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Original Research Article

Comparative Evaluation of Effectiveness of Intravenous Paracetamol and Intravenous Diclofenac as Post-operative Analgesia in Laparoscopic Cholecystectomy

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ABSTRACT:

Introduction: Though the development of minimally invasive surgery has revolutionized the field of surgery, post-operative pain is still a significant issue. Unlike in the past, concerns about adverse effects have limited the role of opioids in post-operative pain management. This study aims to compare the effectiveness of intravenous paracetamol and diclofenac as post-operative analgesia in laparoscopic cholecystectomy. **Methods**: One hundred and twenty eight patients of American Society of Anesthesiologists (ASA) categories I and II included in this study were divided into two groups. Anesthesia induction and maintenance were standardized. The first group received 15mg/kg (maximum 1gm) intravenous paracetamol and the second group received 2mg/kg (maximum 75mg) intravenous diclofenac 30 minutes prior to ending of surgery. A questionnaire was responded by patients and chart was maintained by visual analogue scale. Data management and analysis were done using computer softwares MS Excel and SPSS version 20. Mann Whitney U test was used to analyze quantitative data and Chi-square test for categorical data. P value <0.05 was considered statistically significant. **Results**: Profiles of hemodynamic changes were almost similar in both groups with respect to heart rate and blood pressure. However, paracetamol infusion provided hemodynamic stability in post-operative period. We observed statistically significant differences in visual analogue scale between the two groups. Most of the patients in paracetamol group had low mean pain scores in post-operative period and provided an extended analgesia compared to diclofenac. No serious postoperative complication was observed in paracetamol group. **Conclusion**: Administration of intravenous paracetamol has better and prolonged analgesic effect with low mean pain score and less requirement for rescue analgesia compared to diclofenac.

Keywords: Diclofenac, Laparoscopic Cholecystectomy, Paracetamol, Post-operative Analgesia, Visual Analogue Scale (VAS)

INTRODUCTION:

The advent of minimally invasive surgery has revolutionized the field of surgery. Laparoscopic surgery has become popular in recent days. Patients are more motivated to undergo laparoscopic surgery because of small incision, less blood loss and decreased length of hospital stay. However, pain is still the most common complaint after surgery.

Post operative pain following surgical insult is mostly nociceptive. Inadequate pain control after surgeries is significant in terms of both physical and psychological trauma. Adequate analgesia is therefore of utmost importance for early ambulation and discharge, reduced hospital stay and cost. Post operative pain differs from patient to patient depending upon the site and nature of surgery. Individual variations in response to pain are influenced by the genetic makeup, cultural background and gender.[1] Till last decade, opioids

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were the mainstay for managing severe pain, mostly via intramuscular route. However, fluctuating plasma levels of opioids result in sedation and other adverse effects.[2] Fear of addiction and dependence result in under-treatment of pain as well. To avoid all these side effects , non-opioids like paracetamol and diclofenac are being increasingly used as alternatives.

Paracetamol and diclofenac both belong to nonsteroidal anti-inflammatory drugs (NSAIDs) group which inhibits cyclo-oxygenase enzymes thereby decreasing peripheral and central prostaglandin production. This in turn reduces inflammation and associated pain following tissue injury.[3,4,5,6] However, the question of superiority of paracetamol over diclofenac or vice-versa has been poorly resolved and needs to be further clinically tested, especially in set-ups like ours. This study was therefore conducted to compare the effectiveness of intravenous paracetamol and diclofenac as postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

METHODS:

The present study was conducted in Lumbini Medical College and Teaching Hospital (LMCTH) over a period of 12 months from 15th May, 2016 to 14th May, 2017 with prior permission from the Institutional Review Committee (IRC-LMC).

With alpha error of 0.05, power of 80%, medium effect size (0.5), and equal participants (ratio =1), minimum sample size in each group was calculated to be 64. A total of 128 patients of ASA I and II categories, aged between 20-60 years undergoing laparascopic cholecystectomy were selected. Informed consent was obtained from the participants prior to enrollment to the study. Visual analogue scale (VAS) and pain severity were explained. Patients were randomized into two groups irrespective of age and gender and randomization was done according to computer generated random number. Those with history of renal dysfunction, bleeding disorder, liver dysfunction, use of NSAIDs and opioids prior to surgery were excluded from the study.

Patients and nursing staff in ward were blinded about drugs. Following a detail pre-anaesthetic examination, preoperative investigations were sent and reports assessed. All the patients were pre-medicated with tablet lorazepam 2 mg the night before surgery. On arrival at operation theatre, an intravenous line was secured with 18 gauze cannula in dorsal aspect of either hand. Patients were connected to standard monitors. Pre-oxygenation was done for three minutes. Induction was done with injection fentanyl 1-2 mcg/kg, propofol 1.5-2.5mg/kg followed by intubation with injection vecuronium 0.1mg/kg. Maintenance of anaesthesia was done by oxygen, isoflurane and vecuronium. Patient was put on mechanical ventilation and $ETCO_2$ was maintained at 35-40 mmHg. Surgical incision time was noted as time zero and parameters as pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded at an interval of every five minutes till the end of surgery. The ECG was constantly monitored.

Two anesthesiologists were involved in the study. The drugs were labeled as A and B. The anesthesiologist who administered the drug in the intra- and post-operative period was not involved in the process of data collection. The second anesthesiologist, blinded to study drug, recorded vitals at different intervals in post operative period. Group A received injection paracetamol 15 mg/kg maximum 1 gm in 100ml infusion over 15–20 minutes 30 minutes prior to ending of the surgery as the first dose of analgesia and subsequent dose was given at eight hourly interval after the patient was shifted to ward. Group B received injection diclofenac 2 mg/kg maximum 75 mg in 100ml normal saline similarly as first dose of analgesia and subsequent dose was given at 12 hourly interval. Duration of surgery was noted.. Extubation was done after reversing effect of muscle relaxant with injection neostigmine 50 mcg/kg with glycopyrolate 20 mcg/kg. After completion of surgery patient was shifted to postoperative ward without prescribing any analgesia. In post operative period pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and respiratory rate were recorded at two hours, four hours, six hours, 12 hours and 24 hours. VAS was recorded at the same interval. The patients were asked to mark the line to indicate pain intensity in relation to 0- no pain to 10- worst pain. Mild pain was considered when VAS score was between one and three; moderate pain when VAS score was between four and six and severe pain when VAS score was seven and above. Rescue analgesic was given when VAS score was between seven to ten or on patient demand. Injection pethidine 25-100 mg intramuscularly was given as rescue analgesia. Any complication like nausea, vomiting, pruritus, sedation or others were recorded.

Statistical analysis:

The data were entered in Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS™) software version 20. Descriptive results were presented in frequencies, percentages, mean, and standard deviation (*SD*). Quantitative data were analyzed with *Mann Whitney U test* and categorical data were analyzed by *Chi square test*. *P* value less than 0.05 was considered statistically significant.

RESULTS:

During the study period, a total of 228 patients underwent laparoscopic cholecystectomy. Out of them, 128 patients were enrolled into the study. There were 11(17.2%) males and 53(82.8%) females in Group A whereas seven (10.9%) males and 57(89.1%) females in Group B (Table1). On analyzing the demographic data, we found no statistically significant variation in age, sex, ASA classification and weight between the two groups (Table1).

The mean pulse rate was lower in Group A but there was no statistically significant variation in mean pulse rate between the two groups (Fig. 1). Pulse rate was higher at two and six hours post-operative in both groups. This was possibly due to anxiety rather than pain. There was mild decrease in pulse rate in both groups afterwards.

The comparison of mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) between the two groups showed no significant variations at different time intervals except that the mean DBP at two and four hours post operative period were higher in Group B (Figures 2 and 3). The mean DBP was 71.14 ±9.31 mm Hg at two hours and 74.06±11.23 mm Hg at four hours in Group A whereas 74.52±5.96 mm Hg at two hours and 76.45±5.95 mm Hg at four hours in Group B. The difference in mean values was statistically significant (Mann Whitney U=1613.000, N=128, p=0.035 for two hours and Mann Whitney U=1602.500, N=128, p=0.032 for six hours).

The comparison of mean respiratory rate between the two groups showed higher mean respiratory rate in Group B throughout the post-operative period (Fig. 4).

In our study, the mean VAS score was lower in

Table 1. Comparison of demographic variables between the two groups.

Variables		Group A	Group B	Statistics
Sex	Male	11(17.2%)	7(10.9%)	X^2 (df=1,N=128) =1.034 , p=0.309
	Female	53 (82.8%)	57(89.1%)	
ASA	I	49 (76.6%)	56 (87.5%)	X^2 (df=1,N=128) =2.597, p=0.107
	II	15 (23.4%)	8 (12.5%)	
Mean age ± SD (years)		43.84±10.40	40.97±10.86	Mann Whitney U=1697.000, N=128, p=0.094
Mean weight ± SD (kg)		55.14±8.215	55.13±11.16	Mann Whitney U=1977.500, N=128, p=0.736

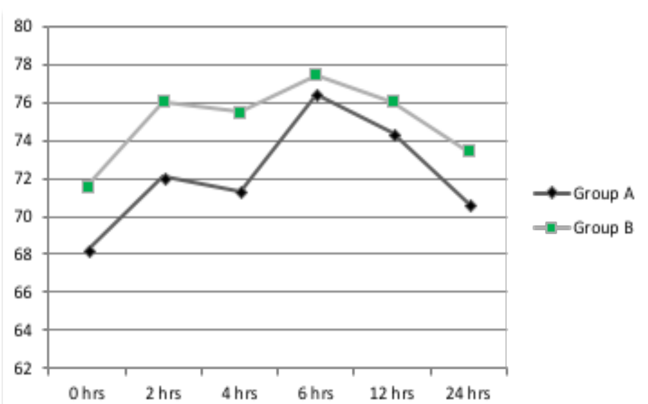

Fig 1. Comparison of mean pulse rate (min^{-1}) at different time periods.

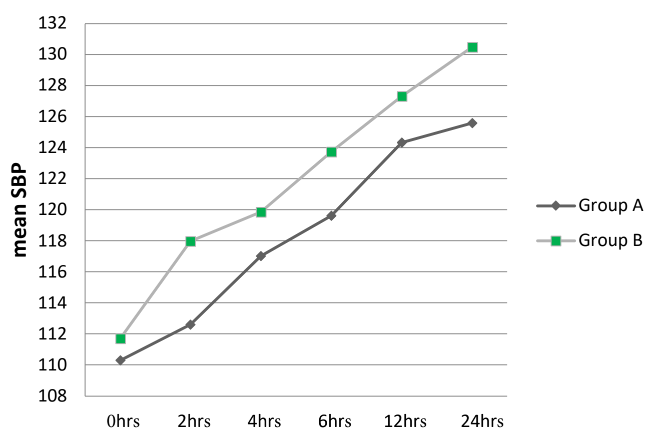

Fig 2. Comparison of mean SBP at different time periods

the paracetamol group (Group A) in comparison to the diclofenac group (Group B) at all the post-operative time periods. These differences in mean VAS scores were found to be statistically significant (Table 2).

The requirement for rescue analgesia in Group A i.e. 10 (15.6%) patients was significantly lower than in Group B i.e. 21 (32.8%) patients. This difference was found to be statistically significant (Table 3).

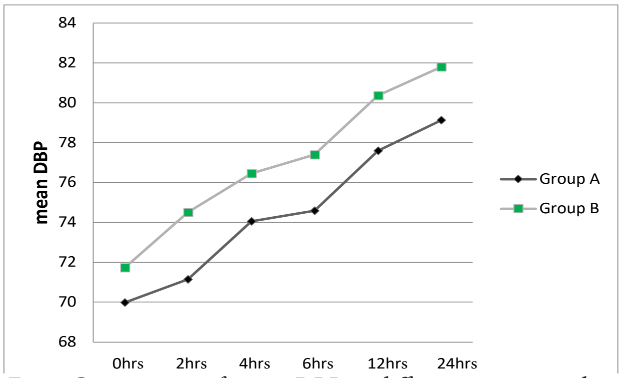

Fig 3. Comparison of mean DBP at different time periods

During the postoperative period, we observed no serious complications in either group. However, seven patients complained of post-operative nausea in Group B.

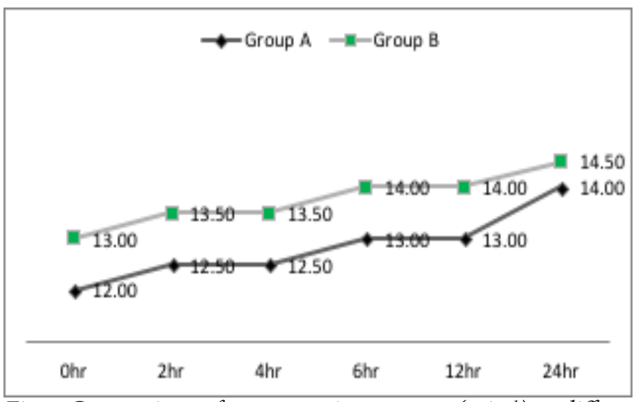

Fig 4. Comparison of mean respiratory rate (min^{-1}) at different time periods

Table 3. Requirement of rescue analgesia in two groups.

Groups	Requirement of rescue analgesia		Statistics
	Yes (%)	No (%)	
Group A	10 (15.6%)	54 (84.4%)	X^2 (df=1,N=128) = 5.151, p = 0.023
Group B	21 (32.8%)	43 (67.2%)	

DISCUSSION:

Post-operative pain is one of the primary concerns because of its close ties with clinical outcome and acute post-operative well being.[7,8] Pain is often associated with autonomic, endocrine-metabolic, physiological and behavioral response.[9] Pain after laparoscopic surgery has three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain) and shoulder pain (referred pain).[10] Despite overwhelming rationale for effective post-operative pain control, the clinical reality is unfortunately still far from satisfactory. As NSAIDs are being increasingly used to avoid the adverse effects of opioids, this study aimed to compare the effectiveness of intravenous paracetamol and diclofenac as post-operative analgesic.

In our study, 82.8% patients in Group A and 89.1.% patients in Group B were females. The higher prevalence in females correlates to the fact that gall stone diseases are more common in females.

The comparison of mean pulse rate showed no statistically significant variation between the two both groups. The increase in mean pulse rate at two and six hours post-operatively in both groups implicates

Table 2. Comparison of mean VAS scores between Group A and Group B

Time interval	Group A (Mean VAS±SD)	Group B (Mean VAS±SD)	Statistics
0 hrs	5.11±0.99	5.73±0.78	Mann Whitney U=1372.000, p<0.001
2 hrs	4.52±0.89	5.34±1.37	Mann Whitney U =1301.500, p<0.001
4 hrs	3.95±1.44	4.50±1.39	Mann Whitney U=1611.000, p=0.021
6 hrs	3.06±1.17	3.36±1.39	Mann Whitney U=1568.000, p=0.012
12 hrs	2.08±0.62	2.55±1.00	Mann Whitney U=1560.500, p=0.002
24 hrs	1.59±0.72	1.92±0.72	Mann Whitney U=1617.500, p=0.006

that the initial increase was because of anxiety. Amin et al in their comparative study observed no satisfactory variation in pulse rate in the paracetamol and diclofenac groups.[11] Similar observations were made in the study by Paul D et al. However in this study, they found low pulse rate in the patients administered with intravenous diclofenac.[12]

Our study observed statistically significant difference in DBP at two hours and six hours of post-operative period. Similar observations were shown by Paul D et al with higher DBP in diclofenac group. The predominant action of diclofenac is to inhibit the enzyme cyclo-oxygenase which mediates the conversion of arachidonic acid to prostaglandin and thromboxanes. The significant increase in DBP in diclofenac might be explained by this effect.[12]

The differences in mean respiratory rate between the two groups is clinically significant. However respiratory rate is higher in diclofenac group throughout the post-operative period which might be due to inadequate pain relief.

In our study, high VAS score was recorded in diclofenac group throughout post-operative period. The mean VAS score in paracetamol group was 3.39±0.79 whereas it was 3.95±1.11 in diclofenac group. Similar finding was reported by Paul D et al. However at four hour post-operative period, differences in VAS score was insignificant in both groups. Following that there was gradual increase in VAS score leading to more analgesic requirement after four hours.[12] In 2013, Goel et al. in their comparative study for pre-emptive analgesia with intravenous paracetamol and diclofenac in patients undergoing different surgical procedures found that the mean pain score was higher in diclofenac group for initial period followed by insignificant difference in pain score at four hours.[13] Similar finding was reported by Anka et al.[11] In our study we found that differences in 24 hours VAS score was statistically significant (*P* value 0.006) .

The mean VAS score was higher in diclofenac group throughout postoperative period requiring more rescue analgesia. In a study by Salihoglu et al, pre-emptive use of 1gm paracetamol caused similar decrease in post-operative pain score and requirement of analgesia.[14] Another study by Arici S et al. demonstrated significant lower post-operative pain score and consumption of rescue analgesia in patients who received one gram pre-emptive paracetamol compared to patients who received normal saline.[15] Khan AH et al. observed that paracetamol had significantly lowered total analgesic consumption, postoperative pain and VAS score as compared to tramadol.[16]

In our study, we observed that there were 10 (15.6%) patients who required intravenous pethidine as rescue analgesia and 54 (84.4%) patients who didn't require rescue analgesia in Group A. In Group B, 21(32.8%) patients had received rescue analgesia whereas 43 (67.2%) did not. This difference was statistically significant. Similar findings were reported by Goel et al.[13] More requirement of rescue analgesia was also observed in the study of Paul D et al.[12] Paracetamol rapidly crosses the blood-brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by the central nervous system. [17] This central effect has been regarded primarily as an indirect and reciprocal influence through cyclo-oxygenase enzyme inhibition, and probably through the serotoninergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory influence, although this effect is somewhat limited.[18]

In this study, we observed that seven patients had post-operative nausea in diclofenac group while none in the paracetamol group. A related study done by Apfel et al. concluded prophylactically administered intravenous acetaminophen reduced post-operative nausea and vomitting, mainly mediated through superior pain control.[19]

CONCLUSION:

Administration of one gram of intravenous paracetamol intra-and post-operatively conferred satisfactory analgesia with low mean pain scores and decreased post-operative rescue analgesia compared to intravenous diclofenac. No immediate side effects were observed with paracetamol. Intravenous paracetamol was thus found to be more effective than diclofenac for post-operative analgesia in laparoscopic cholecystectomy.

Conflict of interest:
None Declared.

Financial Disclosure:
No funds were available.

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