Original article:

Preoperative Intravenous Paracetamol Reduces Postoperative Opioid Consumption in Laparoscopic CholecystectomyPatients - An Experience of A Tertiary Specialized Hospital in Bangladesh

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Abstract:

Background: Afferent blockade of nociceptive (pain) impulses by paracetamol can bein effect throughout intraoperative and postoperative period. ***Objective:*** To see the effect of preoperative intravenous paracetamol administration in laparoscopic cholecystectomy patients. ***Methods:*** This single blind, randomized, prospective, case-control studywas conducted in Department of Anesthesiology, Square Hospitals, Dhaka, Bangladesh, between July and December of 2014. A total of 60 adult patients scheduled for laparoscopic cholecystectomy under general anesthesiawere enrolled in this study. Patients were randomly allocated equally into two groups – A (cases) and B (controls), through a computerized random table, with 30 patients in each group. Patients of group A (cases) received intravenous paracetamol 10mg/kg (in 100ml of normal saline) 10 minutes before skin incision, while group B (controls) received only 100 ml of normal saline 10 minutes before skin incision. Postoperative pain score, duration of demand of first analgesic after operation and amount of opioid requirement were noted down. ***Results:*** The mean age of group A was 39.3±4.3 years and in group B 37.4±4.4 years (P>0.05).The mean pain score after 1 hour of operation was 4.4±0.3 in group A and 4.7±0.3 in group B, which reduced to 2.7±0.3 and 2.9±0.2 after 6 hours, then 1.7±0.2 and 1.8±0.2 after 12 hours and 1.0±0.1 and 1.1±0.2 after 24 hours respectively (P<0.05). Early demand of postoperative analgesic within 10 minutes was observed much less in the group A, compared to group B (P<0.001). The mean amount of pethidine required at 1st hour was 34.8±5.4 mg and 36.6±5.0 mg in group A and group B respectively, which increased up to 77.3±10.7 mg and 92.1±8.5 mg respectively at 6th hour. However, the amount steeply decreased at 12th hour to 29.4±5.4 mg and 28.1±4.7 mg respectively (P<0.001). The total amount of pethidine needed was significantly lower in the group A than that of group B (126.8±14.4 vs. 139.6±9.5 mg; P<0.05). ***Conclusion:*** Preoperative load of intravenous paracetamol increases the duration of further analgesic requirement as well as reduces postoperative opioid consumption in laparoscopic cholecystectomy patients.

Keywords: Intravenous paracetamol, opioid consumption, pain score, laparoscopic cholecystectomy.

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Introduction:

Preoperative analgesia by administering intravenous paracetamol (acetaminophen) is a method of analgesia that starts before the noxious stimulus comes into action, blocking peripheral and central nociception[1]. It is assumed that this afferent blockade of nociceptive (pain) impulses can be in effect throughout intra-operative and post-operative periods[1,2].Any antinociceptive treatment inducing before surgery to prevent establishment of altered central afferent input from injuries and pain sensation by timing the analgesic's peak pharmacodynamic effect with anticipated onset of pain or peak pain response, is termed as 'preemptive analgesia'[2,3]. Paracetamol when given before tissue damage (pre-emptive) may play an important role in preoperative pain management by reduction of the inflammation

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mechanism and decreasing sensitization of peripheral nocicptors[2]. Paracetamol is more safein comparison to risks related to opioid and can act on both central and peripheral pain pathways byinhibiting N-methyl-D-Aspartate receptors and blocking the cyclooxygenase 2 (COX2) pathway of inflammation[4,5]. Paracetamol is known for itscapacity of 'preemptiveanalgesia' in different operative procedures, such as laparoscopic cholecystectomy[6-8], total abdominal hysterectomy[9,10], orthopaedic surgery[11,12]. All those studies were done in the western countries. However, no such reports are available in our country to date. Given the circumstances, the present study was designed with the aim tosee the 'preemptive effect' of preoperative intravenous paracetamol administration in laparoscopic cholecystectomy patients in terms of how much it increases the duration of further analgesic requirement as well as reduces postoperative opioid consumption.As proper pain management, particularly postoperative pain management, is a major concern for the clinicians, the findings of the present study are expected to enrich our information pool in pain medicineas well asfacilitate to planpostoperative pain management more efficiently and cost effectively.

Methods:

A single blind, randomized, prospective, case-control studywas conducted in Department of Anesthesiology of Square Hospitals, Dhaka, Bangladesh, one of the largest tertiary specialized hospitals in the country, between July and December of 2014. All the patients enrolled for laparoscopic cholecystectomy surgery in Department of Surgery of the same hospital during the study period. However, we adopted the convenient sampling technique. The patients were selected after fulfilling the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Adult surgical patients for laparoscopic cholecystectomy who are mentally sound and able to understand the procedure; and
2. Fulfilled ASA Physical Status Classification I or II (according to Sweitzer)[13].

Exclusion criteria:

1. Unable to understand the procedure or declined consent;
2. Known allergy to paracetamol (acetaminophen);
3. History of usage of paracetamol, opioids, or any other NSAIDs for a long time (≥3 months);
4. Uncontrolled hypertension or diabetes mellitus, severe renal or hepatic impairment or chronic obstructive airway disease.

Then a total of 60 adult patients were randomly enrolled in this study. Primary data collection was done after taking written informed consent from each patient who fulfilled the criteria. Demographic profile, pulse, blood pressure, body weight, height, waist circumference – all were recorded. Patients were randomly allocated equally into two groups – A (cases) and B (controls), through a computerized random table, with 30 patients in each group. Pre-anaesthetic check-up was done on the day before surgery. Each patient was kept fasting for at least 6-8 hours pre-operatively. Each patient was administered with Ringer's lactate solution 30 minutes before the induction of anesthesia, and the infusion was maintained at 8-10ml/kg/hour throughout the operative procedure. After standard monitorization, baseline heart rate (HR), non-invasive blood pressure (BP), oxygen saturation (SpO_2), and respiratory rate (RR) values were recorded. General anesthesia was intravenously induced with 5mg/kg thiopental and 1μg/kg fentanyl, and the trachea was intubated with an endotracheal tube under muscle relaxant (0.5 mg/kg atracurium). Anesthesia was maintained with isoflurane (1.5%) in 50% nitrous oxide with oxygen. Patients of group A (cases) received intravenous paracetamol 10mg/kg(100ml) 10 minutes before skin incision, while group B (controls) received only 100 ml of normal saline 10 minutes before skin incision. Each patient was sent to postoperative ward and observed for 24 hours. Both groups received opioid through patient-controlled analgesia (PCA)[14] in postoperative ward and postoperative pain was assessed using Visual Analogue Scale (VAS)[15]. Total opioid dose measured in the both groups. Intensity of pain (VAS –painscore), duration between operation and first analgesic demand after operation and opioid requirement to manage postoperative pain – all were noted down in the data collection sheet.

The results were presented in tables. Quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency and percentage. Statistical analyses were performed using SPSS (Statistical Packages

for Social Sciences) version 17.0 (SPSS Inc, Chicago, IL, USA). Association between variables were done by unpaired Student 't' test, Repetitive measure paired t-test and Chi-square ($\chi 2$) test. P value <0.05 was considered as statistically significant.

Results:

In the present study, 30 patients were enrolled in each group – group A (cases) and B (controls). The mean age of the patients of group A was somewhat higher than that of the group B (39.3±4.3 years vs. 37.4±4.4 years). However, the difference was not statistically significant (P>0.05) (Table 1). Female patients were predominant in the both group A (63.33%) and groupB (66.67%). The mean pain score at 1 hour after operation was 4.4±0.3 in group A and 4.7±0.3 in group B, which reduced to 2.7±0.3 and 2.9±0.2 after 6 hours, 1.7±0.2 and 1.8±0.2 after 12 hours and 1.0±0.1 and 1.1±0.2 after 24 hours respectively (P<0.05) (Table 2).Over half of the patients in the group A required postoperative analgesic (pethidine) at>20 minutes after operation (53.33%), while 40% required between 10-20 minutes and the rest (6.67%) within 10 minutes. In contrast, majority (80%) of patients in the group B required postoperative analgesic within 10 minutes and rest (20%) between 10-20 minutes. Early demand of postoperative analgesicwithin 10 minutes was observed much less in the groupA,in comparison togroupB, which was statistically significant (P<0.001)(Table 3). The mean amount of pethidine required at 1st hour was 34.8±5.4 mg and 36.6±5.0 mg in group A and group B respectively, which increased up to 77.3±10.7 mg and 92.1±8.5 mg respectively, after 6 hours. However, the amount steeply decreased at 12th hour to 29.4±5.4 mg and 28.1±4.7 mg respectively (P<0.001). The total amount of pethidine required was significantly lower in the group A than that of group B (126.8±14.4 vs. 139.6±9.5 mg; P<0.05) (Table 4).

Table 1. Comparison of age between two groups

Age (in years)	Group A (n=30)	Group B (n=30)	P value
<35	4 (13.33%)	10 (33.34%)	
35-40	16 (53.33%)	13 (43.33%)	
>40	10 (33.34%)	7 (23.33%)	
Mean±SD	39.3±4.3	37.4±4.4	>0.05

Student's t test was used to reach P value.

Table 2. Comparison of postoperative pain score (VAS) between two groups

Duration	Group A (n=30)	Group B (n=30)	P value
After 1hour	4.4±0.3	4.7±0.3	
After 6 hours	2.7±0.3	2.9±0.2	
After 12 hours	1.7±0.2	1.8±0.2	<0.05
After 24 hours	1.0±0.1	1.1±0.2	

Data presented as mean±SD; Repetitive measure paired t-test was used to reach P value.

Table 3. Comparison of first postoperative analgesic demand between groups

Duration (in min.)	Group A (n=30)	Group B (n=30)	P value
<10	2(6.67%)	24(80%)	<0.001
10-20	12(40%)	6(20%)	
>20	16 (53.33%)	-	

Chi-square (χ^2) test was used to reach P value.

Table 4. Comparison of postoperative pethidine requirement between groups

Duration	Group A (n=30) (in mg)	Group B (n=30) (in mg)	P value
At 1st hour	34.8±5.4	36.6±5.0	
At 6th hour	77.3±10.7	92.1±8.5	<0.001
At 12th hour	28.1±4.7	29.4±5.4	
Total	126.8±14.4	139.6±9.5	<0.05

Data presented as mean±SD; Student's t- test was used to reach P value.

Discussion:

Apart from affecting patients' well-being and satisfaction from medical care, postoperative pain results in tachycardia and hyperventilation, gradual transition towards chronic pain, subsequent disruption in wound healing and insomnia – all together worsen the operative outcomes[16]. In the present study, our data showed that the preemptive intravenous paracetamol administration reduces opioid requirements through prolongation of duration of first demand of analgesia and a tremendous reduction in post-operative pain scores in our patients. Similarly, Salihoglu et al.[6] studied on a total of 40 patients (20 in each group)

and found that verbal and visual pain scores of the paracetamol group were significantly lower than control group (P<0.05). First morphine requirement and total administered morphine dose and duration of staying in recovery room were significantly decreased in the paracetamol group (P<0.05). Arslan et al.[8] also found that time to first analgesic requirement was longer in paracetamol preemptive group, compared to placebo group (P<0.05), along with a significant reduction in total analgesic consumption and postoperative VAS pain scores (P<0.05).However,Goushehet al.[7]studied on 30 patients (15 in each group) and concluded that the pain score was lower in paracetamol preemptive group in comparison to placebo group (P=0.01), but the morphine consumption showed no significant difference between the groups (up to 6 hours postoperatively).Hence, our findings are more or less supported by Salihoglu et al.[6], Gousheh et al.[7] and Arslan et al.[8].

The results of these controlled clinical studies, as mentioned above, demonstrated that the recommended therapeutic dose of intravenous paracetamol is safe and well tolerated, with a profile that supports the high reliability similar to placebo. The reduction in total opioid consumption may result from opioid sparing effect of preemptive load of paracetamol which was observed in those studies as well as in others' studies[6-12]. Moreover, paracetamol is considered a safe drug with no or minimum gastrointestinal and central nervous system side effects like opioids and other NSAIDs[4,5,17-19].

Limitations of the study:

This was a single-center trial. The study population was selected from an urban hospital setting for a short period of time, which was confined to Dhaka city only. Hence, the results of the study may not be generalized and does not necessarily reflect the overall picture of the country. Small sample size was another limitation of the present study.

Conclusion:

Our study revealed that preoperative load of intravenous paracetamol increases the duration of further analgesic requirement as well as reduces postoperative opioid consumption in laparoscopic cholecystectomy patients. However, we recommend further multi-center trials with larger sample and high technical back up.

Conflict of interest: None to disclose.

Ethical approval issue: The study was approved by the Institutional Ethical Committee of Square Hospitals Ltd., Dhaka, Bangladesh.

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Authors' contribution: Concept and study design: SR; Data collection and compilation: SR, TH, MIKH, ARC, SMM, SMFS, SMAH; Data analysis: SR, SMFS, SMAH; Critical writing, revision and finalizing the manuscript: SR, TH, MIKH, ARC, SMM, SMFS, SMAH.

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