyl and significant hemodynamic variation related to different stages of laparoscopy with the control group. Intraoperative consumption of a mean dose of fentanyl was 41.50 ± 32.40 in paracetamol Group (A) as compared to the control Group (B) which was 84.66 ± 32.32 with statistically significant *P* value (*P* = 0.000). Similar results found in a study done by Salihoglu *et al.*,[15] there was less opioid consumption intraoperatively inpatient received IV paracetamol [Table 17].

Rescue Analgesia and Opioid Consumption (Post-operative)

Adequacy of analgesia was assessed postoperatively by Visual Analogue Scale score. We found a significant difference (*P* = 0.012) in mean VAS score between two groups. The mean VAS score immediate postoperatively and after 1 h was lower in paracetamol group 3.9 ± 1.21 and 3.13 ± 0.57 whereas in control group it was 3.53 ± 1.04 with significance *P* = 0.018 and 0.003, respectively. There was the significant efficacy of paracetamol plus fentanyl for post-operative analgesia. A comparison was made in regard with rescue anaesthesia and opiod consumption in the present study with studies by various authors[15,18-21] and found that, Longer time for first rescue analgesia and less opioid consumption in paracetamol group with mean 5.84±4.44(h) and 1.83±1.09 (h) in fentanyl group (*P*=0.000) was observed, [Table 18]. Overall, the VAS score was lower in the paracetamol group compare with other groups. In this study, the VAS score immediate post-operative and at 1st h was significantly lower in the paracetamol group. This may be because of an initial loading dose of paracetamol before induction which provides higher plasma concentration.

Sedation Score

In the present study, we found the mean time required in hours for first rescue analgesia was 5.84±4.44 in paracetamol group as compared to 1.83±1.09 in control group, respectively, and post-operative fentanyl consumption in terms of a number of doses (frequency) was less in paracetamol group with statistical significance. Our study is comparable with a study done by various studies [Table 19]. Wininger *et al.*[18] and Salihoglu *et al.*[15] observed there was the longer time required for first rescue analgesia in paracetamol group with less opioid consumption in post-operative period. Choudhery *et al.*[21] observed prolonged time required for the first dose of rescue analgesia in paracetamol group with a mean of 76.0 ± 24.7 and 48.0 ± 15.8 (min) in fentanyl group.

In this, it was observed that the sedation score in paracetamol group was less as compared to fentanyl group at 1, 6, and 12 h postoperatively with significant *P* = 0.023, 0.019, and 0.003, respectively. Memis *et al.*[19] also noted less sedation score in paracetamol group compared to placebo with significant *P* value (*P* < 0.05). Hong *et al.*[22] found the sedation score was significantly lower (*P* = 0.019) in the paracetamol group.

Table 17: Pain intensity score or VAS score observation

Author and year	VAS score in different group observed
Goroc *et al.*,[16] 2009	Majority of patient VAS score <3 cm at 15 min at the end of surgery in paracetamol group
Semih *et al.*,[17] 2009	VAS score in the control group at rest and movement was higher than the paracetamol group
Wininger *et al.*[18] 2010	VAS over 24 h more favorable for paracetamol group than placebo. Group with *P*<0.007 with 1 g IV paracetamol and *P*<0.019 with 650 mg IV paracetamol, respectively
Memis *et al.*,[19] 2011	VAS score significantly lower in the paracetamol group than placebo group
Choudhury *et al.*[20] 2011	VAS (mean) score at 1 h was 5.2±0.9 and 3.3±0.4: 2 h was 4.3±0.3 and 3.1±0.4 in fentanyl group and paracetamol group, respectively
Present study	VAS mean score at the immediate post-operative period and 1st h was 3.53±1.04 and 3.03±0.41, and 1 h was 3.9±1.21 and 3.13±0.57 in fentanyl (control) group and paracetamol group, respectively

Table 18: Requirement of rescue analgesia and opioid consumption

Author and year	Rescue analgesia observation
Salihoglu *et al.*[15] 2009	Longer time for first rescue with paracetamol
Wininger *et al.*[18] 2010	Longer median time to first rescue, less proportion of requirement of rescue analgesia in paracetamol group
Memis *et al.*[19] 2011	Significant lower postoperative opioid consumption (*P*<0.005)
Choudhury *et al.*[21] 2011	Prolonged time of first rescue analgesia in paracetamol group with mean of 76.0±24.7 (min) and 48.0±15.8 (min) in fentanyl group
Present study	Longer time for first rescue analgesia and less opioid consumption in paracetamol group with mean 5.84±4.44(h) and 1.83±1.09 (h) in fentanyl group (*P*=0.000)

Table 19: Sedation score

Author and year	Sedation score observed
Memis *et al.*[19] 2011	Less sedation in paracetamol group with significant *P*<0.05
Hong *et al.*[22] 2012	Sedation score was significantly lower in paracetamol group with *P*=0.019
Present study	Sedation score was lower in paracetamol group postoperatively with significant *P*=0.023, 0.019, and 0.003 at 1st, 6th, and 12th h, respectively

Post-operative Side Effects

There was no significant difference found in the incidence of PONV and pruritus between two groups in our study. This was in agreement with the study done by Petterson *et al*.[23] and Choudhury *et al*.[21] they found that there was no significant difference in PONV in two comparable groups.

SUMMARY

The present study entitled "A prospective randomized double-blind study comparing IV paracetamol plus fentanyl and IV fentanyl alone for post-operative analgesia during Laparoscopic cholecystectomy" was conducted in the Department of Anaesthesiology, CSI Holdsworth Memorial Hospital, Mysuru - 21 during the period of May 2012–May 2013. 60 patients, scheduled for elective laparoscopic cholecystectomy belonging to ASA Class I and II, age group 18–65 years were included in the study. Patients with known hypersensitivity to paracetamol and fentanyl, abnormal coagulation profile, hepatic or renal insufficiency, and open cholecystectomy were excluded from the study. Based on the computer-generated randomization numbers, patients were randomly divided into two groups with 30 patients in each group. Group A (paracetamol + fentanyl group): Received 100 mL of paracetamol IV (1 g) 10 min before induction. Group B (fentanyl alone group): Received 100 mL of normal saline 10 min before induction. After the preoxygenation for 3 min, patients in both the groups were induced with injection fentanyl 2 µg/kg, injection propofol 2 mg/kg, and injection rocuronium 0.6 mg/kg. Laryngoscopy and endotracheal intubation were done, and lungs were mechanically ventilated. Anesthesia was maintained with O_2 in N_2O (66%:33%), isoflurane 1%, and intermittent bolus dose of rocuronium. Fentanyl was repeated in a dose of 1 µg/kg intraoperatively if both HR and MAP increased >15–20% from baseline despite maintaining adequate depth of anaesthesia. The intraoperative hemodynamic monitoring such as SBP, DBP, MAP, and HR was done after induction of the patient in every 15 min interval, and intraoperative requirement of IV fentanyl was noted and recorded. There was better intraoperative hemodynamic stability with paracetamol group compared to fentanyl group. There was a significant reduction in pain intensity score (VAS) immediate postoperatively and at 1 h with IV paracetamol. The intraoperative and post-operative requirement of opioid was less with patients receiving IV paracetamol and IV fentanyl than the IV fentanyl alone. The sedation score was lesser with IV paracetamol as the number of doses opioid requirement was lesser compared to fentanyl group. There was no difference found in PONV, pruritus, and other opioid-related side effects such as bradycardia, hypotension, and respiratory depression in both the groups.

CONCLUSION

The use of IV paracetamol 1 g for preemptive analgesia as an adjunct to IV fentanyl in patients undergoing laparoscopic cholecystectomy had better intraoperative hemodynamic parameters, good quality post-operative analgesia, reduced consumption of fentanyl doses and lesser sedation in post-operative period. Therefore, we recommend preemptively administered IV paracetamol 1gm can be safely administered for postoperative analgesia in laparoscopic cholecystectomy.

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