

A COMPARATIVE STUDY OF PREEMPTIVE ANALGESIC PROPERTY OF INTRAVENOUS PARACETAMOL AND DICLOFENAC SODIUM

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ABSTRACT

BACKGROUND

Effective pain management is an important component of intra and post-surgical care. In untreated cases it could lead to chronic postoperative pain after surgery. Lack of proper analgesia may cause the patients to hypo ventilate, thereby causing the reduction in vital capacity and other lung functions. A Concept of Preemptive analgesia involves application of treatment prior to trauma and surgical intervention to prevent central sensitization of pain pathways that reduces the amount of analgesic requirements. This results in reduced morbidity and shorter duration of hospital stay. The aim of this study was to compare the effects of I.V. paracetamol and diclofenac aqua as preemptive analgesia in laparoscopic cholecystectomy.

MATERIALS AND METHODS

This prospective, randomized, double blinded study was conducted in a tertiary care hospital. Total of 100 patients posted for laparoscopic surgery were included and randomly allocated into two groups (50 in each group), Group-D and Group-P. Group D- Patients received diclofenac aqua 75 mg (infusion) in 100 ml NS 15 minutes before induction. Group P- Patients received I.V. paracetamol 1 gm (infusion) in 100 ml NS 15 minutes before induction. VAS score, PR, SBP, DBP, RR were recorded at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours & 12 hours after surgery. The data were compiled and expressed as mean \pm standard deviation (SD) and percentages. Statistical software SPSS (version 20.0) was used to carry out the statistical analysis of data.

RESULTS

Although diclofenac aqua was significantly better analgesic option in comparison to I.V. paracetamol in early post-operative period; the overall efficacies of both drugs were comparable post 4 hours of extubation. The time at which rescue analgesia was given was early in the paracetamol group. However, the differences in both groups were not statistically significant. While comparing the hemodynamic parameters no significant differences found. However respiratory rate was significantly higher in paracetamol group.

CONCLUSION

Both drugs are safe while diclofenac aqua is slightly better in controlling post-operative pain in comparison to I.V. paracetamol. However, both drugs can be used in Indian patients, depending on cost and availability.

KEYWORDS

Pre-emptive Analgesia, VAS Score, I.V. Paracetamol, Diclofenac Aqua.

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BACKGROUND

Since the introduction of laparoscopic surgery by Phillippe Mouret in 1987.¹ becomes the most popular trend in recent days because of lower post-operative morbidity including

faster recovery time, shorter hospital stay, less pain and in some cases fewer complications. Despite the minimal invasive nature of this surgery, pain in patients undergoing laparoscopic surgery may be substantial and limit an otherwise speedy recovery.

Effective pain management is an important component of intra and post-surgical care. Post-operative pain not only affects the patients operative outcome, wellbeing and satisfaction from medical care, but also may in some cases result in complications of serious nature. In untreated cases it could lead to chronic postoperative pain after surgery. Inadequate analgesia may cause the patients to hypo ventilate, thereby causing the reduction in vital capacity and other lung functions.

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Acute pain after laparoscopic cholecystectomy starts with the surgical trauma and ends with tissue healing.^{1,2} Although less in intensity some patients still feel considerable discomfort during first 24-72 postoperative period which can delay their discharge. The origin of the pain after the surgery is multifactorial.³

A Concept of Preemptive analgesia involves application of treatment prior to trauma and surgical intervention. The purpose is to prevent central sensitization of pain pathways that reduces the amount of analgesic requirements. This results in reduced morbidity and shorter duration of hospital stay.⁴⁻⁶

The use of opioid analgesic is marred with the adverse effects e.g. nausea, vomiting, sedation and respiratory depression which precludes its use under all circumstances. Non-opioid analgesics are devoid of these side effects. A combination of analgesics from different classes may provide additive effect than a single drug.⁷⁻⁸

NSAIDS like diclofenac act by inhibition of cyclooxygenase-1 (COX-1) and COX-2 enzymes necessary for prostaglandin synthesis. Systemic use of diclofenac is an effective post-operative analgesic even for major surgeries. I.V. paracetamol is a newer agent gaining popularity in post-operative pain relief.⁹⁻¹²

Paracetamol and diclofenac are being used in postoperative period. Use of paracetamol, one of the most ubiquitous drugs in hospitals and community settings, available as intravenous formulation has been revitalized in the perioperative setting. Diclofenac is cheaper than paracetamol, but runs the risk of gastric bleeding, increased incidence of stroke, renal complications and bronchospasm.¹³

Study was conducted to compare the effects of paracetamol and diclofenac as preemptive analgesia in laparoscopic cholecystectomy. Parameters observed were postoperative pain by visual analogue pain scores (VAS) and duration of analgesia. Additionally the side effect of both the drugs were noted.

MATERIALS AND METHODS

This prospective, randomized, double blinded study was conducted in a tertiary care hospital.

Inclusion Criteria

- Patients with ASA grade I and II
- Patients aged between 18 and 60 years
- Patients willing to give written informed consent to be a part of the study.

Exclusion Criteria

- Patients with bleeding disorder or on anticoagulants.
- Patients with abnormal liver and renal functions.
- Patients with history of hypersensitivity to drugs.
- Gastrointestinal bleeding.
- Patients unable to comprehend VAS Score.

Method of Collection of Data- Total of 100 patients posted for laparoscopic surgery were included and written informed consent was obtained. All patients underwent pre-anaesthesia check-up with routine and subjective investigations as per requirement. All the patients were familiarized with pain scoring. Demographic data was obtained, and study population was randomly allocated into two groups (50 in each group), Group-D and Group-P. (Table-1).

Group D- Patients received diclofenac aqua 75 mg (infusion) in 100 ml NS 15 minutes before induction.

Group P- Patients received I.V. paracetamol 1 gm (infusion) in 100 ml NS 15 minutes before induction.

All the patients were pre-medicated with ranitidine 150 mg and alprazolam 0.5 mg night before surgery and kept fasting overnight.

IV line was secured in the operating room. Patients were monitored for HR, NIBP, ECG, EtCO₂ and SPO₂. Patients were premedicated with midazolam 0.02 mg/kg, glycopyrrolate 0.004 mg/kg, pentazocine 0.6 mg/kg. Study medication was given 15 minutes before induction. Induction was done with Propofol 2 mg/kg and intubation with appropriate size endotracheal tube was achieved with inj. vecuronium 0.12 mg/kg. Anaesthesia was maintained with oxygen, nitrous oxide, isoflurane and vecuronium.

After completion of surgery residual neuromuscular blockade was reversed with inj. Neostigmine (2.5 mg) + inj. Glycopyrrolate (0.5 mg) and extubated. Patients were monitored till complete recovery. Then shifted to the ward.

VAS score, PR, SBP, DBP, RR were recorded at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours & 12 hours after surgery.

VAS score reading was taken as follows: The patients were simply asked to mark the line to indicate pain intensity in relation to 0 (no pain) to 10 (worst possible pain).

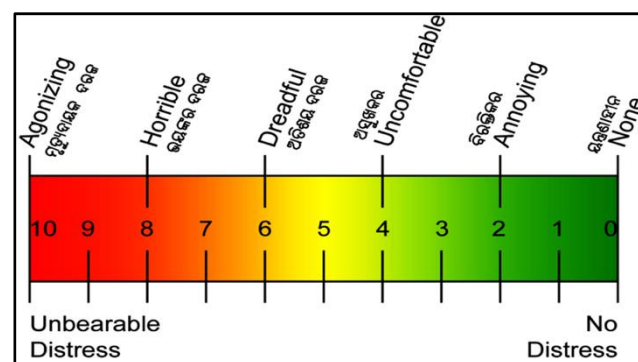


Chart 1

VAS Scored as
 Mild pain 1 to 3
 Moderate pain 4 to 5
 Severe pain >5

Tramadol (100 mg) was given as rescue analgesic when VAS score was >5.

Side effects such as nausea, vomiting, respiratory depression and any on-towards effect were recorded.

Statistical Analysis- The data was compiled and expressed as mean ± standard deviation (SD) and percentages. Statistical software SPSS (version 20.0) were used to carry out the statistical analysis of data. Data was analysed by means of descriptive statistics viz, means, standard deviations and percentages and presented by means of Bar and Line diagrams. For parametric data, Student's independent t-test was employed. Chi-square test or Fisher's exact test, whichever appropriate, was used for non-parametric data. A P-value of less than 0.05 was considered statistically significant.

The study was successfully conducted on all the 100 adult patients. There was no perioperative protocol deviation. All the patients underwent laparoscopic cholecystectomy by experienced surgeons. Fifty cases received paracetamol and other 50 received diclofenac infusion 15 minutes prior to induction of anaesthesia.

RESULTS

- VAS score is significantly higher in the group-P as compared to group-D at 30 minutes, 1 hour and 2 hour post-surgery with significant P value (<0.05)
- In group-P 46 patients needed rescue analgesia compared to 41 in group-D 12 hrs post-surgery.
- Most of the patients in group-P needed rescue analgesia 2 hrs earlier than in group-D.
- Mean duration of analgesia was 5.4 hrs in group-D as compared to 3.1 hrs in group-P which is statistically significant.

Variables	Group D (n=50)	Group P (n= 50)	P value
Age (years)	43.8 ± 10.4	40.6 ± 11.2	0.142
Weight (Kg)	62.1 ± 7.2	61.2 ± 7.1	0.955
ASA (I/II)	31/19	28/22	0.060
Sex (Male/Female)	32/18	32/18	0.284
Duration of Surgery	52.7 ± 7.6	52.8 ± 7.5	0.468

Table 1. Demographic Profile of Patients

There was no statistically significant difference among the groups in respect to age, gender, weight, ASA physical status, duration of anaesthesia (p value >0.05).

Baseline Parameters	Group D	Group P	P value
HR (/min)	79.6 ± 5.41	81.1 ± 4.16	0.13
SBP (mmHg)	126 ± 3.12	126.1 ± 2.16	1.00
DBP (mmHg)	80.33 ± 2.83	80.61 ± 2.51	0.57
RR (/min)	13.1 ± 1.03	13.2 ± 1.19	0.52

Table 2. Baseline Hemodynamic Parameters

Vital parameters are comparable in both the groups and no statistically significant difference was observed.

Analgesic Activity of Diclofenac and Paracetamol- VAS score at 15 min, 30 min, 1 hr, 2 hr, 6 hrs and 12 hrs post-extubation. Patients with VAS score >5 received rescue

analgesia in form of tramadol 100 mg (IV). The exact time at which the patient needed rescue analgesia was noted.

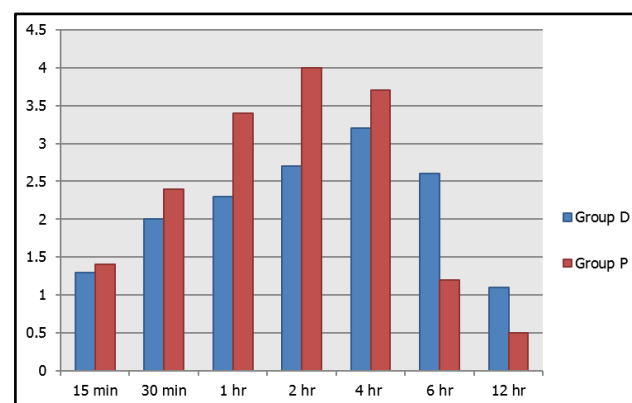


Figure 1. VAS score at Different Time Interval

VAS score is significantly higher in the paracetamol group as compared to diclofenac group at 30 minutes, 1 hour and 2 hour post-surgery with significant P value (<0.05).

The pain intensity score reveals that pain intensity score increased with hours. It is also observed that the higher VAS score in paracetamol group lasted for more than 4 hours. After 4 hours there was no significant difference in the VAS score between both the groups till 12 hours.

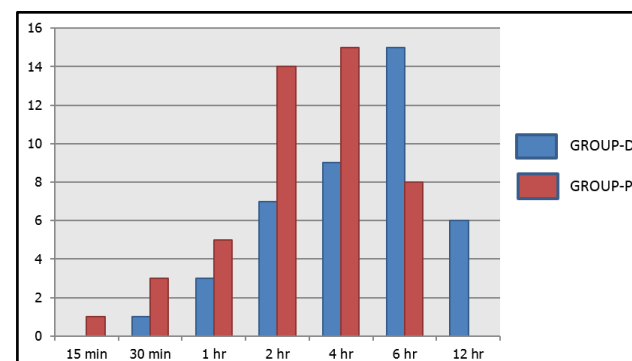


Figure 2. No. of Patients Needing Rescue Analgesia in Both Groups at Different Time Intervals

I.V. paracetamol group received rescue analgesia at 2-4 hours which is at least 2 hours earlier than diclofenac group who needed rescue analgesia at 4-6 hours.

Patients with VAS score more than 5 received rescue analgesia. In diclofenac group most of the patients needed rescue analgesia at 4-6 hours post-surgery (Figure 2). The total number of patients needing rescue analgesia was 41 till 12 hours post-surgery.

In paracetamol group the need of rescue analgesia was significantly earlier as compared to diclofenac group. Most of the patients received rescue analgesia at 2-4 hours which is at least 2 hours earlier than diclofenac group. Nine patients received rescue analgesia before 1 hour of post-surgery. The total number of patients needing rescue analgesia was 46 till 12 hours post-surgery in paracetamol group.

So it was observed that patients who received diclofenac pre-surgery tolerated pain better than the patients who received paracetamol.

Duration of Analgesia	Group D	Group P
< 1 hour	01(02%)	04(08%)
1-2 hours	02(04%)	05(10%)
2-4 hours	09(18%)	15(30%)
4-6 hours	13(26%)	14(28%)
6-12 hours	18(36%)	07(14%)
> 12 hours	07(14%)	05(10%)

Table 3. Overall Duration of Analgesia of both Drugs

The mean duration of analgesia was 5.4 hours among the patients in group D whereas the corresponding time was only 3.1 hours in group P. This difference is statistically significant with a p value of <0.05.

Hemodynamic parameters post-surgery- All the hemodynamic parameters (pulse, blood pressure, heart rate, respiratory rate etc.) were measured at different time intervals till 12 hours post-surgery and no significant difference among both groups were found.

Adverse effects- The secondary aim of the current study was to look for the adverse effects of both the drugs during the peri-operative as well as post-operative period. No major adverse reactions to the drugs were noted in our study. Over all Incidences of side effects are statistically insignificant.

DISCUSSION

Relief of pain is of paramount importance to the patients as it causes discomfort and also increases risk of pulmonary complications. Inadequately relieved pain can result in various complications like atelectasis, pneumonitis, hypoxemia, delayed recovery of bowel function, urinary retention and residual psychological trauma.^{14,15} Postoperative pain relief helps in effective coughing and adequate ventilation. Despite the availability of a wide variety of analgesics, routine management of post-operative pain remains a continuing challenge.

Systemic opioid analgesics are regarded as gold standard in the treatment of severe postoperative pain. Unfortunately, their use is associated with adverse effects e.g:- nausea, vomiting, pruritis and respiratory depression.^{16,17} To minimize the opioid requirement after surgery some additive and synergistic drugs such as local infiltration through trocar sites, NSAIDs, paracetamol are used in pain management after laparoscopic surgery.¹⁸⁻¹⁹

With this in mind this clinical study was conducted on 100 patients, randomly allocating them into 2 equal groups i.e. into Group P (received pre-emptive IV Paracetamol) and Group D (received pre-emptive Diclofenac aqua) to evaluate analgesic efficacy of IV Paracetamol to control post-operative pain and compare it with diclofenac aqua. Efficacy of two drugs, paracetamol and diclofenac sodium was compared with regard to their duration of action, degree of analgesia and side effects. The effect of both drugs on

hemodynamic response of the patients in both groups was also evaluated.

Analgesic Effects of Both Drugs- In this study significant high VAS score was found in the paracetamol group in the initial 2 hrs post-operatively whereas from 4hr 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. More number and early rescue analgesia were needed in paracetamol group than the diclofenac group.

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.²⁰

Debashish Paul et al in their comparative study also observed analgesic effect of paracetamol effective up to more than 5 hours and high mean VAS score of patients administered diclofenac.

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 group P than the group D. They observed the patients for initial 30 min and 60 min in the post-operative period. Those findings are similar to our study.²⁰

In our study, in patients undergoing laparoscopic cholecystectomy surgery, we found that diclofenac aqua appears to be slightly superior post-operative analgesic compared to intravenous paracetamol, in terms of rescue analgesic requirements.

Both the drugs are proven to be effective when used pre-emptively. Intravenous paracetamol 1 gram has analgesic activity in moderate to severe post-operative pain similar to ketorolac 30 mg, Diclofenac 75 mg, morphine 10 mg. It reduces the need for the patient's total opioid by 24-46% and increase in patient satisfaction.²¹⁻²³ Similar findings are also found when diclofenac is used alone as pre-emptive analgesia in laparoscopic abdominal surgeries.^{24,25}

Hemodynamic Parameters- Mean changes of pulse rate at different intervals is insignificant. Similar results were observed by Amin et al.²⁶ In their comparative study for preemptive analgesia with IV paracetamol and IV diclofenac sodium in patients undergoing various surgical procedures, Goel et al found that pulse rate was almost equal to base line value in both the groups.²⁰ 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.

There was no significant variation in SBP and DBP, in both the groups.

Regarding respiratory rate Amin *et al* didn't find any significant difference between two groups. In the present study increased respiratory rate from the base line was

observed in both the groups. The difference in respiratory rate amongst the groups is clinically significant in our study. Patients with paracetamol group had significantly higher RR after 15 minutes of extubation. However, this difference was not significant in first 15-30 minutes of post-surgery. Post-operative shallow and rapid breathing is a feature of inadequate pain relief. The increased respiratory rate in the paracetamol group, after 30 minutes of extubation might be explained by lesser pain relief in the paracetamol group.²⁶

Adverse Effect- In the present study it was observed that there were no differences in postoperative complication in patients although few patients had nausea and vomiting in both groups. Again, if we see the data for patients requiring rescue analgesia, few numbers of patients were present in both groups. So, the complications such as nausea, vomiting can be attributed to use of opiates.

Limitations of the Study

- Rescue analgesic was administered based on a particular VAS score, which may vary with subjective experience of the patient and interpretation of the observer.
- VAS scores are measured at fixed time points so length of analgesic effect of study drugs could not be investigated.
- Primary outcome of our study was rescue analgesic requirement which may not truly reflect the efficacy of study drugs as analgesics.
- The sample size of this study was relatively small; hence it might be difficult to generalize the results, larger and multi-centric trials are required for the same.
- We didn't have a healthy control group to compare individual efficacy of both drugs.

SUMMARY AND CONCLUSION

- Effective pain management is an important component of intra and post-surgical care.
- Preemptive intravenous paracetamol and diclofenac are commonly used to control the post-operative pain following laparoscopic cholecystectomy and other abdominal surgeries. However conflicting results were observed while reviewing the literature.
- So, the current study aimed at evaluation of analgesic efficacy of preemptive paracetamol and diclofenac by comparing VAS score in both groups along with the need of rescue analgesia in form of tramadol. We also looked at different hemodynamic parameters at different time intervals. Associated side effects were also observed.
- Although IV diclofenac was significantly better analgesic option in comparison to IV paracetamol in early post-operative period; the overall efficacies of both drugs were comparable post 4 hours of extubation.
- The time at which rescue analgesia was given was early in the paracetamol group. However, the differences in both groups were not significant statistically.

- While comparing the hemodynamic parameters we didn't find significant differences in pulse rate, systolic BP and diastolic BP. However respiratory rate was significantly higher in paracetamol group while the patients were under severe pain.
- Regarding the various adverse effects, we didn't find significant differences in both groups.
- So, we conclude that both drugs are safe while diclofenac is slightly better in controlling post-operative pain in comparison to paracetamol. However, both drugs can be used in Indian patients, depending on cost and availability.

Abbreviations

ASA	:	American Society of Anesthesiologists
CNS	:	Central Nervous System
COX	:	Cyclooxygenase
DBP	:	Diastolic Blood Pressure
ECG	:	Electrocardiogram
IV/iv	:	Intravenous
MOA	:	Mechanism of Action
NPO	:	Nil per Oral
NRS	:	Numeric Rating Scale
NSAID	:	Nonsteroidal Anti-inflammatory Drugs
PAC	:	Preanesthetic Check-up
PD	:	Paracetamol and Diclofenac
PG	:	Prostaglandin
PONV	:	Postoperative nausea and vomiting
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
VAS	:	Visual Analogue Scale

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