

Evaluation of Preoperative Administration of Rectal Indomethacin in Reducing the Severity of Ileus after Open Cholecystectomy

*Ehsan Soltani¹, (MD); Ali Jangjoo², (MD); Mostafa Mehrabi Bahar³, (MD);
Monavvar Afzal Aghaei⁴, (MD)

1. Assistant Professor of Surgical Oncology, Surgical Oncology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

2. Associated Professor of Minimal Invasive Surgery, Surgical Oncology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

3. Professor of General Surgery, Surgical Oncology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

4. Assistant Professor of Social Medicine, Department of Epidemiology and Biostatistics, Mashhad University of Medical Sciences, Iran.

ARTICLE INFO	ABSTRACT
<p>Article type: Original Article</p> <hr/> <p>Article History: Received: 01-Jul-2020 Accepted: 22-Oct-2020</p> <hr/> <p>Key words: Cholecystectomy, Indomethacin, Postoperative ileus, Rectal administration.</p>	<p>Introduction: Ileus or transient intestinal motility disorder is one of the problems after surgery, which poses challenges facing the medical team. Previous studies approved the preemptive effects of non-steroidal anti-inflammatory drugs (NSAIDs) on ileus; however, the majority of them have focused on animal models. This study aimed to investigate the effects of administration of rectal indomethacin in reducing ileus in patients who underwent cholecystectomy.</p> <p>Materials and Methods: This randomized controlled trial included 40 patients with cholelithiasis who were divided into two groups of indomethacin (n=20) and placebo (n=20). The indomethacin group received 100 mg rectal indomethacin before the operation. Cholecystectomy was performed using an open technique. The recovery of bowel functions (i.e. the time of the first flatus passage, return of appetite, and total dosage of opioid analgesic medications) was evaluated in this study.</p> <p>Results: Time of the first ileus passage (P=0.004), return of appetite time (P=0.06), and reduction of opioid usage (65.62±5.5 mg/day versus 93.26±2.56) were significantly shorter in the indomethacin group, compared to the placebo group. Furthermore, none of the patients had any significant indomethacin-related complications.</p> <p>Conclusion: According to the outcomes of this study, it is concluded that preoperative administration of NSAIDs can be helpful in postoperative ileus reduction.</p>
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***Corresponding Author:**

Department of Cancer Surgery, Omid Cancer Center, Mashhad, Iran.

E-mail: Soltanie@mums.ac.ir

Introduction

Following open abdominal surgery, the medical team encounters ileus in some cases. Ileus is a clinical problem and is known to reduce the motility of the gastrointestinal tract, especially the intestines after the operation (1). Moreover, it increases postoperative morbidity, hospital stay, and medication costs through abdominal distention, nausea and vomiting, as well as prolonged fasting time (2-4). There have been several studies investigating the correlation between preoperative NSAIDs administration and postoperative ileus; however, the majority of them have focused on animal models (5-11). Therefore, this randomized controlled trial aimed to investigate the effect of administration of rectal indomethacin on postoperative ileus in patients who underwent open cholecystectomy with or without choledochal exploration.

Materials and Methods

Study design

After obtaining the ethical approval of the Clinical Trial Committee of Mashhad University of Medical Sciences, Mashhad, Iran (99/228278), this randomized, double-blind clinical trial was conducted on patients suffering from cholelithiasis from March 2006 to February 2008. The patients were divided into two groups by one of the researchers using the simple randomization technique. The indomethacin group (n=20) (C1) received 100 mg of rectal indomethacin 2 h before surgery (sufficient time to reach the maximum serum concentration). On the other hand, the placebo group (n=20) only received paraffin (C2). Informed consent was obtained from all patients who participated in this study.

Sample size calculation

Based on similar studies that calculated the time interval between the end of the operation and the first gas passing as a criterion for eliminating ileus, the sample size was calculated considering alpha 0.1 ($Z_{1-\alpha/2}=1.645615867$) and beta 0.2 ($Z_{1-B}=0.841623031$), and at least 20 patients were included in each group.

Study Population

In total, 40 patients (age range: 28-65 years) participated in this study who were candidates for elective open cholecystectomy. The exclusion criteria were: 1) hypersensitivity to indomethacin, 2) presence of underlying conditions that worsen with NSAIDs administration, such as asthma, gastrointestinal bleeding, and renal failure, 3) coagulation disorders or conditions in which ileus is more common, such as diabetes mellitus, liver failure, or substance abusers, and 4) pregnancy.

Furthermore, the patients who consumed chronic special medicines, such as NSAIDs, corticosteroids, or opiates, and those who received TCA antidepressants, antihistamines, opiates, sedatives, NSAIDs, or corticosteroids 24 h before the operation were excluded from the study.

Interventions

In order to prevent the effect of anesthetics on postoperative ileus, all patients were anesthetized with a standard protocol (induction with midazolam, fentanyl, atracurium, and thiopental sodium, and maintenance with propofol and N₂O). The abdominal wall was opened with a Kocher incision. In case the operating time was over 45 min or there was a need for any other interventions, such as biliary tract bypass, the patient would be excluded from the study.

Outcome Measurements

During the first 24 h after surgery, the symptoms were monitored and recorded by our observer, who was a nurse blinded to the groups. The time intervals between the end of the surgery and the first flatus and return of the appetite (for drinking or eating) in addition to the total opiate dose in 24 h were recorded in this study. It should be mentioned that the rescue analgesia (IV-Pethidine) was given with the patient-controlled analgesia technique. During hospitalization, the patients were evaluated regarding the possible side effects of indomethacin, such as gastrointestinal bleeding, surgical site bleeding, and renal failure.

Statistical Analysis

The collected data were analyzed in SPSS software (version 16) through student t-test, Mann-Whitney test, Fisher's exact test, and Cochran test using mean \pm 2 SE to determine the confidence interval of 95%.

Results

Table 1 tabulates the patients' characteristics. Out of 40 patients enrolled in the study, 33 (80%) cases were female (C1: n=17; C2: n=16), and the mean age of the patients was approximately 46 years (age

range: 28-65 years). As mentioned earlier, the evaluation of the onset of gastrointestinal activity was conducted by considering the return of appetite and having the first gas passing in the patients. According to Table 2, the return of appetite in the C1 occurred approximately and significantly earlier than that in the C2 (P=0.06). In addition, the number of patients in whom the time of first flatus occurred in the first 24 postoperative hours was significantly more in the C1, compared to the C2 (P=0.004) (Table 3).

Table 1: Patients' characteristics based on age and gender

Groups		Indomethacin	Placebo	Total
Gender	Male	3 (15%)	4 (20%)	7 (17.5%)
	Female	17 (85%)	16 (80%)	33 (82.5%)
	Total	20 (100%)	20 (100%)	40 (100%)
	P-value	0.204		
Age (year)	Mean	46.45 \pm 3.9	45.35 \pm 3.6	
	P-value	0.838		

Table 2: Frequency distribution of appetite return after surgery

Groups		Indomethacin	Placebo
Appetite return (hour)	Mean	13.9 \pm 1.16	16.9 \pm 1.05
	P-value	0.064	

Table 3: Frequency distribution of the time of first gas passing within the first postoperative 24 h

Groups		Indomethacin	Placebo	Total
Gas passing	Yes	15 (75%)	6 (30%)	21 (52.5%)
	No	5 (25%)	14 (70%)	19 (47.5%)
	P-value	0.004		

According to the obtained results, the total opiate dose was significantly lower in the C1 (65.62 \pm 5.5 mg/day), compared to the C2 (93.26 \pm 2.56) (P=0.000). Moreover, the mean lengths of hospital stay were 3.2 and 3.7 days in the C1 and C2, which showed no statistically significant difference between the groups in this regard (P=0.356). It should be mentioned that none of the patients

experienced abnormal bleeding during and after surgery. However, three and four cases in C1 and C2 complained of rectal irritation due to using the suppositories, respectively, which was not statistically significant. There was no evidence of indomethacin side effects in the evaluation of patients' laboratory tests as well as their history and physical examination.

Discussion

Although ileus is a well-known complication of abdominal surgery, its exact physiopathology remains unclear. Studies have shown that other interventions, such as laparoscopic surgery, thoracic epidurals or intravenous lidocaine, consumption of NSAIDs, early feeding and getting out of bed, perioperative fluid restriction, laxatives, prokinetic agents, and neostigmine, reduce the incidence, severity, or complications of ileus (11,12). Although there was no significant difference between the two groups in terms of the patient's first postoperative gas excretion in this study, other findings demonstrate the effectiveness of preoperative administration of rectal indomethacin in the reduction of postoperative ileus following elective open cholecystectomy.

The time when ileus is over is not clear since there are no precise subjective criteria for its assessment. There was no significant difference between the two groups regarding the length of hospital stay. The present study did not only aim to reduce this time but also prevent other complications, such as the risk of aspiration and other abdominal complaints to achieve a better outcome.

These results support the hypothesis of a preemptive effect of preoperatively administered rectal indomethacin on postoperative ileus in elective surgeries, which previously were confirmed by numerous studies (5-11).

To our knowledge, surgical trauma can cause the production of prostaglandins and inflammation. Indomethacin, an anti-inflammatory therapeutic agent, inhibits the production of prostaglandins by the inactivation of the cyclooxygenase enzyme, which is a starter in the induction of inflammation (4,14-17). Several studies approved the role of prostaglandins as a local regulatory agent to control the digestive motility system. They also indicated that indomethacin caused increased intestinal motility in dogs and acted as prokinetic agents in rats with gastric emptying of the meal (18). Additionally, decreased nausea and vomiting, improved recovery, and short

hospital stay are of the major advantages attributed to the use of NSAIDs before surgery (19-22).

Furthermore, the obtained results demonstrated a significantly lower dose of total opiate in C1, compared to C2. Although the use of opiates is beneficial to control the pain after surgery, their side effects, such as intestinal motility disorders, should not be neglected (14-19,23).

The combination of narcotic and non-narcotic medications to control the pain is a sensible approach to reduce these side effects. Alternative analgesia options, such as non-steroidal anti-inflammatory medicines should be considered a part of multimodal protocols (24). Although some studies have raised concerns about the use of NSAIDs, such as increased bleeding during surgery and renal dysfunction, the others have shown that these medicines do not cause serious platelet dysfunctions, and therefore, are safe to use. Accordingly, considering the right choice of the patients, preoperative NSAIDs can be used without any serious concern; however, meticulous hemostasis should be considered before wound closure. Moreover, the patients should receive enough perioperative intravenous fluid to prevent volume depletion and renal failure.

Limitations of the study

Since the incidence of ileus is low in patients undergoing surgery for cholelithiasis, the comparison between the two intervention groups is generally inaccurate; therefore, it is recommended that a similar study be performed on surgeries with a higher incidence of ileus (such as colon cancer).

Furthermore, although efforts were made to reduce the confounding factors in the development of ileus after surgery (i.e., selection of patients without underlying diseases; utilization of specific medications, standard techniques, and anesthetics; as well as reducing the duration of surgery), numerous factors cause ileus.

As a result, the number of patients under study should be increased to eliminate these factors. It is worth mentioning that the present study suffered from a small sample size.

Conclusion

Based on the results of this study, preoperative administration of rectal indomethacin in elective open cholecystectomies has improved postoperative ileus without significant complications.

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