

A PROSPECTIVE, RANDOMIZED CONTROL STUDY EVALUATING THE POSTOPERATIVE ANALGESIA USING RECTAL DICLOFENAC IN PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY SURGERIES

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HOW TO CITE THIS ARTICLE:

A. Padmaja, T. A. R. S. Varma, K. Aparanji. "A Prospective, Randomized Control Study Evaluating The Postoperative Analgesia Using Rectal Diclofenac in Patients Undergoing Elective Laparoscopic Cholecystectomy Surgeries". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 19, May 11, 2015; Page: 2882-2888.

ABSTRACT: BACKGROUND: To assess the efficacy of rectal diclofenac suppository in patients undergoing elective laparoscopic cholecystectomy surgeries in management of postoperative pain, in reduction of intra operative opioid requirement and in prolongation of postoperative analgesic initiation time. **OBJECTIVES:** This prospective randomized single blinded clinical trial evaluates the efficacy of rectal diclofenac suppository for the management of postoperative pain. **MATERIALS AND METHODS:** 100 patients undergoing elective laparoscopic cholecystectomy surgeries were randomized into two groups, Group 1 patients receiving 100mg diclofenac rectal suppository after induction of general anaesthesia, Group 2 patients does not receive any diclofenac rectal suppository. Intra operative hemodynamic monitoring, post-operative VAS score and adverse reactions were recorded over period of 24 hrs. Intra operative opioid (fentanyl) was repeated when heart rate and blood pressure variability of more than 20% from base line are noted. Post operatively if VAS score is more than 4 rescue analgesia with inj. Tramadol is given intramuscularly. **RESULTS:** Administration of single dose of rectal diclofenac had statistically significant reduction in VAS score post operatively compared to control group, reduced requirement of intra operative opioids (fentanyl). Post-operative rescue analgesia initiation time is prolonged in group 1 mean 9.56 hrs compared to group 2, mean 0.72 hrs (p-0.000). **CONCLUSION:** Rectal Diclofenac used in laparoscopic cholecystectomy cases provide adequate, effective prolonged analgesia in the post-operative period with good safety profile. **KEYWORDS:** Analgesics, Non-opioids, Diclofenac sodium, Laparoscopic cholecystectomy, Post-operative pain.

INTRODUCTION: After laparoscopic surgeries, pain is the most frequent complaint and most common cause for post op morbidity.^(1,2) Pain associated with laparoscopic surgeries is usually managed with opioid analgesics or nonsteroidal anti-inflammatory analgesics.

Cholecystitis is inflammation of the gallbladder, which occurs most commonly due to obstruction of the cystic duct with gallstones. General anaesthesia is preferred for laparoscopic cholecystectomy as there is control of respiration, and good hemodynamic control and also the patient positioning will become hard to manage in case of regional anaesthesia.

Diclofenac sodium is an analgesic, antipyretic, anti-inflammatory drug which specifically inhibits prostaglandins. Also it is one of the most cost effective analgesic available in hospital setup.

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Main aim of this study is to evaluate the post-operative analgesia using rectal diclofenac in patients undergoing elective laparoscopic cholecystectomy surgeries. The use of non-opioid analgesic in the intraoperative period can decrease the dose of opioid requirement both intra and post operatively there by significantly reducing the complications and side effects of opioid analgesics.

AIM OF THE STUDY: To assess the effectiveness of rectal diclofenac suppository in patients undergoing elective laparoscopic cholecystectomy surgeries with respect to post-operative analgesia using visual analogue scale pain score, Intra operative opioid requirement, post op analgesic initiation time.

MATERIALS AND METHODS: This prospective randomized control study was conducted after approval by the ethics committee, written informed consent was obtained from each patient. Patients aged between 20-50 years, weight 40-70kgs, ASA I, and II, undergoing elective surgeries, thoroughly assessed and investigated are included in the study. Exclusion criteria were acute cholecystitis, patient refusal to enter or continue the study, morbid obesity (body mass index ≥ 30), chemical substance abuse, chronic or recent use of analgesics, chronic pain, a history of significant cardiopulmonary, hepatic or renal disease, hypersensitivity to the medications, any contraindication of non-opioid analgesics, asthma, peptic ulcer, upper or lower gastrointestinal bleeding, pregnancy, and breastfeeding. The patients who required analgesic the night before surgery.

All patients participating in the study were randomly allocated into group 1 or group 2.

Group 1: Patients in this group receive single dose of diclofenac rectal suppository 100 mg, introduced per rectum before starting surgery after giving general anaesthesia.

Group 2: Control group, patients in this group did not receive diclofenac rectal suppository after giving general anaesthesia.

Intra operative heart rate and blood pressure were monitored for every 10 minutes from induction till 1 hour and for every 30 minutes for 3 hours. Intra operative opioid (fentanyl) was repeated when heart rate and blood pressure variability of more than 20% from baseline was noted. Intra operative complications like hypotension, bradycardia, and ECG abnormalities were noted.

VAS score was noted immediately after completion of surgery as "0" hours, Patient was monitored in post-operative ward. Visual analogue scale score was noted every hour in the post op period for 24 hours. When VAS score was greater than 4, patients were given rescue analgesia inj. Tramadol 100 mg intramuscular.

OBSERVATIONS AND RESULTS: This study is a prospective, randomized, single blinded, case control study evaluating the postoperative analgesia using rectal diclofenac in patients undergoing elective laparoscopic cholecystectomy surgeries under general anaesthesia.

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Results were expressed as mean, median and standard deviation. All statistical analysis were carried out using SPSS PC plus version 20.0. t- Test was used for comparison of quantitative variables and qualitative variables were compared using chi-square test. P-value of <0.05 was taken as significant.

Demographic profile: Both the groups were comparable with regard to age distribution, weight distribution, height distribution and body mass index in Table I. P value was not significant with respect to age (0.79), height (0.57), weight (0.62), and body mass index (0.99).

	GROUP I		GROUP II		t-value	DF	p-value
	MEAN	SD	MEAN	SD			
AGE	44.84	4.49	43.64	6.77	0.27	98	0.79
HEIGHT	1.57	0.07	1.58	0.08	0.57	98	0.57
WEIGHT	56.78	6.82	57.48	7.27	0.5	98	0.62
BMI	22.96	1.8	22.97	1.57	0.02	98	0.99

Table 1: Demographic data

TIME [Min]	GROUP I		GROUP 2		t-value	Df	p-value
	MEAN	SD	MEAN	SD			
Base	81.58	9.35	78.66	8.81	1.61	98	0.11
10	94.76	13.07	87.78	9.33	3.07	98	0
20	105.7	10.36	98.04	8.27	4.06	98	0
30	87.88	9.46	96.44	9	4.64	98	0
40	81.16	9.05	90.48	7.67	5.56	98	0.01
50	79	9.85	83.74	6.61	2.65	98	0.1
60	79.28	9.8	82.38	8.82	1.66	98	0
90	78.1	9.18	84.24	6.6	3.84	98	0
120	77.6	8.26	85.9	7.47	5.27	98	0.001
150	78.11	7.7	83.89	5.72	3.62	98	0.06

Table 2: Baseline and intraoperative heart rate

There is statistically significant variability in heart rate between the two groups in intra operative period. In group 1 patient had a constant decreasing trend of heart rate throughout the procedure with less fluctuation, compared with group 2 whose subjects had frequent fluctuation in heart rate greater than 20% of baseline value intra operatively for which intravenous opioids were repeated frequently. Even with frequent use of opioids (p =0.000) value was significant showing greater variability between the two groups.

Table 3 shows variability of mean arterial blood pressure between the two groups. There was a good blood pressure maintenance in group 1 compared to group 2. Variability was statistically significant between the two groups.

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Time (min)	GROUP I		GROUP II		t-value	df	p-value
	MEAN	SD	MEAN	SD			
BASE	91.94	7.81	89.54	8.56	1.34	98	0.18
10	99.16	9.41	96.8	8.97	1.28	98	0.2
20	110.1	8.83	110.8	7.63	0.42	98	0.67
30	106.9	9.54	107.3	6.73	0.25	98	0.8
40	100.4	8.08	101.6	6.76	0.85	98	0.4
50	96.1	6.93	114.3	6.82	1.01	98	0.31
60	92.68	5.62	96.72	8.2	2.87	98	0.005
90	91.32	5.88	101.5	5.2	9.17	98	0
120	90.58	6.66	102.8	6.9	9	98	0
150	89.32	4.54	100.4	5.3	7.65	98	0

Table 3: Baseline and intra operative map (Mmhg)

Hours	Group I Median	Group II Median	P –value
0	0	4.00	0.000
1	1.00	6.00	0.000
2	2.00	8.00	0.000
4	3.00	-	
6	4.00	-	
8	4.00	-	
10	6.00	-	

Table 4: Visual analogue score (Median)

There was significant statistical difference between group 1 and group 2 in immediate post-operative VAS score, with the median VAS score being 0 in group 1 and 1 in group 2, thus it is statistically significant.(p=0.000). VAS of less than or equal to 4 was considered adequate analgesia, when it is more than 4 rescue analgesia is initiated.

Fentanyl (µgms):

	GROUP I		GROUP II		t- value	Df	p-value
	MEAN	SD	MEAN	SD			
FENTANYL	122	11.9	180.8	16.14	20.61	98	0

Table 5: Total Intraoperative Opioid Requirement

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Intra-operative Fentanyl requirement was 122.40µgms in group 1 and 180.80µgms in group 2, this include initial dose of 100µgms (2µgms/kg body weight) at the time of induction. Thus it is statistically significant ($p < 0.01$).

INJ. TRAMADOL 100 MG INTRAMUSCULAR:

	Group I		Group II		t-value	Df	p-value
	Mean	sd	Mean	sd			
Initiation time	9.56	0.93	0.72	0.54	58.26	98	0

Table 6: Postoperative rescue analgesia initiation time (hrs)

Postoperatively when VAS score becomes greater than 4 rescue analgesia is given with intramuscular Inj. Tramadol. The time from "0" hrs of postoperative period till VAS score becomes >4 is assumed as postoperative analgesia initiation time in hours. It was statistically significant at a mean of 9.56hrs in group 1, compared to mean of 2.38hrs in group 2 ($p < 0.01$).

Complications and side effects: Out of 50 patients in group 1, 6 patients had post-operative nausea and vomiting, in group 2, 4 out of 50 patients had nausea and vomiting which was not statistically significant. No other side effects were recorded in both the groups.

DISCUSSION: This study is to assess the effectiveness of rectal diclofenac in patients undergoing elective laparoscopic cholecystectomy surgeries with respect to, postoperative analgesia using VAS pain score, Intra operative opioid requirement and post-operative analgesic initiation time. Diclofenac have been shown to be effective analgesic as judged by reduction in pain score or opioid sparing effect. The pharmacokinetic and pharmacodynamic properties of diclofenac and nociceptor modulation necessitates their administration in advance of the anticipated time of analgesic requirement pre-emptively.⁽³⁾ Diclofenac administered rectally is a safe and convenient approach resulting in complete absorption and sustained release of drug providing early onset and long duration of post-operative analgesia. Rapid onset of action with diclofenac suppository and slower absorption, which prolongs its duration and its anti-inflammatory action, which may exert tissue reaction to surgery in lesser degree of perceived pain.⁽⁴⁾

Drug administered through the rectal route has greater bioavailability as more than 50% is absorbed directly into the general circulation bypassing the liver. T max is reached in one hour, which is quite faster than the oral route. It has advantage of avoidance of gastric irritation as caused by oral drugs.⁽⁵⁾

With reference from studies we used single dose of 100 mg of diclofenac suppository, introduced per rectum after induction of general anaesthesia in group 1. In group 2 (control group) no placebo was used as suppository after induction of general anaesthesia.

There is statistically significant variability in heart rate between the two groups in intra operative period. The baseline heart rate in both the groups was 81.58 and 78.66 per minute in

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group 1 and 2 respectively. After a brief increase in heart rate in both groups 10-20 minutes after induction, the heart rate showed a decreasing trend more towards baseline value in group 1, whereas in group 2 there were frequent increase than 20% of baseline value, for which intravenous opioid was repeated. Also in group 1 patients, only few needed repeat doses of intravenous opioids, also repeat doses were needed only in first 30-40 minutes after induction of anaesthesia.

Intraoperative mean arterial blood pressures varied significantly in both groups, with greater stable hemodynamic in group 1. After induction both groups showed increasing trends in blood pressures for first 30-40 min, after that group 1 patients showed plateau towards the baseline value with less opioid requirement than group 2 patients. Group 2 patients on the other hand showed increase in blood pressure after first 30-40 min, also frequent rise in blood pressures throughout the intra operative period, requiring more of opioids intra operatively. There is statistically significant difference in mean arterial blood pressure between both groups (p value-0.000).

The immediate post-operative median VAS score after extubation at 0 hours were 0 and 4, in group 1 and group 2 respectively. At 1 hour median VAS score was 6 in group 2 compared to 1 in group 1. In group 1 median VAS score of 4 was reached at 8 hours showing the prolonged post-operative effect of rectal diclofenac. This results are similar to Vynkatesh et al compared rectal diclofenac suppository with injection tramadol for post-operative analgesia.⁽⁶⁾

Post-operative rescue analgesia initiation time in hours, taken as total time duration taken for duration of rescue analgesic, injection Tramadol 100mg intramuscularly given when post-operative VAS score of >4 is reached. Mean of 9.56hrs in group 1 compared to 2.38 hrs in group 2. Thus is statistically significant p value (p<0.05). Rashid et al concluded that rectal diclofenac provides effective analgesia postoperatively with minimum opioid requirement.⁽⁷⁾

Both the groups varied in intra operative opioid consumption (Fentanyl) with group 2 requiring more opioids. Mean fentanyl used in group 2 was 180.80µgms compared to 122.40µgms in group 1. It is statistically significant with p value (p <0.05). Ng et al compared the effect of suppository diclofenac to intravenous parecoxib on post-operative pain. They showed that there is no statistical. Significance between both the groups.⁽⁸⁾ Mohammadreza Arab et al in there study Diclofenac rectal suppository provided simple and safe pain relief in laparoscopic cholecystectomy.⁽⁹⁾ No untoward or specific side effects or complications observed in both the groups. Out of 50 patients in both the groups 6 in group 1 and 4 in group 2 had post-operative nausea and vomiting which is statistically nil significant.

CONCLUSION: Rectal diclofenac used in laparoscopic cholecystectomy cases provide adequate effective prolonged postoperative analgesia for significant duration of time, also with decreased requirement of intra operative opioids (Fentanyl). The intra operative hemodynamic were also well maintained to a great extent. Post operatively the patient have low pain score for prolonged period of time there by delaying the need for rescue analgesia. Rectal diclofenac is cost effective with no side effects.

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Date of Submission: 18/04/2015.
Date of Peer Review: 20/04/2015.
Date of Acceptance: 02/05/2015.
Date of Publishing: 11/05/2015.