Indian Journal of Clinical Anaesthesia 2020;7(2):213–218

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical Anaesthesia

Journal homepage: www.ipinnovative.com

Origirnal Research Article

Efficacy of diclofenac transdermal patch and diclofenac rectal suppository for postoperative pain management following open cholecystectomy: A single blind prospective comparative study

Md Tanweer[1], Manas Ranjan Panigrahi[1,*], Bhabananda Mukhapadhyay[1]

[1]*Dept. of Anesthesiology, ESI-PGIMSR, ESIC Medical College and Hospital, Kolkata, West Bengal, India*

ARTICLE INFO

Article history:
Received 15-11-2019
Accepted 31-01-2020
Available online 03-06-2020

Keywords:
Open cholecystectomy
Diclofenac sodium rectal suppository
Diclofenac epolamine
Patch
PCA pump.

ABSTRACT

Introduction: Postoperative pain control is an important component of surgical patient care. Inadequate pain control in postoperative period increases mortality and morbidity to great extent. Studies have shown transdermal diclofenac is as effective as intramuscular diclofenac injection in postoperative analgesia, but a comparison of diclofenac rectal suppository and transdermal route is lacking. This research proposal intends to study and compare the effectiveness of Diclofenac transdermal patch and rectal suppository.
Study Design: Randomized, Single Blind, Prospective, Comparative study.
Materials and Methods: ASA 1 and 2 patients scheduled for open cholecystectomy withsample size 60 patients divided between group TD (transdermal patch, n=30) and RS (rectal suppository, n=30). 100 mg diclofenac epolamine patch was applied on inner aspect of left arm in TD group's 1hr before incision Patch was changed 12hrly for 48 hrs. 100 mg diclofenac sodium was introduced per-rectally in PR group just before induction of anesthesia and repeated 12hrly for 48hrs. Each patient was monitored and data collected in PACU, PCA remote was again shown to patients and advised them to press button whenever they feel.
Result: It has been found that both the groups were comparable in their demographic distribution, in terms of age and sex. 14 readings were taken from just after OT till 48hrs from starting surgery. None of the patients in the study showed the sign or symptoms of opioid overdosing. The pain was better controlled with Diclofenac through per rectal route than the transdermal route.
Conclusion: Considering mean rank of VAS till 6hrs after skin incision and drugs given during 1^{st}, 2^{nd} and 3^{rd} readings at 6^{th} hr., 12^{th} hr., 18^{th} hr. and continue 6hrly and total drugs given till 48hrs, pain after open cholecystectomy was better controlled with diclofenac sodium rectal suppository in comparison to diclofenac epolamine patch.

1. Introduction

The International Association for the study of pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Postoperative pain control is an important component of surgical patient care. Inadequate pain control in postoperative period increases mortality and morbidity to great extent.[1] In the busy schedule of hospitals and among rush, postoperative is pain often mismanaged. A pfelbaum JL1, Chen C, Mehta SS, Gan TJ, on 2003, conducted a study on random sample of 250 adults who undergone operative procedures with telephone questionnaires about severity of postsurgical pain, treatment, satisfaction with pain medication, patient education, and perceptions about postoperative pain and pain medications. Approximately 80% of patients experienced acute pain after surgery. Of these patients, 86% had severe, or extreme pain, and patients experiencing pain after than before discharge.[2] An effective postoperative pain control ensures patient comfort

* *Corresponding author*.
E-mail address: rashmimanas1976@gmail.com (M. R. Panigrahi).

https://doi.org/10.18231/j.ijca.2020.039

and satisfaction, help to gain early mobility, decreases pulmonary and cardiovascular complications, decreases risk of deep vein thrombosis, and helps in early discharge. Some of methods usually applied for postoperative pain control includes incisional local anesthetic drug infiltration, peripheral nerve block, epidural block, patient-controlled analgesia, oral and intramuscular injections and transdermal analgesic patch and rectal suppository. Opioid and NSAID are central drugs for post-operative pain control. Diclofenac sodium is an NSAID and very effective pain killer. It is one of first choice of surgeons for postoperative pain control. American society of pain control recommend use of diclofenac as part of multi modal analgesia for postoperative pain control unless and until contra indicated.[1] At present diclofenac is mainly used as oral and intramuscular route for pain control. Oral administration of diclofenac before and after surgery is limited and intramuscular repeated injections further add a pain source for patient. Studies have shown transdermal diclofenac is as effective as intramuscular diclofenac injection[3–5] in postoperative analgesia, but a comparison of diclofenac rectal suppository and transdermal route is lacking. This research proposal intends to study and compare the effectiveness of. Diclofenac transdermal patch and rectal suppository.

2. Materials and Methods

The study has been undertaken at the Department of Anesthesiology of ESI- PGIMSR, Manicktala, Kolkata, after obtaining approval from Institute Ethical Committee's.

2.1. Inclusion criteria

ASA 1 and 2 patients scheduled for open cholecystectomy under general anesthesia

2.2. Exclusion criteria

1. Patient not willing to take responsibility or being afraid to press PCA machine button to take medicine.
2. Allergic to drug use in study as diclofenac Na, fentanyl.
3. Patient having physical status ASA 3 and above.
4. Any renal condition that can decrease diclofenac clearance.
5. Any serious liver condition that can interfere with diclofenac metabolism and excretion through bile.
6. Patient with cardiovascular disease.
7. Patient with acid peptic disease, gastritis, chronic constipation, eczema.
8. Patient with obstructive or restrictive lung disease which can be complicated by fentanyl use in iv-PCA.
9. Dementia or any neurological or psychological disease or having difficulty to understand PCA machine.

2.3. Sample size

60 ASA 1 and 2 patients divided between group TD (transdermal patch, n=30) and RS (rectal suppository, n=30).

2.4. Study design

Randomized, Single Blind, Prospective, Comparative study.

2.5. Study technique

All the patients were carefully evaluated during pre-anesthetic outpatient visits and an informed consent was taken in their own language with comprehensive information of the procedure and its possible adverse effects. Each patient was explained when and how to use PCA remote. A VAS score chart was explained to patient to explain how indicate his or her pain intensity on chart. All patients were asked to fast overnight, and one hour before surgery ranitidine 50 mg and metoclopramide 10 mg were administered intravenously. Inside the Operating room, the patient's identity was verified. Monitors were attached and baseline parameters noted down. An intravenous cannulation was done with 18G cannula on the non-dominant forearm and co-loading started with 10 ml/kg Ringer lactate solution. The patients were randomly divided into two groups, TD (transdermal) and PR (per-rectal) of 30 each. Using a sealed envelope technique to determine the drug that used for post open cholecystectomy pain relief. 100 mg diclofenac epolamine patch was applied on inner aspect of left arm in TD group's 1hr before incision. Patch was changed 12hrly for 48 hrs. 100 mg diclofenac sodium was introduced per-rectally in PR group just before induction of anesthesia and repeated 12hrly for 48hrs. Each patient was pre-medicated with 0.2mg glycopyrrolate and 1mg midazolam before general anesthesia for surgery. General anesthesia was with use of propofol 1 to 2mg/k, inj fentanyl 1.2 mcg/kg and rocuronium 0.6-1.2 mg/kg and maintained with 1-2 Mac isoflurane. Infusion of Inj paracetamol 1% was used for intra-operative pain and 4 mg ondansetron in RL was given before the end of surgery. Each patient was provided with incisional local anesthetic infiltration before closure of skin. Intravenous PCA machine with inj fentanyl, 10mcg/ml was attached with each patient intra-operatively. A lock-out interval with 10mins and patient demand dose 10 mcg (1ml) was set on PCA machine. No background continuous infusion or 24hrs limit was set in PCA machine. Just after operation each patient was given 10mcg inj fentanyl bolus dose by anesthesiologist and patient was taken to post anesthesia care unit (PACU). In PACU, PCA remote was again shown to patients and advised them to press button whenever they feel pain. PCA remote was tied with patient dominant hand with a soft gauge so that they did not lose it on bed. Patients were shifted from PACU to surgical care unit. Study period

ended at 48hrs after giving skin incision. All parameters like Pulse, Systolic, diastolic and mean blood pressure, Peripheral O2 saturation, Pain score with visual analog scale, Respiratory rate. Sedation with Modified Ramsay Scale, no of successful attempt (attempt followed by drug delivery) made by patient on iv-PCA machine. Drugs given by iv-PCA machine to patient. Were recorded from just after operation till 48hrs of giving skin incision during operation. Operation time of 1hr was assumed and fixed for every patient. Clinical parameters were recorded just after operations, at 30mins intervals for 1hr, at 1hr interval for 4hrs, at 6hr interval for up to 48hrs from starting the surgery. Intravenous patient-controlled analgesia (iv-PCA) with fentanyl was used as rescue analgesic. Visual analog scale (VAS) score, drugs are given (DG) by PCA machine over different intervals, and the total drug given (TDG) by PCA machine over 48hrs were measured.

2.6. Statistical analysis

Individual observations were noted on case sheets, which were then compiled into a 'Master Chart' with Microsoft Excel 2016. The data has been analyzed with IBM SPSS Statistics 25. The Group Transdermal is abbreviated as TD and Per Rectal as PR. All resultant numeric data have been formatted as mean ± SD. Test for normality was performed using Kolmogorov Smirnov and Shapiro Wilk test. Independent sample t test was used to analyze the parametric demographic data and chi-square for nonparametric ones. Parametric Dependent variables were analyzed using ANOVA, if assumptions are met. ANOVA was supplemented by Brown Forsythe test, if the data was nonhomogeneous (i.e. if groups had unequal variances for a parameter). Nonparametric dependent variables were analyzed using Kolmogorov Smirnov test or Mann-Whitney U test, as appropriate. Correlation for any significant finding was investigated using Pearson correlation test for parametric data and Spearman Rank correlation for non-parametric data. Considering an estimated α = 0.95, the results with p value <0.05 would be considered significant.

3. Result

By coincidence, there were 30 males and 30 females in both group (PR and TD) combined Mean age 41.43, SD = 7.592 in comparison to 42.43, SD = 8.507 in TD group. Found statistically not significant. Also, for Pulse rate, respiratory rate, SpO2, systolic BP, diastolic BP, Mean BP in respective intervals, Pearson test of co-relation was performed and found variability in differences in mean values and was not statistically significant most of times.

3.1. Visual analog scale

In order to test the hypothesis that VAS scores across both group, PR and TD, were same in different intervals non parametric Kruskal Wallis test (Table 1) was conducted and found statistically significant ($p < 0.05$). VAS score between groups in some intervals as shown in Table 1 was done with respective intervals of Drug Given (DG) by PCA machine and found statistically not significant most of times with p value < 0.05. Drugs given (DG) by machine in different intervals describing drugs given (DG) by machine in different intervals. We found Pearson test of co-relation was performed between intervals with statistically significant difference in mean amount drugs given by PCA machine with VAS of same intervals and found no relation was not significant most of times.

3.2. Total drugs (TDS) by PCA machine over 48 hrs.

The descriptive statistics for total drugs given across both group (PR and TD) is reported in Table 2. PR was associated with numerically smaller mean (M = 346, SD = 37.009) and TD was associated with numerically higher mean (M = 403, SD = 70.343). In order to test the hypothesis that mean TDG across both groups were equal, we found numerically and statistically significant difference in mean value of total drugs (TDG) given by PCA machine across groups (PR and TD) over 48 hr.

4. Discussion

NSAIDS are among the most widely used medication for postoperative pain control because of their demonstrated efficacy in reducing pain and inflammation in different routes.[4] Oral diclofenac is not appropriate in operative settings most of the times due to NPO status. Intramuscular preparation is another source of pain for the patients. Intravenous preparation instead of higher bioavailability is associated with increased risk of gastrointestinal and cardiovascular side effects in comparison to Transdermal diclofenac epolamine patch and rectal diclofenac suppository, are two non-injectable routes of administering diclofenac. Both have several advantages over conventionally used intramuscular routes. route as half-life of 9-12 hours after patch application, which implies the presence of a tissue reservoir, as the half-life after oral intake of diclofenac is 1-2 hours. responsible for lesser side effects. Diclofenac rectal suppository has greater bioavailability as more than 50% are absorbed directly into general circulation bypassing the liver. It also avoids the gastric irritation caused by oral drugs and the pain of needle prick as in intramuscular route.[6,7] With the above background in mind, in this study efficacy of transdermal diclofenac epolamine patch was compared with diclofenac rectal suppository in postoperative pain control in patient's undergone open cholecystectomy. A group of 60 patients, equally divided into two groups, TD (transdermal diclofenac patch) and PR (per-rectal diclofenac), were included in the study.

Table 1: Nonparametric test

	Mean Rank of VAS		Chi Square and P value		
	Grouping Information	Mean Rank	Chi- Square	df	P value
VAS after OT	PR	25.62	5.67	1	0.017
	TD	35.38			
VAS 30 Min Interval 1st reading	PR	22.22	16.327	1	0
	TD	38.78			
VAS 30 Min Interval 2nd reading	PR	29.1	0.543	1	0.461
	TD	31.9			
VAS 1hr Interval 1st reading	PR	21.57	22.194	1	0
	TD	39.43			
VAS 1hr Interval 2nd reading	PR	24.27	9.597	1	0.002
	TD	36.73			
VAS 1hr Interval 3rd reading	PR	23.25	13.409	1	0
	TD	37.75			
VAS 1hr Interval 4th reading	PR	26.15	5.107	1	0.024
	TD	34.85			
VAS 6hr Interval 1st reading	PR	28.23	1.406	1	0.236
	TD	32.77			
VAS 6hr Interval 2nd reading	PR	28.77	0.852	1	0.365
	TD	32.23			
VAS 6hr Interval 3rd reading	PR	28.17	2.681	1	0.095
	TD	32.83			
VAS 6hr Interval 4th reading	PR	28.3	1.85	1	0.174
	TD	32.7			
VAS 6hr Interval 5th reading	PR	31.48	0.246	1	0.62
	TD	29.52			
VAS 6hr Interval 6th reading	PR	32.55	1.127	1	0.289
	TD	28.45			
VAS 6hr Interval 7th reading	PR	30.65	0.007	1	0.933
	TD	30.35			

Table 2: Descriptions

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
PR	30	346	37.0089	6.7569	332.181	359.819	280	430
TD	30	403.667	70.3432	12.8428	377.4	429.933	270	610
Total	60	374.833	62.8555	8.1146	358.596	391.071	270	610

Table 3: Homogeneity if Variances

Levene Statistic	Df1	Df2	P value
7.033	1	58	0.01

Table 4: One-way Anova

	Sum of Squares	df	Mean Square	F	P Value
Between Groups	49881.667	1	49881.667		
Within Groups	183216.667	58	3158.908	15.791	0
Total	233098.333	59			

Table 5: Robust test of equality of Means

	Statistic	df1	df2	P value
Brown-Forsythe	15.791	1	43.912	0

It has been found that both the groups were comparable in their demographic distribution, in terms of age and sex. 14 readings were taken from just after OT till 48hrs from starting surgery. More frequent readings and PCA based rescue analgesia with fentanyl were used to ensure better patient compliance with study and less analgesia free episode. A lockout interval of PCA machine was set at 10mins and patient demand dose was set at 10 mcg/demand, to avoid overdosing of fentanyl. None of the patients in the study showed the sign or symptoms of opioid overdosing and MRS (Modified Ramsay Scale) did not cross > 2 in any patient.

The statistically significant difference in Mean of VAS just after OT, 2 (1) = 5.670 was reported with Mean of VAS = 25.62 in PR group and 35.38 in TD group. Similarly, statistically significant differences were noted in the mean of VAS score across both groups (TD and PR) during intervals, from just after OT till 4reading of 1 hourly interval (6hr from starting the surgery) VAS score in TD(15.7422) group were more than PR(11.5917) group. During same intervals, DG by PCA machine was statistically not significant across both groups. Probable reason of such findings could be, the patients were taking every possible dose from PCA machine and at a high VAS score benefit of diclofenac through any route (PR or TD) was shielded. Similarly, mean rank of VAS score after 4reading of 1 hourly interval (6hrs from starting surgery) till 7were statistically not significant s. As VAS indicates the status of pain just at a point of time and here it is at the end of respective 6hrs intervals, therefore probably more time gap of 6hrs instead of 30mins or 1hr between readings, allowed patients to cover their VAS with more demands on PCA machine. On the contrary, DG by the PCA machine over same 6hrs intervals indicates a cumulative status of pain. There was the statistically significant difference in drug given (DG) by PCA machine across the groups (TD and PR) in 1, 2 and 3 readings at each 6hrs intervals group (32.23) was higher than the PR route (28.77) in each of these same intervals. This is indicating higher efficacy of diclofenac through per rectal route than the transdermal route.

Parallel with these findings it was also noted that mean total drugs (TDG) given across both group (PR and TD) was statistically significantly different (Tables 4 and 5) and PR route was associated with the smaller mean (M = 346, SD = 37.009) in comparison to TD route (M = 403, SD = 70.343). As total drugs given (TDG) is reflecting the cumulative status of pain over 48hrs in both groups. Therefore, it can be explained that the pain was better controlled with Diclofenac through per rectal route than the transdermal route.

Gulcin Ural S et al. blindly randomized 90 patients into three groups, per-oral (PO), transdermal (TD) and intramuscular (IM), 30 patients in each group and compared analgesic effects of various routes of diclofenac sodium administration in the early postoperative period after laparoscopic cholecystectomy operations. He found the statistically significant difference in VAS score between TD and PO group with VAS score in TD group more than PO group in 0mins, 15mins, 30mins, and 60mins after OT.[3]

M.E. Bone and D, Fell did a comparative study of rectal diclofenac with intra muscular papaveretum as placebo for pain relief after tonsillectomy. He found rectal diclofenac superior to relief pain than placebo.[8]

Sadafgulchinural and Ozlen Yener, did a comparative study of efficacy of oral, im and transdermal route of diclofenac Na for postoperative pain control. They did their randomized double blinded study among 90 ASA 1 and 2 patient and used tramadol infusion consumption for one hour as indicator of efficacy of analgesia. among different mode of application of diclofenac Na. They noticed tramadol consumption among transdermal and intra muscular group was low than oral group. They concluded transdermal route was as effective as im and oral route and may be preferred above two.[9]

Different forms of diclofenac sodium (oral, rectal, intravenous and intra muscular) were used in pain management following postoperative laparoscopy in the studies found in literature.[10]

Alessandri F et al. administered transdermal diclofenac sodium into the incision area in postoperative period to a study group which is conducted on 120 patients undergoing gynecological surgery, they also gave placebo treatment to a second group in the same study. They have observed in the study group who had transdermal diclofenac sodium in postoperative period that there was significantly less analgesic consumption and a shorter duration of hospital discharge.[11]

The timing of application of the patch and rectal suppository in this research was based on Yanchicket et al work. In his study, he divided 274 patients with acute knee strain into two groups as placebo and diclofenac sodium patch groups and noted analgesia levels for 7 days. They reported the earliest pain decrease in the study at 1.27 hours when compared with the placebo group.[12] Similarly, after the administration of 50 mg diclofenac rectal suppositories, peak plasma concentrations attained on average within 1 hour. Yanchick et al. also reported that with 50 mg rectal suppository, maximum concentration reached in plasma was about $2/3^{rd}$ of those reached after gastrointestinal resistant tablet, and AUC was about $\frac{1}{2}$ of the parenteral route.

5. Conclusion

Considering mean rank of VAS till 6hrs after skin incision and drugs given during 1^{st}, 2^{nd} and 3^{rd} readings at each 6hrly interval, and total drugs given over 48hrs, pain after open cholecystectomy was better controlled with diclofenac sodium rectal suppository in comparison to diclofenac epolamine patch.

6. Source of Funding

None

7. Conflict of Interest

None.

References

1. Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson PD. Changes in mortality after total hip and knee arthroplasty over a ten-year period. *Anesth Analg*. 1995;80(2):242–8.
2. Apfelbaum J, Chen C, Mehta S, Gan T. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. 2003;97(2):534–40.
3. Ural SG, Yener O, Sahin H, Simsek T, Aydinli B, Ozgok A. The comparison of analgesic effects of various administration methods of diclofenac sodium, transdermal, oral and intramuscular, in early postoperative period in laparoscopic cholecystectomy operations. *Pak J Med Sci*. 2014;30(1):96–100.
4. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient . *Gastroenterol*. 2001;120(3):594–606.
5. Peterse B, Rovati S. Diclofenac epolamine (Flector) patch: evidence for topical activity. *Clin Drug Investing*. 2009;29(1):1–9.
6. Heitz JW, Witkowski TA, Viscusi ER. New and emerging analgesics and analgesic technologies for acute pain management. *Curr Opin Anaesthesiol*. 2009;22(5):608–17.
7. Bhagatetal H. Evaluation of preoperative rectal diclofenac for perioperative analgesia in ENT surgery. *Indian J Anaesth*. 2003;47(6):463–6.
8. Bone ME, Fell D. A comparison of rectal diclofenac with intramuscular papaveretum or placebo for pain relief following tonsillectomy. *Anaesth*. 1988;43:277–80.
9. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. A clinical practice guideline from the American pain society, the american society of regional anesthesia and pain medicine, and the American society of anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. *J Pain* . 2016;17(2):131–57.
10. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs—Rationale for use in severe postoperative pain. *Br JAnaesth*. 1991;66(6):703–12.
11. Alessandri F, Lijoi D, Mistrangelo E, Nicoletti A, Crosa M, Ragni N. Topical diclofenac patch for postoperative wound pain in laparoscopic gynecologic surgery: A randomized study. *J Minim Invasive Gynecol*. 2006;13:195–200.
12. Yanchick J, Magelli M, Bodie J, Sjogren J, Rovati S. Time to significant pain reduction following DETP application vs placebo for acute soft tissue injuries. *Curr Med Res Opin*. 2010;26(8):1993–2002.

Author biography

Md Tanweer PG Trainee

Manas Ranjan Panigrahi Associate Professor

Bhabananda Mukhapadhyay Associate Professor

Cite this article: Tanweer M, Panigrahi MR, Mukhapadhyay B. Efficacy of diclofenac transdermal patch and diclofenac rectal suppository for postoperative pain management following open cholecystectomy: A single blind prospective comparative study. *Indian J Clin Anaesth* 2020;7(2):213-218.