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Case control

Pre-emptive Effects of Preoperative Diclofenac Suppository on Pain Management in Patients Undergoing Laparoscopic Cholecystectomy: a Case-Control Study

Running Title: Effects of Diclofenac on Laparoscopic Cholecystectomy Pain

Aiiub Asheghvatan[1], Zahra Ahmadi[1], Farzad Kakaei[2], Mohammadtaghi Khodayari[3], Mojtaba Ziaee[4], Allahverdi Arjmand[1]*

[1]Department of General & Vascular Surgery, Maragheh University of Medical Sciences, Maragheh, Iran.
[2]Department of General & Vascular Surgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Department of Statistics, Maragheh University of Medical Sciences, Maragheh, Iran.
[4]Department of Pharmacology, Maragheh University of Medical Sciences, Maragheh, Iran.

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Corresponding author
Department of Surgery, Maragheh University of Medical Sciences, Maragheh, Iran.
Tel: +98 41 33 37 22 52/ +98 914 321 3396
E-mail
drarjmand1281@gmail.com

Abstract

Introduction: Postoperative pain following laparoscopic cholecystectomy is common in abdominal surgeries. Opioids and non-steroidal anti-inflammatory drugs are used in the management of postoperative pain. The current clinical study was undertaken to evaluate the efficacy of a preemptive diclofenac suppository for the alleviation of post-surgery pain and opioid consumption in laparoscopic cholecystectomy patients.

Methods: A total of eighty patients aged 18 to 65 who underwent laparoscopic cholecystectomy in Sina Hospital of Maragheh University of Medical Sciences were included in this prospective, matched case-control study and were randomly allocated to two groups of 40 each. Subjects received 100 mg diclofenac suppository or placebo within 2 h before surgery. The pain score and analgesic consumption data were recorded up to 24 h postoperatively. An Independent *t*-test was utilized for the analysis of results.

Results: Visual Analogue Scale (VAS) scores in the diclofenac group were statistically lower at 2, 4, 8, and 12 hours compared to the placebo-controlled group. Opioid consumption was statistically significantly reduced in the treatment group compared to the control group (20.0 ± 3.48 vs 54.7 ± 3.63 ml, respectively. Rescue analgesia usage was significantly higher in the control group. Half of the patients in the diclofenac group did not need any opioid drug. Besides, postoperative side effects and hospital staying duration were decreased in the diclofenac group in comparison to the control group.

Conclusion: Current study demonstrates that preemptive diclofenac 100 mg administration could be taken into consideration to alleviate postoperative pain and is a valuable addition to the standard treatment following cholecystectomy pain management.

Keywords: Diclofenac, Analgesics, Morphine, Pain Management, Cholecystectomy

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Introduction

Surgical trauma is the major culprit of pain, morbidity, prolonged hospital stays, re-hospitalization, delayed recovery, and excessive treatment costs (1). Postoperative pain is one of the major concerns of doctors and patients in surgery wards.

Laparoscopic cholecystectomy is a frequent surgical technique that is used for uncomplicated gallstone disease (2). Most patients suffer from mild to moderate postoperative pain in this surgical approach (3). Moreover, acute abdominal and shoulder pains are the most relevant complaint of patients after an operation. As a direct consequence, patients need to receive analgesic medication such as potent nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids to alleviate pain.

Diclofenac is one of the most accepted medications in postoperative pain control in hospitals with considerable anti-inflammatory, analgesic, and antipyretic characteristics (4). NSAIDs inhibit cyclooxygenase enzymes (COX), which leads to a decrease in prostaglandins production. NSAIDs commonly relieve post-surgical pain and inflammation adequately and satisfactorily (5, 6). Despite this, sometimes patients are affected with a considerable degree of discomfort that could not be tolerated adequately with NSAIDs making it inevitable to prescribe opioid medications to control postoperative pain. Despite the comprehensive findings on pain management, no prior research has examined the analgesic activity of the diclofenac suppository on postoperative pain prevention in patient candidates for laparoscopic cholecystectomy. Thus, the goal of the current research was to determine the clinical therapeutic effects of 100 mg of diclofenac sodium through an investigation of pain thresholds, inflammation, potential adverse effects, and the volume of narcotic painkillers (morphine) consumption following laparoscopic cholecystectomy by a prospective, case-control matched study.

Material and Methods

This case-control matched study was conducted on 80 patients between 18 to 65 years old with a body mass index (BMI) from 18 to 30 who was a candidate for laparoscopic cholecystectomy surgery at Sina Hospital in Maragheh City, Iran in 2019-2020. All the patients had physical status I-II of the American Society of Anesthesiologists (ASA) and were divided into 2 groups. Patients were excluded from the study if they met any of the following criteria: acute cholecystitis, bile duct disorders, laparoscopic surgery must proceed in the course of an open procedure, inadequate knowledge to use visual analog scale (VAS), allergy to any drugs in the study, alcohol or drug abuse and drain in situ and choledocholithiasis.

The registration ID of the Ethics Committee of MRGUMS is IR.MARAGHEHPHC.REC.1397.022 and written consent was obtained from the patients. Based on previous studies sample size was calculated at 33 patients in each arm of the study, finally, we intended to enroll a total of 80 patients in the final sample size to reduce exclusions and data errors.

Group 1 (diclofenac) received standard preoperative medications and diclofenac sodium as a 100 mg suppository 2 hours before transferring to the operating room; group 2

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(control) received standard preoperative medications and glycerin suppository as a placebo in the control group.

Patients' overall health was checked which was carried out by the investigators on the night before the surgical operation. All the participants were instructed in the use of a visual analog scale (VAS) and were required to express their pain sensation on a standard scale (0 for no pain, 10 for worst pain). In the operating room, routine anesthetic procedures (heart rate, electrocardiogram (ECG), blood pressure, and pulse oximetry were performed. Propofol (2 to 2.5 mg per kg) was used for inducing anesthesia until verbal response disappeared in all participants. Vecuronium (0.1 mg per kg) was administrated for intubation. Maintenance of anesthesia was carried out by inhalation anesthesia using O2 50%, NO2 50%, and 1 MAC (minimum alveolar concentration) isoflurane. Laparoscopy gas pressure was adjusted to 12 mmHg in all participants.

All surgeries have been conducted by the same surgical team. The patients were assessed for postoperative pain scores, nausea, vomiting, morphine request, and duration of hospitalization stay. The postoperative pain score was measured by the visual analog scale (VAS), and the volume of rescue analgesic medication (morphine) prescribed for every patient was evaluated. All the participants were followed up by a well-trained nurse who was unaware of the study groups at 2, 4, 6, 12, and 24 hours after surgery. Postoperative standard pain control which was initiated 2 hours after recovery consisted of intravenous acetaminophen 500 mg in 100 mL normal saline was infused over 20 minutes every 6 hours and morphine as a rescue analgesic was prescribed as demanded. Heart rate, blood pressure, and respiratory rate were checked at every mentioned time. The anesthesia method and prescribed drugs during and after the operation were similar for all participants in both groups.

Statistical Analysis

SPSS software, version 23.0 (SPSS Inc, Chicago, Illinois) was used for statistical analysis. Variables with a normal distribution were expressed as the mean (standard deviation; SD). Mann-Whitney U test or Pearson w2 tests were used for nonparametric data. Student t-test was used to identify the significance between normally distributed continuous variables. Analysis of variance on repeated measures was used for other clinical parameters. Qualitative variables were analyzed by the Chi-square test. A confidence interval was used to show the difference in the results. In this study, $p< 0.05$ was considered significant.

Results

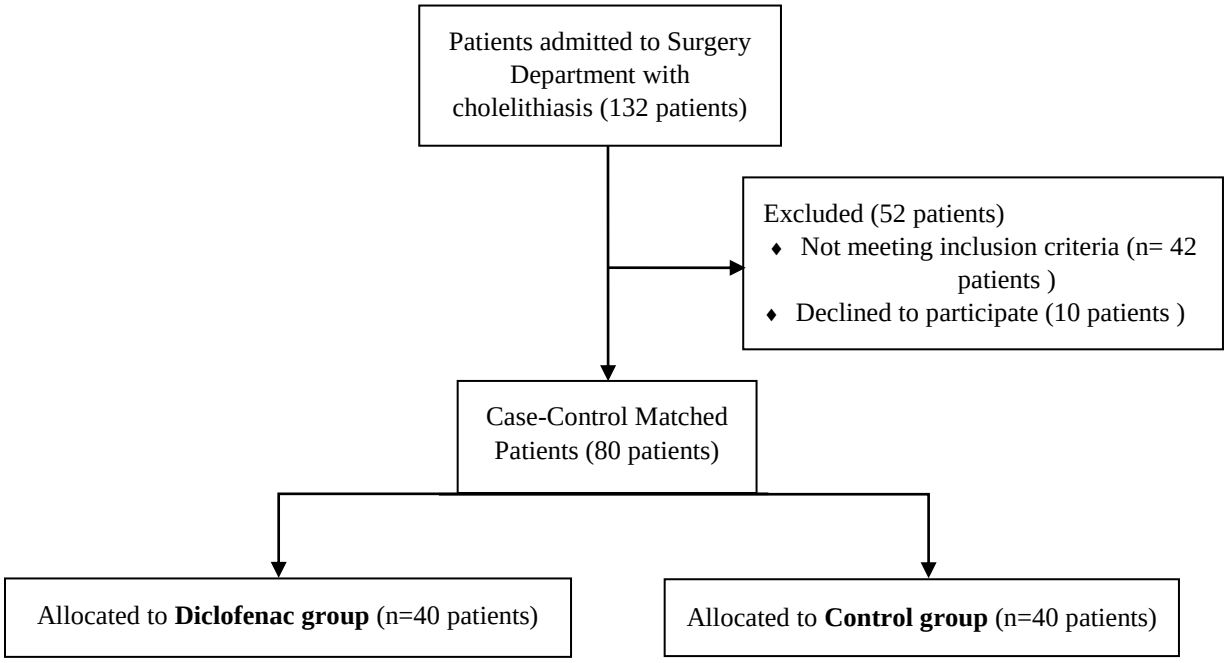
Between December 2019 and November 2020, a total of 80 patients diagnosed with gallstones and candidates for laparoscopic cholecystectomy surgery were matched and divided into two groups in this study, and no cases were excluded. There was not any significant difference in participants' sex, age, BMI, ASA class, intraoperative drug consumption, and anesthesia duration **(Table 1)**.

Table 1. Demographic data, duration of anesthesia, and duration of surgery (mean ± SD, n).

	Diclofenac (n=40)	Control (n=40)	*p* Value
Age (year)	47.15 ± 12.8	47.1 ± 11.5	0.985
Sex M/F (n)	12/28	16/24	-
Single/Married	4/36	2/38	-
Smoker/None	16/24	18/22	-
Height (cm)	167.2 ± 9.65	165.3 ± 7.31	0.102
Weight (Kg)	74.2 ± 11.77	76.25 ± 12.55	0.723
BMI	26.56 ± 3.81	27.92 ± 4.68	0.347
ASA I/II (n)	15/25	19/21	-
Duration of anesthesia (min)	79 ± 14.2	82 ± 13.7	0.504
Duration of Surgery (min)	38 ± 22	40 ± 18	0.814

Among a total of 132 patients admitted to the surgery department with cholestasis symptoms, 42 patients were excluded and 10 patients did not participate in the study. Finally, 40 cases were matched with 40 controls **(Figure 1)**. All the patients were admitted the day before surgery and hospitalized for one night after the procedure.

Figure1. CONSORT flow diagram of the case-control study.



The first-time patients' complaints of pain was demonstrated in **Figure 2**. There was a significant difference between the placebo and diclofenac groups ($p < 0.05$). Preoperative administration of diclofenac significantly lowered postoperative pain score (VAS) at 2, 4, 8, and 12 h follow-up periods in comparison to the placebo-controlled group ($p < 0.05$) **(Figure 3)**. The median VAS score was reduced among the patients in the diclofenac group. **Figure 4** demonstrated the time of the first rescue analgesic (morphine) requirement during postoperative clinical follow-up periods in both groups. The first analgesic requirement time was significantly longer in the patients who received preoperative diclofenac ($p < 0.05$). Moreover, the total number of patients

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who received morphine was higher in the control group ($p < 0.05$). The length of hospital stay was statistically similar in both groups. The findings demonstrated that the control group had higher demand for rescue analgesia ($p< 0.05$), undoubtedly, there was a positive correlation between the use of diclofenac suppository and postoperative morphine usage in the patients. As shown in **Figure 5**, the Mann-Whitney U test revealed that morphine consumption in the diclofenac group was 20 ± 3.4 significantly lower in comparison to the control group (54.7 ± 3.6) in all postoperative follow-up periods ($p < 0.001$).

Figure 2. The time of the patient's first complaint of postoperative pain. Time as hours **p <0.05.

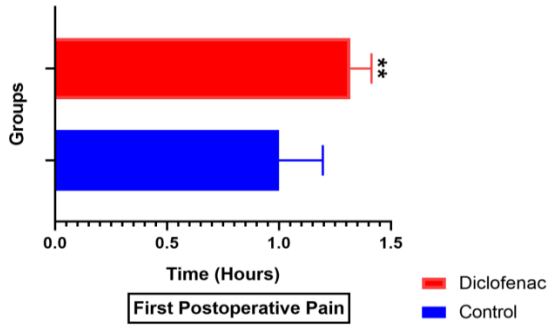


Figure 3. Time-specific pain intensity visual analog score (VAS) values through time **p < 0.05 for diclofenac vs. control.

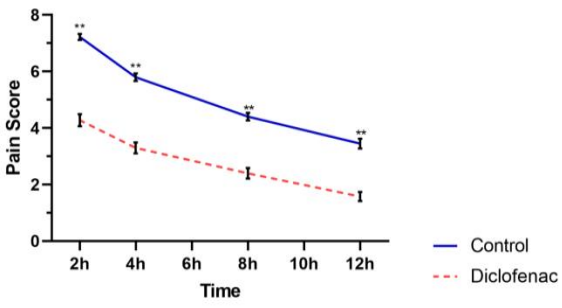


Figure 4. First rescue narcotic requests after the operation **p < 0.05 for diclofenac vs control.

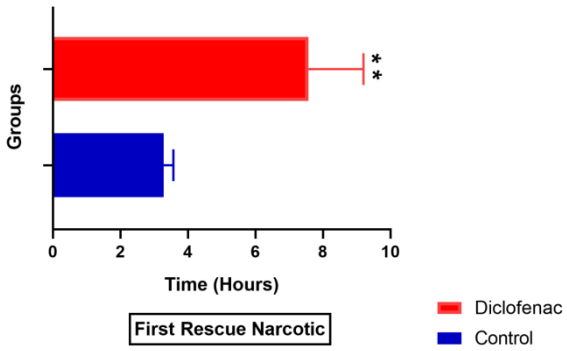
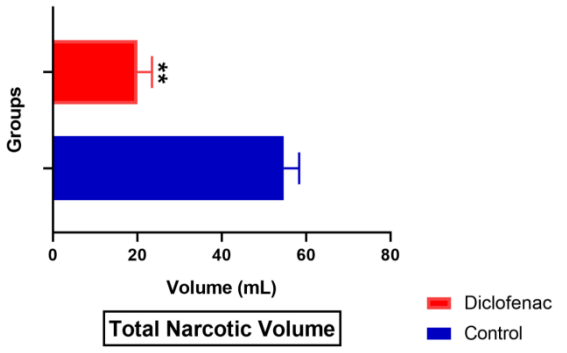
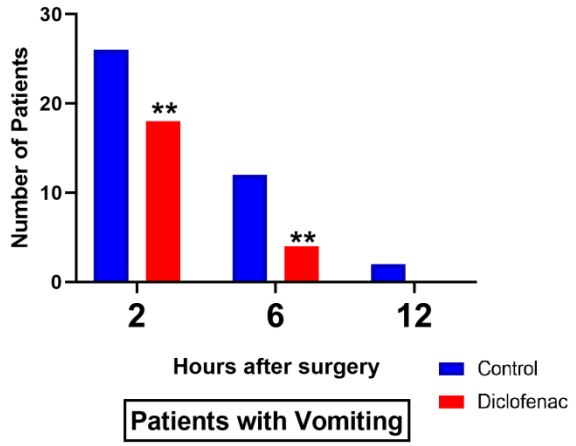


Figure 5. Total narcotic volume used after the operation. **p < 0.001 for diclofenac vs. control.



Common side effects of NSAIDs, including gastrointestinal symptoms and bleeding disorders were not observed. In addition, morphine-associated side effects such as respiratory or airway compromise or severe sedation were not detected in the patients. Other opioid adverse effects such as urinary retention, nausea, and vomiting were significantly higher in the placebo group. **Figure 6** demonstrates the vomiting rate difference between diclofenac and placebo-controlled groups ($p < 0.05$). Fatigue was observed at an equal rate in both groups in the recovery room (P=0.10) and was reduced during the following 2, 6, and 12 h in both groups. However, the reduction in the diclofenac group was more obvious.

Figure 6. Vomiting rate after the operation in hours. **p < 0.05 for diclofenac vs control.



Discussion

Laparoscopic cholecystectomy is one of the frequent surgical procedures in the patients with gallbladder disease, which has some beneficial properties such as faster recovery as well as less invasive trauma compared with conventional techniques (7). Laparoscopic cholecystectomy is associated with moderate postoperative pain and attenuates better post-surgery discomfort compared with the conventional open method (8). Nevertheless, a reduction of postoperative pain and discomfort in patients seems to be inevitable in the early hours after the laparoscopic cholecystectomy procedure due to sensory response to tissue damage.

Several trials have been designed to evaluate preemptive NSAID administration on postoperative pain, but their findings were unclear. Some studies on knee replacement, lower abdominal surgery, and C-section support the NSAIDs' benefit as preoperative analgesia (9, 10). Whereas some other studies did not recommend pretreatment with NSAIDs to reduce postoperative pain (10). These variations may in part be caused by the controversy linked to the preventive analgesia definition and how the clinical trials are carried out. Some trials demonstrated that preoperative NSAIDs are a valuable addition to standard laparoscopic cholecystectomy pain management lessen postoperative opioid consumption and improved postoperative pain results (11-15). Other reports did not show any significant changes in opioid demand and pain scores between the study groups (10, 16).

In the current case-control, matched study comparing the analgesic efficacy of preoperative single-dose diclofenac sodium suppository in postoperative pain control after laparoscopic cholecystectomy, narcotic (morphine) consumption after surgery and rescue analgesic demand were reported to be lower and the time of first analgesic requirement was considered to be postponed in diclofenac group. In subjects who received preoperative rectal diclofenac, VAS scores, and prevalence of adverse effects following the surgical operation were lower in the diclofenac group statistically. However, our results showed that the postoperative opioid requirement and first analgesic demand period were significantly reduced as well as VAS score. Besides these findings, the first analgesic request time was delayed in the diclofenac group. Our results suggest that a lower VAS score along with prolonged analgesic requirement in the diclofenac group lead to a favorable reduction in rescue analgesia and morphine consumption. In addition, the overall morphine consumption decreased considerably during the postoperative time in the diclofenac group in comparison to the control. In conclusion, the hypothesis that pain following laparoscopy is partly due to peritoneal

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inflammation is supported by this research. Diclofenac can also minimize postoperative pain not only through its analgesic but also anti-inflammatory properties. This study had some limitations to be considered such as a small sample size in each group, only a single dose of 100 mg diclofenac was used, regardless of patients' weights, and was not continued after surgery.

Conclusion

Diclofenac has the potential to play a key role in reducing post-surgical opioid demands. In patients who underwent laparoscopic cholecystectomy, a single preoperative 100 mg dose of rectal diclofenac led to better pain management by reducing postoperative pain score and opioid demand in the first 24 hours. It also reduced the use of rescue analgesics and opioid side effects in the postoperative period, such as nausea.

Preemptive treatment of 100 mg diclofenac with the advantages of reduced opioid consumption, pain score, and rescue analgesics before laparoscopic cholecystectomy is recommended by this study.

Conflict of interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions: AAV, AAR, and FK contributed to the conception and surgical procedures of the study. ZA contributed to data gathering. MZ organized the database and wrote the draft of the manuscript. MTK performed the statistical analysis. All authors contributed to the manuscript revision, and read and approved the submitted version.

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