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Original Article

Pharmacology Section

Efficacy of Diclofenac Transdermal Patch versus Diclofenac Rectal Suppository for Management of Postoperative Pain Following Open Cholecystectomy: A Randomised Clinical Trial

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ABSTRACT

Introduction: Postoperative pain can have detrimental effects if proper analgesia is not provided. The most widely used medicines for the management of postoperative pain is Non Steroidal Anti-Inflammatory Drugs (NSAIDs), among the NSAIDs the most commonly used drug for postoperative pain is diclofenac sodium. Repeated intramuscular/intravenous (i.m/i.v.) injections of diclofenac are associated with pain and discomfort while oral use of diclofenac before and after surgery is limited and is also associated with increased risk of gastrointestinal complications like dyspepsia, peptic ulcer etc. Diclofenac Transdermal Patch (TD) and Rectal Suppository (RS) are good methods of drug delivery as they avoid first pass metabolism, gastrointestinal complications and pain associated with i.m/i.v. route.

Aim: To evaluate the efficacy of the transdermal diclofenac patch versus the diclofenac RS for management of postoperative pain following open cholecystectomy.

Materials and Methods: This hospital-based, randomised, prospective, interventional, open label comparative clinical trial was conducted in Department of General Surgery and Department of Pharmacology at FH Medical College and Hospital, Agra, Uttar Pradesh, India, from April 2021 to September 2021. A total of 64 patients were included in the trial and they were randomly divided into two groups using simple randomisation technique. Group A received 100 mg diclofenac TD (n=32) and group B received 100 mg diclofenac RS (n=32) just before induction of anaesthesia and repeated 12 hourly for 48 hours. Pain was assessed postoperatively at 6, 12, 24 hours, respectively using the Visual Analogue Scale (VAS) and adverse effects like gastrointestinal complications were also noted in the both groups. The Student's t-test was applied to compare the mean values of quantitative variables while qualitative variables were analysed using Chi-square test. A p-value <0.05 was considered statistically significant.

Results: Both the groups were comparable with respect to age (p-value=0.1048) and gender distribution (p-value=0.3760). VAS score at 12 hours and 24 hours postsurgery in patients of both groups showed significant decrease (p-value=0.0001), when compared with VAS score values at 6 hours postsurgery of the same group. On comparison of VAS score between the two groups at 6 hour, 12 hour and 24 hour significant decrease (p-value <0.05) in VAS score was observed with a higher decrement in group B patients i.e., those who received diclofenac rectal suppositories. In group A, seven patients needed rescue analgesia while in group B only three patients required rescue analgesia.

Conclusion: Rectal diclofenac suppository had higher efficacy in comparison to transdermal diclofenac patch in management of postoperative pain.

Keywords: New drug delivery, Non steroidal anti-inflammatory drugs, Routes, Visual analog scale

INTRODUCTION

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [1]. Postoperative pain is acute in nature and requires proper management to reduce discomfort to the patients. Recent studies have given evidence that in about 50-70% of patients, postoperative pain is poorly managed [2,3]. If proper analgesia is not provided, postoperative pain can have detrimental effects on organ systems and chronic effects like delayed recovery and chronic pain [4].

Opioids and Non Steroidal Anti-Inflammatory Drugs (NSAIDs), both are used for management of postoperative pain. Opioids though are very useful in relieving postoperative pain but they are associated with many side-effects; therefore, there is a need to reduce the opioid use [5-7]. Currently, NSAIDs are the most commonly used drugs in management of postoperative pain and diclofenac is one of the most commonly used Non Steroidal Anti-Inflammatory Drugs (NSAIDs) for management of postoperative pain [8]. Oral administration of diclofenac before and after surgery is limited and is also associated with increased risk of gastrointestinal complications, while intramuscular/intravenous route is associated with pain, discomfort and increased risk of systemic complications [9].

Diclofenac can also be administrated using Transdermal Patch (TD) and Rectal Suppository (RS). These routes of drug delivery avoid first pass metabolism, have better bioavailability, reduced risk of gastrointestinal complications, systemic side-effects and better patient compliance [9,10].

Comparative trials to evaluate these two routes of drug delivery i.e., diclofenac RS and TD following open cholecystectomy are lacking especially in Indian population. Hence, the present trial was conducted in patients undergoing open cholecystectomy with an objective to evaluate the efficacy of transdermal diclofenac patch against the diclofenac RS for postoperative pain management. The null hypothesis made was that there was no significant difference in the efficacy of the two groups i.e., diclofenac RS and diclofenac TD.

MATERIALS AND METHODS

This hospital-based, interventional, randomised, open label comparative clinical trial was conducted in the Department of

General Surgery and Department of Pharmacology at FH Medical College and Hospital, Agra, Uttar Pradesh, India, from April 2021 to September 2021. The ethical approval from the Institutional Ethical Committee (IEC no. 03/21) was obtained. Trial was registered in clinical trial registry India (CTRI/2021/03/032257). Patients were explained about details regarding the study and written informed consent was obtained from all the patients.

Sample size calculation: Sample size was calculated using the formula $n=Z^2 \times pq/d^2$, where 'n' is the estimated sample size, d is desired level of precision (±5%, at confidence level of 95%), z=1.96 (at confidence level 95%), 'p' is prevalence {prevalence of cholelithiasis was taken as 4.15% according to previous study on prevalence of gall bladder diseases in north India [11]}, q=1-p, so the final sample size was calculated as 62 patients.

Inclusion criteria: Patients of both the genders, aged between 18 to 65 years, scheduled for open cholecystectomy due to cholelithiasis under spinal anaesthesia during the study period were included in the study.

Exclusion criteria: Patients not willing to participate in the study, patients scheduled for emergency surgery, allergic to NSAIDs, any renal, hepatic and cardiovascular disorder, patients with acid peptic disease, bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD) and with co-morbid diseases like diabetes, hypertension, neurological, psychiatric or neuro-vascular disorders were excluded from the study. Also, patients having absolute contraindication for spinal anaesthesia, pregnant and lactating females were excluded from the study.

A total of 64 patients were enrolled in the study in accordance with inclusion and exclusion criteria during the study period. They were randomly divided into two groups using simple randomisation technique, patients were allotted numbers and the odd numbers were assigned to diclofenac TD group and even numbers to diclofenac RS group.

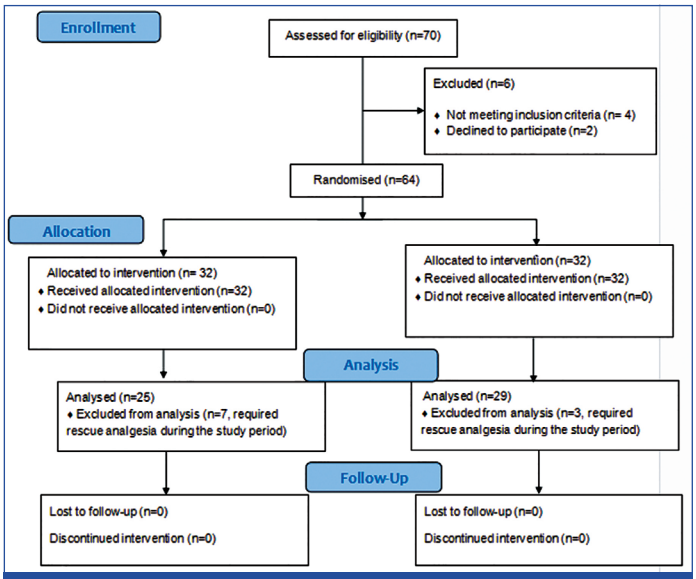
- Group A received 100 mg diclofenac TD (n=32) and
- Group B received 100 mg diclofenac RS (n=32).

Procedure

One night before the surgery, all the patients were pre-medicated with tablet ranitidine 150 mg and tablet clonazepam 0.5 mg and were asked to fast overnight. One hour before the surgery pantoprazole 40 mg, ondansetron 4 mL and ceftriaxone 1 gm were administered intravenously. At time of induction of anaesthesia glycopyrrolate 0.2 mg and midazolam 1 mg were given intravenously. Spinal anaesthesia was given using injection bupivacaine, dose was adjusted according to body weight and duration of anaesthesia needed.

Each patient in group A was given 100 mg diclofenac TD (DicloPLAST, Zuventus Healthcare Ltd.,) applied on inner aspect of left arm before induction of anaesthesia. Patch was changed 12 hourly for 48 hours. Each patient in group B was given 100 mg diclofenac introduced per-rectally (Dynapar 100, Troikaa Pharmaceuticals Ltd.,) just before induction of anaesthesia and repeated 12 hourly for 48 hours. Pain was assessed postoperatively at 6, 12, 24 hours, respectively using Visual Analogue Scale (VAS) [12] which is a scale ranging from 0-10 showing the minimal and maximum pain score, respectively. As in this study short term pain management was evaluated postoperatively therefore VAS score was observed till 24 hours only.

During the study period, if any patient belonging to either of the groups had VAS more than or equal to 7.5, then injection tramadol 100 mg was administered intravenously as a rescue analgesia. Time of administration of rescue analgesia and number of patients who required rescue analgesia in both the groups were noted. If any patient requires rescue analgesia within 24 hours i.e., within the study duration that patient was excluded from analysis. Any adverse effects like gastrointestinal complications were also observed in both the groups. All the patients received the allocated intervention and none were lost to follow-up in both the groups; although those patients who received rescue analgesia within 24 hours i.e., within the study duration were excluded from further analyses [Table/Fig-1].



[Table/Fig-1]: CONSORT 2010 flow diagram.

STATISTICAL ANALYSIS

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 21.0, IBM, USA. The Student's t-test was applied to compare the mean values of quantitative variables while qualitative variables were analysed using Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Age and gender distribution of the both the groups is demonstrated in [Table/Fig-2]. Out of 64 patients included in the study 49 were females and 15 were males, indicating female predominance. Whereas, the average age of the patients was 37.85 years.

Parameters	Group A (N=32)	Group B (N=32)	p-value
Male/Female	6/26	9/23	0.3760#
Age (years)	38.47±2.11	37.23±3.54	0.1048*

[Table/Fig-2]: Gender and age distribution in both the groups.
*Student's t-test, #Chi-square test

[Table/Fig-3] shows VAS score at 12 hours and 24 hours postsurgery in patients of group A was 4.56±0.38 and 3.23±1.14, respectively; whereas VAS score at 12 hours and 24 hours in group B was 3.21±1.24 and 2.27±0.59. In both the groups significant decrease (p-value <0.05) in VAS score was observed at 12 hours and 24 hours when compared with VAS score values at 6 hours postsurgery of the same group. In [Table/Fig-4] significant decrease (p-value <0.05) in VAS score was observed when the values in both the groups was compared with a higher decrement in group B patients.

Parameter	Group A (N=25)	Group B (N=29)
VAS Score (Mean±SD) 6 hours	6.12±0.57	5.37±0.48
VAS Score (Mean±SD) 12 hours	4.56±0.38 (t-value=12.8817) (p-value=0.0001)	3.21±1.24 (t-value=9.1894) (p-value=0.0001)
VAS Score (Mean±SD) 24 hours	3.23±1.14 (t-value=12.8266) (p-value= 0.0001)	2.27±0.59 (t-value=23.0561) (p-value=0.0001)

[Table/Fig-3]: Intra group comparison of Visual Analogue Scale (VAS) score.
p-value<0.05 considered significant

In group A seven patients needed rescue analgesia i.e., inj. tramadol 100 mg intravenously i.e., one patient required rescue analgesia at 7 hours, three patients at 8 hours, two patients at 9 hours and one

VAS score	Group A (N=25)	Group B (N=29)	t-value	p-value*
6 hours	6.12±0.57	5.37±0.48	5.6934	0.0001
12 hours	4.56±0.38	3.21±1.24	5.8884	0.0001
24 hours	3.23±1.14	2.27±0.59	4.2307	0.0001

[Table/Fig-4]: Comparison of Visual Analogue Scale (VAS) score between the two groups.
(*Unpaired t-test); p-value <0.05 considered significant

patient 10 hours postoperatively, while in group B only three patients required rescue analgesia, two patients at 9 hours and one patient at 10 hours postoperatively. This shows that requirement of rescue analgesia was more and at early time period postsurgery in the patients who received transdermal diclofenac patch in comparison to patients with rectal diclofenac suppository. No significant adverse effects like gastrointestinal complications in either of the groups during the study duration were observed.

DISCUSSION

Diclofenac TD and RS are two emerging non injectable drug delivery methods for postoperative pain management as they avoid first pass metabolism and gastrointestinal complications associated with oral route and pain associated with intramuscular/intravenous route [10,13]. However, there is lack of research work especially a comparative analysis to evaluate efficacy of these two routes of drug delivery, hence this study was conducted.

Tanweer M et al., conducted a comparative prospective study to evaluate efficacy of diclofenac TD and diclofenac RS for postoperative pain management following open cholecystectomy [14]. Total 60 patients were divided into two groups, TD (n=30) and RS (n=30). Just before induction of anaesthesia 100 mg diclofenac patch and 100 mg diclofenac was given per rectally in TD and RS groups respectively and repeated 12 hourly for 48 hours. Mean VAS score was noted from just after Operation Treater (OT) till four reading of 1 hourly interval (6 hour from starting the surgery), mean VAS score in TD group was more than RS group hence pain was better controlled with diclofenac RS. Similar results were observed in the present study, where on comparison of VAS score between the diclofenac TD and RS group, significant decrease (p-value <0.05) in VAS score was observed at 6, 12 and 24 hours postsurgery with a higher decrement in group B patients i.e., those who received diclofenac RS.

Choudry ZA et al., compared postoperative pain management with diclofenac rectal suppositories and intramuscular diclofenac in patients undergoing laparoscopic cholecystectomy [15]. Mean VAS score was 6.41±0.89, 4.03±0.92, 2.16±0.84 in group that received diclofenac rectal suppositories as compared to 7.78±0.83, 5.86±0.92, 4.4±1.33 in group that received intramuscular diclofenac after 6 hour, 12 hour and 24 hour, respectively. Therefore, it was concluded diclofenac rectal suppositories were more effective in postoperative pain management [15]. In the present study also, diclofenac RS had higher efficacy in comparison to diclofenac TD in management of postoperative pain, VAS score in TD group was 6.12±0.57, 4.56±0.38, 3.23±1.14, whereas in RS group it was 5.37±0.48, 3.21±1.24, 2.27±0.59 at 6 hour, 12 hour and 24 hour, respectively.

Shrimali V et al., compared caudal bupivacaine and rectal diclofenac for management of postoperative pain in paediatric genitourinary and lower limb surgery, postoperative pain was assessed by Hannallah score and analgesia given only when the score was more than 7 [16]. It was observed that mean duration of time interval for first dose of analgesic was significantly longer in group receiving rectal diclofenac (8.56 hours) than group receiving caudal bupivacaine (4.2 hours). A total of 16 patients required rescue analgesia in caudal group as compared to 12 patients in rectal group concluding that rectal diclofenac is a useful alternative to caudal bupivacaine. Similarly in the present study, authors observed that only three patients required rescue analgesia at mean time interval of 9.6 hours in the group receiving rectal diclofenac as compared to those who received diclofenac TD (seven patients required rescue analgesia at mean time interval of 8.4 hours).

Arab M et al., Adhikari N et al., and Padmaja A et al., conducted different studies to evaluate the efficacy of rectal diclofenac suppository in management of postoperative pain following laparoscopic cholecystectomy [17-19]. In these studies, it was noted that mean pain score in patients receiving RS was significantly lower than those patients in the control group who did not receive rectal diclofenac. Similar results were noted in the present study concluding that diclofenac RS is good alternative to administer diclofenac for postoperative pain management. No adverse effects like gastrointestinal complications or any other systemic complications were observed in both the groups in the present study, which is similar to study conducted by Padmaja A et al., [19].

Limitation(s)

Limitations of the present study are small sample size, short study duration i.e., VAS score was noted only upto 24 hours and evaluation of postoperative pain management was done only in one type of surgery i.e., following open cholecystectomy therefore in future to overcome these limitations, evaluation of both these routes of drug delivery should be done on more number of patients, VAS score should be noted for longer period (upto 48 hours) and effect on postoperative pain management should also be studied in other surgical procedures like laparoscopic surgery.

CONCLUSION(S)

In the present study, Diclofenac RS was well suited for postoperative pain management. Patients receiving rectal diclofenac have low pain score and less number of patients required rescue analgesia as compared to patients who received diclofenac TD. However, more trials are required to prove its efficacy and safety in various other types of surgeries.

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