

A Randomized Control Study on Effect of Pre-Emptive Paracetamol on Postoperative Analgesic Requirement in Patients undergoing Laparoscopic Cholecystectomy

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Abstract:

Background: Pre-emptive paracetamol has been shown to decrease postoperative analgesia requirement in many patient populations; however evidence supporting its role in laparoscopic cholecystectomy is lacking. Our aim was to determine the effect of Pre-emptive paracetamol on postoperative analgesia requirement in patients undergoing laparoscopic cholecystectomy.

Methods: Ninety patients belonging to American Society of Anesthesiologists physical status I or II were randomly assigned to 3 groups. Group I received 1 gram of paracetamol intravenously 30 min prior to surgery; Group II received 1 gram of paracetamol intravenously intraoperatively at time of skin closure and Group III was the control group and did not receive any paracetamol. The postoperative pain scores by VAS and analgesia requirement was compared in the 3 groups' upto 6 hours postoperatively.

Results: The postoperative pain scores remained comparable in the 3 groups for most of the duration of study. The post-operative fentanyl consumption was significantly lesser in Groups I and II as compared to group III. There was no difference in the sedation scores and in the incidence of PONV in the two groups.

Conclusion: Pre-emptive intravenous paracetamol is effective in the treatment of postoperative pain after laparoscopic cholecystectomy.

Keywords: Pain, Paracetamol.

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Introduction

The development of minimally invasive surgery has not only revolutionized techniques of surgical procedures in the recent times, but has also influenced the practice of anaesthesiology. Although laparoscopic surgery results in substantially less severe and less prolonged discomfort compared with the corresponding open procedure, postoperative pain is still considerable and needs to be treated effectively with minimal side effects, to reduce post-operative complications and hospital stay.

Pre-emptive pain control, where regional or systemic analgesics are applied before the start of the surgical procedure, thus preventing central sensitization of pain pathways, is intended to reduce analgesic requirement. [1]By taking anti-nociceptive action before the administration of

nociceptive stimulus, it has an ability to reduce the requirement the amount of analgesia needed, which was demonstrated experimentally. [2,3] However, data from several clinical studies has shown differences, and do not support this hypothesis at all times. [4] Post-operative pain can be managed by various drugs such as opioids, non-steroidal anti-inflammatory drugs (NSAID's), paracetamol, local anaesthetics, ketamine and adjuvants; which have also been used as pre-emptive analgesics in recent times.

The intravenous preparation of paracetamol has a good safety profile and is used to provide effective analgesia for acute post-operative pain. The pre-emptive use of intravenous paracetamol can give rise to a subsiding pain pattern and a decrease in analgesic requirement during the post-operative

period. [5]Hence, we attempted to evaluate the effect of pre-emptive intravenous paracetamol on post-operative analgesic requirement in patients undergoing laparoscopic cholecystectomy under general anaesthesia with placebo controlled trial.

Materials and Methods

The present study was a prospective randomized controlled study conducted in the Department of Anaesthesiology, Darbhanga Medical College and Hospital, Laheriasarai, Bihar during the period of April 2023 to December 2023.

After obtaining informed consent, 90 ASA I and II adult patients aged 18-60 years undergoing laparoscopic cholecystectomy under general anaesthesia with duration of less than or equal to ninety minutes were included in the study.

The exclusion criteria included ASA grade III or above, patient refusal, history of allergic reactions to study drug, chronic alcoholism, obesity, pregnancy, gastro oesophageal reflux disease, patients having neurological or bleeding disorder or history of usage of paracetamol, opioids, or non-steroidal anti-inflammatory drugs 48 hours before surgery.

All patients after the pre-anaesthetic check-up were pre medicated with tablet alprazolam 0.25 mg and tablet ranitidine 150 mg the night before the surgery. Tablet ranitidine 150 mg was given on the morning of the surgery with a sip of water. After recording baseline parameters, an IV line was secured and ringer lactate infusion was started.

Visual analogue scale (VAS) for pain was explained to all the patients during the pre-anaesthesia check-up.

Patients were randomly allocated into three groups via computer generated randomization namely:

1. Group I (n=30, pre-emptive group): Received IV paracetamol 1 g (100 ml) 30 min prior to induction, and 100 ml of IV normal saline prior to skin closure.
2. Group II (n=30, intra-operative group): Received 100 ml IV normal saline 30 min before induction, and IV paracetamol 1 g (100 ml) prior to skin closure.
3. Group III (n=30, control group): Receiving 100 ml IV normal saline 30 min before induction, and prior to skin closure.

Anaesthesia was induced with propofol 2 mg/kg IV, fentanyl 2 µg/kg IV, and vecuronium 0.1 mg/kg IV. Anaesthesia was maintained by isoflurane in 40/60 oxygen/nitrous oxide ratio with top up doses of vecuronium as required. All the patients were monitored for heart-rate (HR), non-invasive blood pressure (NIBP), pulse oxygen saturation (SpO₂) and end tidal carbon dioxide (ETCO₂) throughout the procedure. Patients were extubated after reversal with glycopyrrolate (0.01 mg/kg) and neostigmine (0.05 mg/kg) and thorough suctioning.

In the post anaesthesia care unit, postoperative pain score was measured by using VAS of 0-10 (0 indicated no pain and 10 indicated worst imaginable pain).

Postoperative pain was observed postoperatively at 15 minutes, 30 minutes, one hour, two hours and six hours after shifting the patient to the post-anaesthesia care unit.

Injection fentanyl 1 µg/kg IV was used as rescue analgesic, if the VAS >3.

The pain score assessment was done by a trained nursing professional who was blinded to the study drugs administered.

A sample size of 30 patients by group was calculated to detect a significant difference of 20% or more in opioid consumption with a power of 80% and a significance level of 5%. The quantitative variables were expressed as mean±SD and compared using ANOVA and unpaired t-test. The qualitative variables were expressed as frequencies/percentages and analysed using Chi-square test. SPSS version 23.0 was used for statistical analysis. A p value of less than or equal to 0.05 was considered as statistically significant.

Results

A total of 95 patients were assessed for eligibility to participate into the study. 4 patients were excluded due to history of liver disease while 1 patient refused to participate in the study and was excluded.

There were no differences between the three groups at baseline in terms of age, sex, weight, ASA physical status score or duration of surgery. (Table 1)

Table 1: Variables of study subjects

Variables	Group I	Group II	Group III	p-value
Age (Mean S Din years)	45.07±11.10	43.83±12.39	43.27±9.58	0.814
Weight (Mean S Din kgs)	62.8±6.27	60.27±6.14	60.57±6.43	0.238
Gender (M/F)	10/20	12/18	7/23	0.38
ASA I/II	20/10	17/13	17/13	0.659
Duration of surgery (Mean±SD in min.)	70.40±9.00	72.07±7.44	71.07±7.08	0.713

In Group I vs II, mean VAS scores were significantly higher in group II (2.90 ± 0.92) at two hours as compared to Group I (2.50 ± 0.51). At 15 min, 30 min, one, and six hours, mean pain scores of group I and II were comparable and statistically not significant ($p > 0.05$). In Group I vs III, mean pain scores were significantly higher in Group III (3.97 ± 1.47 and 2.90 ± 0.80) at 15 min and two hours as compared to Group I (3.03 ± 0.76 and 2.50 ± 0.51).

At 30 min, one, and six hours, mean pain scores of group I and III were comparable and statistically not significant. In Group II vs III, mean VAS scores were significantly higher than in Group III (3.97 ± 1.47) at 15 min as compared to Group II (2.87 ± 1.11).

At 30 min, one, two, and six hours, mean pain scores of group II and III were comparable and statistically not significant ($p > 0.05$).

Table 2: Post-operative VAS Score in Group I, II and III

	15 min.	30 min.	1 hour	2 hours	6 hours
Group I (Mean±SD)	3.03 ± 0.76	3.17 ± 1.21	2.80 ± 0.89	2.50 ± 0.51	2.67 ± 0.92
Group II (Mean±SD)	2.87 ± 1.11	3.37 ± 1.52	2.97 ± 0.96	2.90 ± 0.92	2.77 ± 0.77
Group III (Mean±SD)	3.97 ± 1.47	3.00 ± 0.59	3.10 ± 0.88	2.90 ± 0.80	2.67 ± 0.84
Overall	<0.001	0.692	0.134	0.108	0.440
P-value	0.500 0.003 0.002	0.574 0.499 0.223	0.489 0.195 0.579	0.042 0.025 1.000	0.651 1.000 0.634

Overall, post-operative fentanyl consumption was 24.87 ± 34.32 mcg in Group I, 43.87 ± 32.17 µg in Group II, and 60.67 ± 44.98 µg in Group III. The requirement of fentanyl as a rescue analgesic in group III was significantly more than group I, and requirement in group II significantly more than in group I ($p < 0.05$). In Group II vs III, fentanyl consumption was found to be more in Group III as

compared to Group II but this difference failed to reach statistical significance with P value > 0.05 .

There was no difference in the length of stay in PACU, incidence of PONV and in the incidence of sedation.

The sedation scores were similar in both the groups. No postoperative complications were reported from any of the groups.

Table 3: Fentanyl consumption(mcg) in Group I, II and III

	Upto 1 hour	1 to 2 hours	2 to 6 hours	Total
Group I (Mean±SD)	14.20 ± 26.37	4.30 ± 16.41	6.37 ± 19.55	24.87 ± 34.32
Group II (Mean±SD)	26.03 ± 30.56	16.17 ± 27.41	3.33 ± 12.69	43.87 ± 32.17
Group III (Mean±SD)	38.40 ± 30.17	15.93 ± 27.04	6.33 ± 19.50	60.67 ± 44.98
Overall	<0.001	0.032	0.887	0.001
P-value	0.114 0.002 0.120	0.046 0.049 0.974	0.479 0.995 0.483	0.031 0.001 0.102

Discussion

Adequate management of post-operative pain is one of the most important challenges, which not only provides comfort for the patient, but facilitates early mobilization and decreases length of hospital stay. The pain experienced after laparoscopic surgeries is a conglomerate of three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (referred to visceral pain). Besides, showing individual variation in intensity and duration, the pain is often unpredictable. [6] There have been many recent studies exploring various modalities for control of pain after laparoscopic cholecystectomies. [7-9]

Pre-emptive analgesia has been defined as treatment that: (1) starts before surgery (2) prevents the establishment of central sensitization caused by incisional injury (covers only the period of

surgery) and (3) prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period). The aim of pre-emptive analgesia, which has been investigated in recent years, is to provide analgesia prior to a painful stimulus to prevent central sensitization and, consequently, to decrease the need for postoperative analgesia. Pre-emptive analgesia has been proven to reduce postoperative analgesia requirements. [10]

In the present study, we used 1g IV paracetamol, as a pre-emptive analgesic in laparoscopic surgeries and assessed its effects on post-operative pain scores, and requirement of fentanyl in the post-operative period. We found that there was a significant reduction in pain scores when 1 gm iv Paracetamol was administered pre-emptively 30 min before the beginning of surgery than when 1

gm iv Paracetamol was administered intraoperatively before skin closure.

In 2011, Choudhuri et al. conducted a randomized clinical trial on 80 patients who were candidates for laparoscopic cystectomy. [6] They assessed the analgesic effect of acetaminophen compared to placebo and showed that the mean score of pain relief based on VAS was lower in the acetaminophen group than in the placebo group.

In addition, they reported that the total amount of opioid (fentanyl) taken in the intervention group was less than the control group (50 mg vs. 150 mg respectively). Similar studies, which were conducted by Cakan et al. in 2008 and Salihoglu et al. in 2009, assessed the analgesic effect of acetaminophen on pain after cholecystectomy and showed similar results. [11,12]

In 2011, Tzortzopoulou et al performed a systematic review, including 36 trials involving 3896 patients and assessed the postoperative analgesic effect of acetaminophen compared to placebo in children and adults.

They reported a 50% pain relief in the acetaminophen group compared to 16% in the placebo group. Furthermore, the total amount of opioid taken within the first four hours after surgery in the intervention group was 30% less than in the control group.[13]

These results indicate that sufficient analgesic effectiveness was ensured in the postoperative period in Group I. Additionally, the low values of pain scores in group I may be explained by a decrease in excitability in the central nervous system through blockade of nociceptive stimuli before damaging tissue architecture. We believe that since the preemptively delivered paracetamol prevents central sensitization, its analgesic effect continues longer than its effect period.

We recommend the use of intravenous paracetamol as a pre-emptive analgesic in patients undergoing laparoscopic cholecystectomy with the following advantages: Paracetamol is an effective non-narcotic based analgesic which is easily available, with an effective dose of 15mg/kg.

1. Intravenous route is preferable as compared to intramuscular and oral route in patients
2. Undergoing surgery, due to increased bioavailability.
3. Decreased post-operative opioid consumption.
4. Decreased post-operative discomfort and hospital stay.
5. Economically beneficial.

Our study had a few limitations, namely we had given a single dose of 1g of IV paracetamol instead of TID or QID dosing for all patients. Our study enrolled patients in the age group of 18-60 years,

thus, the results of our study can't be generalised to paediatric and geriatric age group. Also our study enrolled patients with a weight in the range of 50-70 kilograms who were all given 1g of IV paracetamol, with an effective dose of 15-20 mg/kg. Thus, the results of our study can't be generalised for patients in the extreme weight range since a single bolus dose of 1g of paracetamol might cause under-dosing (weight > 70 kgs) or over-dosing (weight < 50 kgs).

Conclusion

To conclude, pre-emptive administration of 1g of IV paracetamol in patients undergoing laparoscopic cholecystectomy provided good quality analgesia with decreased pain scores during the postoperative period, increased patient satisfaction and decreased post-operative.

Fentanyl consumption. Hence, 1g of IV paracetamol can be safely administered preemptively. For post-operative analgesia for laparoscopic cholecystectomy.

References

1. Grape S, Tramèr MR. Do we need preemptive analgesia for the treatment of postoperative pain? *Best Pract Res Clin Anaesthesiol.* 2007;21(1):51–63.
2. Ng QX, Loke W, Yeo WS, Chng KYY, Tan C. A Meta-Analysis of the Utility of Preoperative Intravenous Paracetamol for Post-Caesarean Analgesia. *Med.* 2019;55(8):424.
3. Long JB, Bevil K, Giles DL. Preemptive Analgesia in Minimally Invasive Gynecologic Surgery. *J Minim Invasive Gynecol.* 2019;26(2):198–218.
4. Kayhan Z. Postoperative pain and control. *Klinik Anestezi.* Klinik Anestezi: Logos Publishing; 2005.
5. Bonica JJ, Loeser JD. History of pain concepts and therapies. In: *Bonica's Management of Pain.* Philadelphia: Lippincott Williams & Wilkins; 2001; 3–16.
6. Choudhuri AH, Uppal R. A comparison between intravenous paracetamol plus fentanyl and intravenous fentanyl alone for postoperative analgesia during laparoscopic cholecystectomy. *Anesth Essays Res.* 2011;5(2):196–200.
7. Shrestha A, Kumari A, Acharya B, Ghimire B. Post-operative analgesic effect of intraperitoneal ropivacaine with or without tramadol in laparoscopic cholecystectomy. *Indian J Anaesth.* 2020;64(1):43–8.
8. Samantaray A, Putta PG, Pasupuleti H, Natham H, Rao MH. A comparative evaluation of pre-emptive versus post-surgery intraperitoneal local anaesthetic instillation for postoperative pain relief after laparoscopic cholecystectomy: A prospective, randomised, double blind

- and placebo-controlled study. *Indian J Anaesth.* 2019;63(3):205–11.
9. Jain S, Nazir N, Singh S, Sharma S. A prospective randomised controlled study for evaluation of high-volume low concentration intraperitoneal bupivacaine for post-laparoscopic cholecystectomy analgesia. *Indian J Anaesth.* 2018;62(2):109–14.
 10. Kuberan A, Makkar JK, Jain K, Balasubramanian M, Bhatia N, Singh PM. Pre-emptive multimodal analgesic regimen reduces postoperative epidural demand boluses in traumatic shaft of femur fracture - A randomised controlled trial. *Indian J Anaesth.* 2019; 63(11): 895–9.
 11. Cakan T, Inan N, Culhaoglu S, Bakkal K, Ba,şar H. Intravenous Paracetamol Improves the Quality of Postoperative Analgesia but Does not Decrease Narcotic Requirements. *J Neurosurg Anesthesiol.* 2008;20(3):169–73.
 12. Salihoglu Z, Yildirim M, Demiroglu S, Kaya G, Karatas A, Ertem M, et al. Evaluation of Intravenous Paracetamol Administration on Postoperative Pain and Recovery Characteristics in Patients Undergoing Laparoscopic Cholecystectomy. *Surg Laparosc Endosc Percutaneous Tecc.* 2009;19(4):321–3.
 13. Tzortzopoulou A, Mcnicol ED, Cepeda MS. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. *Cochrane Database Syst Rev.* 2011; (10): CD007126.