Original Article

Preemptive oral paracetamol in laparoscopic cholecystectomy surgery-a comparative study

Nepal Chandra Saha[1*], Mehedi Masud[2], Mohammad Sofiuddin[3], Mushfiqur Rahman[4], Dilip Kumar Bhowmick[5], Md. Shafiqul Islam[5], Prof AKM Akhtaruzzaman[6]

[1]Department of cardiac Anaesthesia, IbnSina Specialized Hospital,Cardiac Unit [3]OSD DG Health [4]Department of Anaesthesiology, Ibrahim Medical College and BIRDEM, [2,5] ,[6]Department of Anaesthesia Analgesia and Intensive Care Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka

***Corresponding Author:** E-mail: dr_nepalsaha21@yahoo.com

Abstract

Background *Laparoscopic cholecystectomy causes a considerable pain in the post operative period. Preemptive use of oral paracetamol decreases the intensity of pain and subsequently reduces the dose of opioid as well as nausea and vomiting.*

Objective *The study was designed to observe the effect of preemptive oral paracetamol reduces the dose of postoperative opioid and nausea and vomiting.*

Methods *Fifty patients of ASA physical status I and II, age range 16-50 years and BMI 18.5-24.9 were randomly selected by cards sampling method. They were equally divided into two groups of 25 patients in each group.* ***Group I*** *received vitamin,* ***Group-II*** *received 1 g oral paracetamol 60 min before surgery. In the recovery room dose of opioid was measured in 1, 6, 12, 24 hours and frequency of nausea, vomiting were assessed.*

Results *The total amount of pethidine needed significantly lower in the case group than that in the control group (p = 0.012). The pain scores were comparatively low in case group than that in the control group from beginning to endpoint of evaluation following operation (p = 0.027). The complaint of nausea at 6 and 12 hours was much less in the case group than that in the control group. Majority (80%) of patients in control group demanded analgesic (pethidine) 10 minutes earlier after operation as opposed to only 8% of the control group (p = 0.014).*

Conclusion *Preemptive paracetamol reduces the intensity of postoperative pain and requirements of pethidine to a large extent with no significant side effects.*

Key words *preemptive, paracetamol, laparoscopic cholecystectomy*

(JBSA 2013; 26(1): 33-38)

Introduction

Preemptive analgesia could be defined as analgesia that prevents the development of pathological pain[1]. With this concept, referred to as preventive 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 [2,3,4].

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[5]. Postoperative pain, which is a form of acute pain caused by noxious stimulation due to injury. It is typically associated with neuro-endocrine stress response that is proportional to pain intensity[6].

It differs from other types of pain in that it is usually, but by no means always, transitory with progressive improvement over a relatively short time course. Four physiological processes are involved: transduction, transmission, modulation and perception [5].

Systemic response to different organ system includes cardiovascular, respiratory, gastrointestinal, urinary endocrine, hematological and immune system[5].

Sensory signal generated by damaged tissue during surgery can generate a prolonged state of increased excitability in CNS. This has encouraged testing whether pre-operative regional, local anaesthetic or pre-medication can preempt postoperative pain by preventing the establishment central or peripheral sensitization.

The importance of peripheral and central modulation in nociception has forced the concept of 'pre-emptive analgesia' in patient undergoing surgery. This type of management pharmacologically induces an effective analgesic state prior to surgical trauma. Preemptive analgesia can effectively attenuate peripheral and central sensitization to pain[3].

In recent editorial, Armitage encouraged the anaesthesiologist to make changes in thought and terminology so that pain management is pre-emptive rather than retrospective. He suggested abolishing the use of the term pain relief in the context of postoperative analgesia and recommends that analgesic techniques should targeted at prevention of pain rather than relief of pain[7].

For the treatment of postoperative pain in the conventional of prescribing intermittent doses of analgesic in response to patient's demand is often ineffective[8]. Breakthrough pain is accepted as normal by many patient, doctors and nurses after surgical procedure[9]. The delivery of opioid nalgesic can be improved using patient control analgesia (PCA)[10].

Preemptive analgesia can be directed at central neurons by using NSAIDs, paracetamol, ketamine, local anaesthetics and opioids either alone or in combination[11].

Although laparoscopic cholecystectomy is less invasive procedure than classical open surgical approach, many laparoscopic patients suffer considerable postoperative pain[12]. One of the main causes of the pain after laparoscopic cholecystectomy is the peritoneal and visceral irritation caused by the pneumoperitonium[13]. Opioid commonly used in post operative has considerable side effect like nausea and vomiting.

Preemptive analgesia with oral Paracetamol reduces the opioid requirement, thus reducing the nausea and vomiting. Paracetamol inhibits also release of prostaglandin in the spinal cord has effect on serotonin mechanism for spinal pain inhibition. It also reduces nitric oxide production in CNS [14]

Methods

After obtaining written informed consent, fifty patients aged between 16-50 years with ASA physical status I & II scheduled for elective laparoscopic cholecystectomy under general anaesthesia were recruited in a double blind, placebo-controlled study. The protocol was approved by the ethical committee of Bangabandhu Seikh Mujib Medical University. The patients with history of hypertension, diabetes, neurological, renal impairment and chronic obstructive airway disease were excluded. The patients were oriented about the Visual Analogue Scale (VAS). The patients were randomly divided into 2 equal groups by cards sampling. In Group-I received one tab of vit-B complex and Group-II received oral paracetamol 1 gm 60 min before surgery. The colour of the paracetamol and vit-B complex were white and yellowish respectively. These drugs were taken orally with half a cup of water one hour before operation. On arrival of the patients in the operation theatre intravenous line was inserted. Before intravenous Induction by thiopental 3-5/mg/kg body weight all patients were pre-oxygenated with 100% oxygen for 2 minutes after receiving a pre-induction dose of fentanyl 1µg/kg body weight. Endotracheal intubation was facilitated by succinylcholine 1.5mg/kg body weight, Vecuronium 0.1 mg/kg body weight was given for muscle relaxation and anaesthesia was maintained with a combination of oxygen 33%, N_2O 66% and halothane 0.5-1%. Ventilation was controlled to maintain $ETCO_2$ between 35 to 40 mmHg. Intra-operative proper hydration was maintained with normal saline or Hartman's solution. Tracheal extubation was performed after reversal of neuromuscular blocking agent by neostigmine 0.04-0.05 mg/kg b.w and atropine 0.02 mg/kg b.w. After completion of operation all patients were taken to postoperative ward and nursed for 24 hours. Both groups received opioid (Pethedine) through patient control analgesia (PCA) in postoperative ward and postoperative pain assessed by means of Visual Analogue scale (VAS). Total opioid dose measured in both groups and Post operative complications like nausea and vomiting were recorded at 1, 6, 12, and 24 hours.

Data was collected in a prescribed form and analyzed by using SPSS (Statistical Package for Social Sciences). The test statistics used to analyze the data were Student's t-Test, Fisher's Exact Test and repeated measure ANOVA. For all analytical tests, the level of significance was set at 0.05 and $p < 0.05$ was considered significant. The summarized data were presented in the form tables and charts.

Results

The present study intended to determine the role of pre-emptive oral paracetamol in laparoscopic cholecystectomy surgery provisionally included 60 subjects. Of them 10 patients withdrew themselves from the study leaving 50 patients to complete the study. Out of 50 patients, 25 treated by oral paracetamol 1 gm 60 min before surgery considered as case and another 25 treated by one tablet of Vit-B complex considered as control. All the clinical variables were followed up at 1, 6, 12 and 24 hours of intervals following intervention. The findings of the study derived from data analysis are presented below:

Age of the patients

Table I *Comparison of age between two groups*

Age (years)	Group		p-value
	Control (n = 25)	Case (n = 25)	
<35	3(12.0)	8(32.0)	
35 – 40	14(56.0)	11(44.0)	
>40	8(32.0)	6(24.0)	
Mean ± SD	39.3 ± 4.3	37.4 ± 4.4	0.133

#Student's t Test was employed to analyse the data and the data presented as **Mean ± SD.**

Gender distribution of the patients:

Figure 1 shows that the female to male ratio was roughly 2:1.

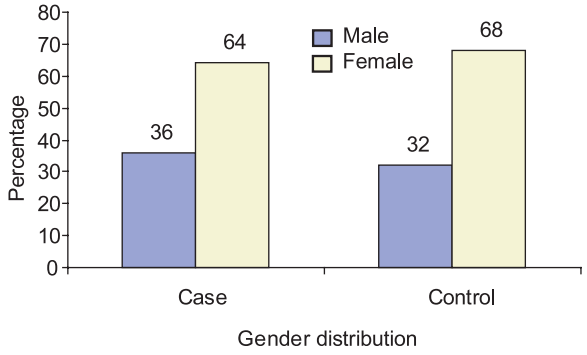

Fig 1 *Comparison of gender between groups*

Body Mass Index (BMI):

Table II *Comparison of BMI between two groups*

BMI (kg/m^2)	Group		p-value
	Control (n = 25)	Case (n = 25)	
Normal weight	(18.5-24.9)	24(96.0)	22(88.0)
Over weight (≥25)	1(4.0)	3(12.0)	
Mean ± SD	23.7 ± 0.8	23.8 ± 1.4	0.908

Figure in the parenthesis denoted corresponding percentage.

#Student's t Test was employed to analyse the data.

Duration of operation

Table III *Comparison of duration of operation between groups*

Operation time (min)	Group		p-value
	Control (n = 25)	Case (n = 25)	
≤60	15(60.0)	17(68)	
>60	10(40.0)	5(32.0)	
Mean ± SD	61.7 ± 8.8	56.5 ± 9.4	0.066

Figure in the parenthesis denoted corresponding percentage.

#Student's t Test was employed to analyse the data.

Pain score:

Table IV *Comparison of pain score between groups*

Pain score	Group		p-value
	Control (n = 25)	Case (n = 25)	
Pain score at 1 hr	4.7 ± 0.3	4.4 ± 0.3	
Pain score at 6 hrs	2.9 ± 0.2	2.7 ± 0.3	0.027
Pain score at 12 hrs	1.8 ± 0.2	1.7 ± 0.2	
Pain score at 24 hrs	1.1 ± 0.2	1.0 ± 0.1	

 # Repetitive Measure ANOVA was used to analyse the data and presented as mean ± SD.

The pain scores were comparatively low in case group than that in the control group from beginning to endpoint of evaluation following operation ($p = 0.027$).

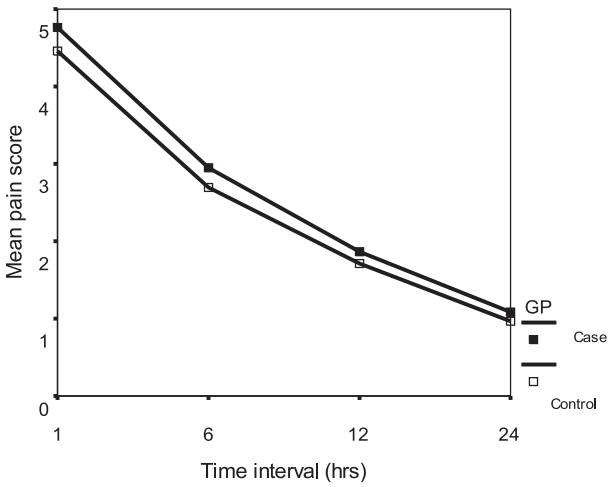

Fig 2 *Pain score at different time interval between groups where*

Amount of pethedine required:

Table V *Comparison of amount of pethedine required between groups*

Required pethedine (mg)	Group		p-value
	Control (n = 25)	Case (n = 25)	
Different time interval (hrs)*			
At 1 hr	36.6 ± 5.0	34.8 ± 5.4	
At 6 hrs	92.1 ± 8.5	77.3 ± 10.7	< 0.001
At 12 hrs	28.1 ± 4.7	29.4 ± 5.4	
Total amount needed#	139.6 ± 9.5	126.8 ± 14.4	0.012

*Repetitive Measure ANOVA was used to analyse the data and presented as mean ± SD.

Data were analysed using Student's t-Test and presented as mean ± SD.

First analgesic demand:

Table VI *Comparison of first analgesic demand between groups*

Duration (min)	Group		p-value
	Control (n = 25)	Case (n = 25)	
<10	20 (80.0)	2(8.0)	
10-20	5 (20.0)	10(40.0)	<0.001
>20	00	13(52.0)	

Data were analysed using χ^2 Test;
Figures in the parenthesis denoted corresponding percentage.

Postoperative complications:

Table VII *Comparison of postoperative complications between groups*

Complications	Group		p-value
	Control (n = 25)	Case (n = 25)	
Nausea			
At 1 hr*	8(32.0)	8(32.0)	0.986
At 6 hr*	14(56.0)	9(36.0)	0.156
At 12 hr#	4(16.0)	2(8.0)	0.334
Vomiting			
At 6 hr#	1(4.0)	00	0.500
At 12 hr#	00	3(12.0)	0.117

* Data were analysed using χ^2 Test;
# Fisher's Exact Test was done to analyse the Data.

Discussion

Preemptive analgesia means that an analgesic intervention is started before the noxious stimulus arises in order to block peripheral and central nociception[3,15,16]. NSAIDs when given before tissue damage (preemptive) may play an important role in peroperative pain management by reducing the inflammatory response in the periphery and thereby decreasing sensitization of the peripheral nociceptors [3,17,18]. Many trials have been able to demonstrate preemptive effect of NSAIDs on the reduction of postoperative pain in laparoscopic cholecystectomy [19]. In our study, pain was less intense in patients who received preemptive paracetamol than those who did not receive the same throughout the whole period of observation (from 1st hour to 24th hour following operation).

In the present study the patients who received preemptive paracetamol were relatively younger than the controls (39.3 ± 4.3 and 37.4 ± 4.4 years respectively). A female preponderance was observed in both groups. Majority of the patients in either group was of normal weight for their height. The mean operation time was a bit higher in control group than that in the case group.

Of the non-opioid analgesics, acetaminophen (also known as paracetamol) is perhaps the safest and most cost-effective non-opioid analgesic when it is administered in analgesic dosages. Although both parenteral and rectal paracetamol produce analgesic effects in the postoperative period, concurrent use with a NSAID is superior to acetaminophen alone (Issioui et al. 2002; Issioui et al. 2002). [20]

The addition of paracetamol, 1 g every 4 h, to patient controlled analgesia (PCA), morphine improved the quality of pain relief and patient satisfaction after major orthopaedic procedures .[21]

In adults, acetaminophen 2 g orally was equivalent to celecoxib 200 mg but less effective than celecoxib 400 mg, rofecoxib 50 mg, or ketoprofen 150 mg in preventing pain after ambulatory surgery [20]. An IV formulation of a prodrug of acetaminophen, propacetamol, has been administered to adults as an alternative to ketorolac in the perioperative period [22]. Propacetamol reduced PCA morphine consumption by 22–46% in patients undergoing major orthopedic surgery [22] which bears consistency with findings of the present study.

Propacetamol has become a popular adjuvant to opioid analgesics for postoperative pain control in Europe; however, this drug may soon be replaced when an investigational IV formulation of acetaminophen becomes available for clinical use [24]. Rectal acetaminophen (1.3 g) has also been successfully used as an adjuvant to NSAIDs and local anesthetics as part of a multimodal fast-tracking surgery recovery protocol [25]. Given the adverse effects associated with both NSAIDs and COX-2 inhibitors in patients with preexisting cardiovascular disease, acetaminophen may assume a greater role in postoperative pain management in the future [26].

In the present study about one-third (32%) of the patients in each group experienced nausea at 1 hour after operation. However, the complaints of nausea at 6 and 12 hours of observation were much less in the preemptive paracetamol group than that in the control group. Vomiting was negligible in either group. The preemptive paracetamol did not cause irritation of stomach or induce allergic reaction. In a study by O'Hanlon in 1996 shown that half-life of NSAID is important for the preemptive effect because of shorter acting analgesics do not have a sufficiently long time of action to provide analgesia. Although etofenamate has a long half-life (8-10 hours), its preemptive effect of VAS scores and meperidine consumptions diminished late postoperative period. VAS scores at 1 and 6 hours in the etofenamate group were significantly lower, VAS scores at 12 and 24 hours were also lower but the differences between etofenamate and placebo group were not found significant.

References

1. Pjevic MK, Omercevid M, Kovacevic S & Gajic S, 'Preemptive analgesia in cholecystectomy using pethedine', *Med Pregl*,1999; 52 : 485-8
2. Wall PD, 'The prevention of postoperative pain', *Pain*, 1998; 33:289-90
3. Dahl JB & Moiniche S, 'Pre-emptive analgesia', *Br Med Bull*, 2004; 71:13-27
4. Miller DR, Acute post operative Pain, Anaesthesia (3rd edn), 1989
5. Morgan GE, Mikhall MS & Murray MJ, 'Clinical anaesthesiology', Lange Medical Books/McGraw-Hill, 2006; 361
6. Cousins MJ, 'Acute pain and injury response; immediate and prolonged effects', *Regional Anaesthesia*, 1989; 14:126-8
7. Armitage EN , 'Postoperative pain-prevention or relief',*Br. J Anaesth*,1989; 63:136-7
8. Kuhn A, Cooke K & Collins M, 'Perception of pain relief after surgery', *Br. Med. J*., 1990; 300:1687-90
9. Lavies N, Hart L, Rouseefell B & Rocimann W , 'Identification of patient medical and nursing stuff attitudes to post operative opiod analgesia: stage 1 of a longitudinal study of postoperative pain', *Pain*, vol.18,pp.313-9
10. Justin- DM & Richandron PH, 'Clinical management of acute pain', *Br. Med. Bull*, 1991;47: no.3,561-83
11. Cliffod JW & Mun SC, 'Preemptive analgesia – Trainingh postoperative pain by preventing the establishment of central sensitization', *Anaesthesia Analgesia*, 1993; 21:no.4, 362-79
12. Cliffod JW & Mun SC, 'Preemptive analgesia-Treating postoperative pain by preventing the establishment of central sensitization', *Anaesthesia Analgesia*,1999; 13: 445-8
13. Pasqualucci A, de Angelis V & Contardo R , 'Preemptive analgesia: intraperitonial local anaesthetic in laparoscopic cholecystectomy. A randomized double blind, placebo controlled study', *Anaesthesiology,* 1996; 85:11-20
14. Charles BB. Paediatric Analgesic Pharmacology in pain 2002-updated review; Refresher course syllabus, edited by Maria, 339

15. Grape S & Tramer MR, 'Do we need preemptive analgesiafor the treatment of postoperative pain', *Best Pract Res Clin Anaesthesiol*, 2007; 21:51-63

16. Moiniche S, Kehlet H & Dahl JB , 'A Qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief', *Anesthesiology*, 2002; 96:725-41

17. Gottschalk A & Smith DS 2, 'New concepts in acute pain therapy: preemptive analgesia', *Am Fam Physician*, 2001; 63:1979-84

18. Woolf CJ & Chong MS , 'Preemptive analgesia— treating postoperative pain by preventing the establishment of central sensitization', *Anesth Analg*.,1993; 77:362–79

19. Kehlet H, Gray AW & Bonnet F , 'A procedure-specific systematic review and consensus recommendations for postoperative analgesia following laparoscopic cholecystectomy', *Surg Endosc*, 2005;19:1396-415

20. Issioui T, Klein KW & White PF, 'Cost-efficacy of rofecoxib versus acetaminophen for preventing pain after ambulatory surgery', *Anesthesiology*, 2002; 97: 931–7

21. Schug SA, Sidebotham DA & McGuinnety M , 'Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain', *Anesth Analg*, 1998; 87:368 –72

22. Varrassi G, Marinangeli F & Agro F , 'A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery', *Anesth Analg*,1999; .88:611–16

23. Recart A, Issioui T & White PF, 'The efficacy of celecoxib premedication on postoperative pain and recovery times after ambulatory surgery: a dose-ranging study', *Anesth Analg*, 2003; 96:1631–5

24. Moller PL, Juhl GI & Payen-Champenois C, 'Ready-to-use IV paracetamol: comparable analgesic efficacy, but better local safety than its prodrug, propacetamol for postoperative pain after third molar surgery', *Anesth Analg*,2005; 101: 90–6

25. Coloma M, Chiu JW, White PF & Armbruster SC, 'The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery', *Anesth Analg*,2001; 92: 352–7

26. Hillis WS, 'Areas of emerging interest in analgesia: cardiovascular complications', *Am J Ther*, 2002; 9:259–69