

Comparative evaluation of efficacy of intravenous paracetamol and intravenous diclofenac as post-operative analgesia in laparoscopic cholecystectomy

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Abstract

Background: Though laparoscopic cholecystectomy is a minimal invasive surgery but inadequate pain management interferes with early discharge of patient. Administration of opioid for pain relief is a concern because of its side effects. To avoid this problem, we planned our study to find out the best alternative of opioid in patients undergoing laparoscopic cholecystectomy.

Methods: 68 patients were enrolled for this study in a stipulated time of 1 year in a tertiary level hospital. A questionnaire was responded by patients and a chart was maintained for pain score in visual analogue scale (VAS) and for side effects. We used paracetamol and diclofenac as post operative analgesic in two different groups and data was recorded in Excel panel and was analyzed by standard statistical test by software MINITAB 1513 with a significant p- value of <0.05.

Results: We have found the significant outcome (p-values are 0.0005 at 0 hrs, 0.003 at 2 hrs, 0.001 at 6 hrs, 0.0005 at 12 hrs) in VAS pain score in between the two groups at different intervals. Patients who were administered paracetamol had shown better outcome with less requirement of rescue analgesia and side effects.

Conclusion: Administration of intravenous paracetamol in the intra operative period 30 minutes prior to the completion of surgery followed by administration of 1g paracetamol every 8 hourly in the post-operative period gives better quality of analgesia.

Keywords: Analgesia, Laparoscopic cholecystectomy, Visual analogue scale of pain (VAS).

1. Introduction

Adequate analgesia is of utmost importance for early ambulation and discharge reducing days of hospital stay. Laparoscopic surgery is the most popular trend in recent days. Patients are motivated to undergo laparoscopic surgery if given a choice between open or laparoscopic abdominal procedures. At the same time, concern for post-operative pain remains the same. Till last decade, opioid remains the preferred choice for severe pain; however, the adverse effect of these class of drug demerits the use of opioid [1,2]. Opioids, such as morphine, may be associated, with respiratory depression, excessive sedation, biliary spasm, depression of gastrointestinal motility, post-operative nausea and vomiting (PONV) and confusion, particularly in older patients [3]. The use of intravenous paracetamol or intravenous

diclofenac for post operative analgesia, using an opioid as rescue analgesic only when needed would reduce the amount of opioid used and ensure a comfortable post operative recovery period. Paracetamol and diclofenac are the two non opioid drugs that are being used in post operative care where uses of opioid are contraindicated [4]. Paracetamol is one of the more ubiquitous drugs in hospital and community settings. Although widely used, its actions are still not fully elucidated. With the relative recent availability of an intravenous solution, its use is revitalized, especially in the peri-operative setting. Diclofenac is a non steroidal anti-inflammatory drug (NSAID) taken or applied to reduce inflammation and as an analgesic reducing

pain in certain conditions. It may be supplied as either the sodium or potassium salt [5].

This study was thus conducted to compare the effects of paracetamol and diclofenac as a post operative analgesic in laparoscopic cholecystectomy. Main aim was to assess the postoperative visual analogue pain scores (VAS) and total analgesic requirement in the first 24 hours and also to study the total requirement of additional analgesic despite administration of either Paracetamol or Diclofenac in postoperative period. We also collected data to study the side effects of Paracetamol and Diclofenac in these patients. It provided scope for an alternative regime for post operative analgesia in laparoscopic surgeries.

2. Materials and Methods

The present study was conducted in a tertiary care teaching hospital over a period of twelve months from October 2012 to September 2013, with prior permission from the institutional ethical committee.

2.1 Selection of Patient

Initially 68 patients undergoing laparoscopic cholecystectomy were selected for the study. 04 patients were excluded as surgery time was less than 30 min and another 04 patients were excluded from the study as procedure was converted to laparotomy. 30 patients were included in each group to achieve the power of the study of β -error > 80%. Written informed consent was taken from all the patients.

2.2 Patient Inclusion Criteria

Age 18-64 years

ASA I and II

Patient's undergone laparoscopic cholecystectomy (with incision to closure time > 30 Mins)

2.3 Patient Exclusion Criteria

- Pediatric age group
- ASA III and IV
- Patients with known allergy to drugs to be used
- Renal dysfunction
- Patients unable to comprehend VAS Score
- Bleeding disorders/patient on anticoagulation
- Liver Dysfunction

2.4 Grouping and Randomization

60 patients were randomized into 2 groups irrespective of age, gender and proposed type of surgery. Randomization was done by drawing one out of the two labeled cards (A and B) from a sealed opaque envelope.

2.5 Double Blinding

Two anesthesiologists were involved in the study; the first anesthesiologist administered the drug in the intra and post-op period. He advised the post

op analgesic instruction with naming the drug as 'A' or 'B'. He was not involved in the process of collecting the data of that patient. The second anesthesiologist recorded the study parameters at different intervals in the post operative period without knowledge of the type of the drug administered. Patient as well as the Nursing Staff in the post-operative ward was blinded about the type of drug administered. Nursing Staff was not involved in administering the drug. She used to inform the anaesthesiologist administering the drug whenever patient complained of pain.

2.6 Description of drugs used in the two groups

Group A: Inj Paracetamol @ 15mg /kg (maximum 1g in 100 mL infusion) over 15-20 minutes, 30 minutes prior to the end of surgery as the first dose of analgesic and subsequent doses at 8 hourly interval after shifting the case to the ward.

Group B: Inj Diclofenac @ 2 mg/kg (max 75 mg) in 100 mL of Normal Saline 30 minutes prior to the end of surgery as the first dose of analgesic and subsequent doses at 12 hourly intervals after shifting the patient to the ward.

Prior to the day of surgery, all patients underwent pre-anaesthesia check up with routine and subjective investigations as per requirement.

Patients were connected to standard monitors and were premedicated with inj midazolam 1 mg IV, Inj fentanyl 2mcg/kg IV and inj dexamethasone 4 mg IV. Induction was done with Inj thiopentone 5 mg/kg followed by intubation with Inj vecuronium 0.1mg/Kg. Maintenance of anaesthesia was done by O₂+N₂O (1:2) + isoflurane(0.6% -1%). Patients were put on mechanical ventilation and end tidal CO₂ was maintained between 35-40 mm of Hg. Inj ondansetron 4 mg intravenously was administered to all patients, 30 minutes before the end of surgery. Extubation was done after reversing the effect of muscle relaxant with Inj neostigmine @ 50µg/Kg and Inj glycopyrrolate 20 µg/Kg.

2.7 Intra-operative

Following surgical incision, time was noted (Time-0) and parameters pulse rate(PR), systolic blood pressure(SBP), diastolic blood pressure(DBP), Mean Arterial pressure(MAP) and oxygen saturation(SpO₂) were recorded at an interval of every 2 minutes (min) from Time-0 for the initial 60 min and thereafter at an interval of every 5 min till the end of surgery. The ECG was constantly monitored in the display screen and only the significant changes (if any) from the base line was recorded under the heading of intraoperative complication. All the patients were given the "test drug" 30 minutes before the completion of surgery. Duration of surgery and type of surgical procedure done was recorded.

Intra-operative complications e.g. fall in SpO₂ < 90%, significant ECG changes etc. were noted.

2.8 Post-operative

After the completion of the surgery patient was shifted to post operative recovery ward without prescribing any analgesics in any form either from anaesthesia or surgical side. Patient was monitored till the complete recovery from general anaesthesia. Once fully recovered, patient was shifted to the ward with post operative instruction for analgesia along with other post anaesthesia instructions.

In the post operative period PR, SBP, DBP, MAP and RR were recorded at 2hr, 4hr, 6hr, 12hr and 24hr in the post operative period.

VAS score was recorded at the same interval as mentioned above. Reading was taken as follows: Scale consisted of a 10 cm line anchored at one end by a label as “no pain” and at the other end by a label such as “the worst pain imaginable” or “pain as bad as can be”. The patients were simply asked to mark the line to indicate pain intensity in relation to 0 (no pain) to 10 (worst possible pain). The result was interpreted as distance in centimeter (cm) between 0 to the point marked by the patient.

0
10
0 = no pain
10 = worst possible pain.

Mild pain was considered when VAS Score is between 1 and 3; Moderate pain when VAS Score is between 4 and 6 and severe pain was recorded when VAS Score is ≥ 7 .

First dose of post-operative rescue analgesic was given on the basis of VAS score between 7-10 or on demand made by the patient (whichever was earlier) and repeated if required. Rescue analgesia was decided as Inj morphine with a dose of 0.05mg/Kg - 0.15mg/kg(max) IM whenever required. Any complication / complain (if any) like nausea and vomiting, pruritus, sedation, RR <10 per minute or any other abnormal findings were recorded.

3. Results

For statistical analysis, we have used the software MINITAB 1513 with p- value of <0.05 was taken as a reference of significance.

While analyzing the demographic variables, we have found that there are no statistically significant variations for age, sex, weight, ASA classification, there are 19(63.33%) females in Group A and 21(70%) females in Group-B (Table-1).

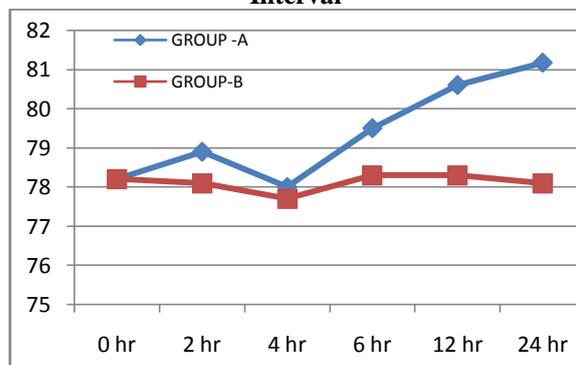
Table-1: Demographic Variables

Variables		Group -A	Group-B	p-Value
Sex	M	11	09	NS
	F	19	21	
ASA	I	20	22	NS
	II	10	08	
Age (in yrs)	M	48.18(\pm 8.34)	49.44(\pm 6.97)	NS
	F	49.95(\pm 9.68)	50.90 (\pm 8.83)	
Weight (in Kg)	M	58.64(\pm 6.87)	58.33(\pm 12.53)	NS
	F	52.89(\pm 8.61)	56.62(\pm 9.24)	

This finding corroborates the fact that gall stone diseases are more common in females. In this study, we have compared the changes in the pulse rate, blood pressure in terms of systolic blood pressure, diastolic blood pressure, mean arterial pressure and changes in the respiratory rate to evaluate the indirect evidences of analgesia and other systemic effects of both the drugs.

While comparing the pulse rate, we found that there is no statistically significant variation in both the groups (Figure 1). Pulse rate was in the increasing trend just after the recovery from anesthesia but at 4 hr interval, there is mild decrease in the values for pulse rate. So we can correlate the initial increasing in pulse rate due to anxiety and not because of pain. Mean changes of pulse rate at different intervals are insignificant but it was observed that mean pulse rate is lower in the Group-B (diclofenac group).

Figure 1: Comparison of pulse rate At Different Interval



While comparing the SBP, DBP and MAP in both the groups, we have observed that there is no significant variation in both the groups in different intervals except the mean values for DBP at 12hr of post-operative period where it was found that DBP is higher in the diclofenac group (Figure 2, 3 & Table-2). The difference in mean values is statistically significant. The mean DBP is 76.53(\pm 9.13) in Group-A whereas it is 81.63(\pm 8.58) in Group -B (P-Value = 0.03).

Table 2: Comparisons for the MAP

Time Interval	Group-A Mean MAP (±SD)	Group-B Mean MAP (±SD)	p-value
0 hr	93.5±(11.6)	95.9±(10.0)	0.388
2 hr	91.83±(8.08)	93.27±(8.93)	0.517
4 hr	92.4±(10.0)	93.23±(6.37)	0.697
6hr	93.72±(9.47)	94.70±(7.25)	0.658
12 hr	94.5±(11.9)	95.73±(7.54)	0.639
24 hr	96.2±(10.1)	96.60±(8.33)	0.866

Figure 2: Comparison of SBP At Different Interval

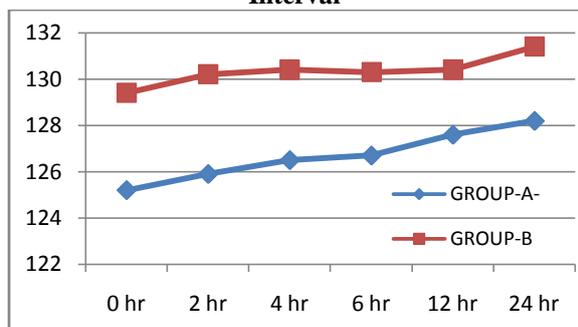
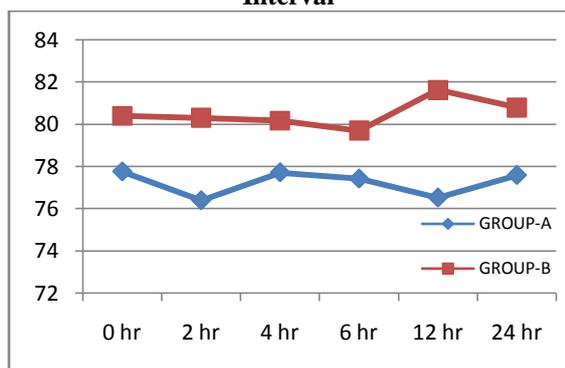
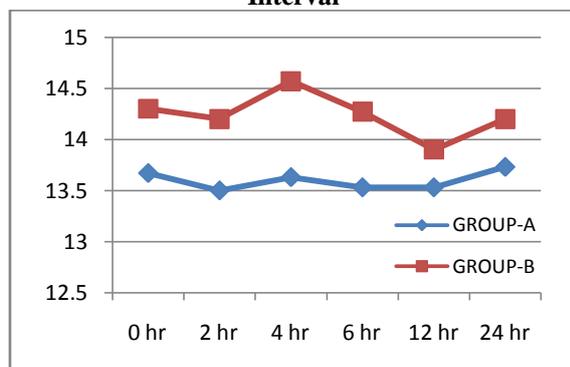


Figure 3: Comparison of DBP At Different Interval



In our study, significant difference in the respiratory rate was observed in between the groups. Respiratory rate is in increasing trend in both the groups. Apart from the baseline values, respiratory rate was significantly higher in the diclofenac group throughout the post-operative period (Figure 4).

Figure 4: Comparison of RR At Different Time Interval



In this study, high VAS Score was found in the paracetamol group in the initial 2 hrs post-

operatively whereas from 6 hr interval onwards, mean pain score was higher in the diclofenac group.

We observed that at 4 hr interval, difference in VAS Score is insignificant. Following that there is gradual increase in VAS Score in the diclofenac group. The mean VAS Score at 24 hr interval is 1.97(±1.40) in Group-A and it is 2.33(±1.92) in Group -B. There is higher VAS Score in Group-B compared to Group-A but difference is statistically insignificant (P-Value =0.401). Insignificant difference in VAS Score at this time interval can be explained by the fact that patients with higher VAS Score in group-B were administered rescue analgesia by this time (Table-3).

Table-3: Comparisons for the vas score

Time Interval	Group-A Mean VAS Score (±SD)	Group-B Mean VAS Score (±SD)	p-value
0 hr	1.53±(1.01)	0.60±(0.77)	0.0005
2 hr	1.67±(0.67)	1.03±(0.89)	0.003
4 hr	2.40±(0.855)	2.63±(1.79)	0.522
6hr	1.40±(0.894)	3.07±(2.33)	0.001
12 hr	1.13±(1.31)	2.77±(2.01)	0.0005
24 hr	1.97±(1.40)	2.33±(1.92)	0.401

We used Two-sample Z-Test to compare the requirement of rescue analgesia. In Group-A, there was only 03 patient for whom morphine was administered and 27 patients (90.0%) did not require rescue analgesia. In Group-B, 8 patients required administration of morphine and 22 patients (73.9%) were not given rescue analgesia. This difference is statistically significant (p-value=0.011).

We observed that in Group-A ,there is not a single case of post-operative complication whereas in Group-B, total no. of patients not requiring management for post-operative complications mainly vomiting is 4 (13.33%).

4. Discussion

Pain in the post operative period is an emotional and mental trauma with unpleasant sensory experience. It is precipitated by surgery and is often associated with autonomic, endocrine-metabolic, physiological and behavioral response [6]. Inadequate pain management leads to delayed mobilization and longer duration of stay in the hospital. Pain after laparoscopic surgery has three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain) and shoulder pain (referred to visceral pain). Pain if inadequately relieved can result in various complications like atelectasis/ pneumonitis/ hypoxemia, deep vein thrombosis, delayed recovery of bowel function, myocardial ischemia and

infarction, urinary retention and residual psychological trauma [7]. Therefore it is important to provide adequate analgesia to the patient in the post operative period[8].

While comparing the pulse rate, we found that there is no statistically significant variation in both the groups. In 2013 Goel *et al.* in their comparative study for pre-emptive analgesia with iv paracetamol and iv diclofenac sodium in patients undergoing various surgical procedures found that pulse rate was almost equal to base line value in both the groups .It was less in diclofenac group which is similar to our finding. But in their study they have found significant variation in mean changes between the groups whereas in our study, both the groups are comparable [9]. In our study, DBP at 12hr of post-operative period was found that DBP is higher in the diclofenac group (statistically significant).The predominant action of diclofenac is to inhibit the enzyme cyclooxygenase (COX), which mediates the conversion of arachidonic acid to prostaglandins and thromboxanes. The significant increase in DBP in diclofenac group might be explained by this effect of diclofenac. Post operative shallow and rapid breathing is a feature of inadequate pain relief. The difference in respiratory rate amongst the groups is clinically insignificant. The increased respiratory rate in the diclofenac group might be explained by lesser pain relief in the diclofenac group.

In this study, significant high VAS Score was found in the paracetamol group in the initial 2 hrs post-operatively where as from 6 hr interval onwards; mean pain score was higher in the diclofenac group. Though the VAS score was higher in the paracetamol group in the initial hours, it was within the values for mild pain. There was no requirement of rescue analgesia.

In 2013, Goel *et al* in their comparative study for pre-emptive analgesia with IV paracetamol and IV diclofenac sodium in patients undergoing various surgical procedures found that mean pain score is higher in the diclofenac group for the initial period followed by insignificant difference in pain score for 4 hrs.

In our study, we observed that at 4 hr interval, difference in VAS Score is insignificant in both the groups. Following that there is gradual increase in VAS Score in the diclofenac group leading to more requirement of rescue analgesia.

Durak *et al* in their study 'Postoperative pain therapy after laparoscopic cholecystectomy: paracetamol versus diclofenac' found that Numeric rating scale (NRS) for pain scores was significantly higher in paracetamol group than the diclofenac

group. They observed the patients for initial 30 min and 60 min in the post-operative period [10].

Remy *et al* in their study 'state of the art of paracetamol in acute pain therapy' showed that 2 g of intravenous paracetamol provides better pain relief than 1 g IV administration, with seemingly no difference in side effect profiles[11].

In our study, we observed that in paracetamol group, there were only 03patients for whom morphine was administered and 27 patients (90.0%) did not require rescue analgesia in diclofenac group, 8patients required administration of morphine and 22 patients (73.9%) were without rescue analgesia. This difference was found statistically significant. Similar finding was postulated by the study by Goel *et al* in their comparative study for pre-emptive analgesia with IV paracetamol and IV diclofenac sodium in patients undergoing various surgical procedures. Observations are mentioned in Health Technology Assessment 2010 that while comparing paracetamol and NSAID that the adjustment of the 24-hour morphine consumption model. The treatment effect estimates of NSAIDs and paracetamol became closer .The adjusted analysis did show a greater reduction in morphine consumption with paracetamol[12].

In a prospective double blind, randomized placebo controlled study conducted on 40 patients undergoing lumbar laminectomy and discectomy, it was demonstrated that IV Paracetamol decreased visual analog scale scores and incidence of vomiting and patient satisfaction [13].

Paracetamol rapidly crosses the blood brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by CNS [14]. This central effect has been regarded primarily as an indirect and reciprocal influence through cyclooxygenase enzyme inhibition and probably through serotonergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory effect although this effect is limited [15].

In our study, we have found that patients in the diclofenac group had more incidences of complications like nausea and vomiting .We have found that in paracetamol group, there is not a single case of post-operative complication whereas in diclofenac group, total number of patients requiring management for post-operative complications is 04 (13.33%). Again if we see the data for patients requiring rescue analgesia, more number of patients was in the diclofenac group. So the complications such as nausea, vomiting can be attributed to use of opiates.

It is clearly evident from this study that patients using paracetamol for post-operative analgesia is better in terms of less requirement of rescue analgesia and thus can avoid the complications associated with opiates.

5. Conclusion

To conclude, administration of intravenous paracetamol in the intra operative period 30 minutes prior to the surgery followed by administration of 1g paracetamol every 8 hourly in the post-operative period gives better quality of analgesia with low pain score. Also it has shown lesser requirement for rescue analgesia in comparison to intravenous diclofenac and thus complications associated with opiates can be avoided. No immediate side effects were observed in patients using paracetamol.

Limitations of the Study

Laparoscopic surgeries are minimally invasive surgery. We have not assessed the analgesic effects of paracetamol or diclofenac in extensive surgeries where replacing opiate is a challenge. Studies can be conducted to find out the effect of this drug in extensive surgeries.

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