

Pre-operative Rectal Indomethacin for Reduction of Postoperative Nausea and Vomiting after Laparoscopic Cholecystectomy: A Double-Blind Randomized Clinical Trial

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ABSTRACT

Objective: To evaluate the effect of pre-operative indomethacin suppository on postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

Study Design: A double blind placebo-controlled randomized clinical trial.

Place and Duration of Study: Hazrat Rasoul Akram Hospital, Tehran, Iran, from February 2010 to September 2012.

Methodology: One hundred and thirty patients, scheduled for laparoscopic cholecystectomy, were randomly divided into case and control groups. Sixty-five patients received indomethacin suppository and 70 patients received rectal placebo in the case and control groups respectively. All patients underwent the same protocol in laparoscopic surgery and anesthesia, then nausea and vomiting was recorded after 1, 6, 12 and 24 hours postoperatively and compared between the two groups. Independent-sample t test or Mann-Whitney tests were used for statistical analysis. Level of statistical significance was set at $P \leq 0.05$.

Results: Patients' nausea was statistically lower in the case group at the 1st hour (43.1 vs. 92.9%), 6th hour (20.0 vs. 68.6%) and 12th hour (7.7 vs. 24.3%) after surgery (for all periods, $P < 0.001$). Fewer patients in the case group experienced vomiting at the first (13.8 vs. 51.4%) and 6th hour (0 vs. 20%) after surgery (for both $P < 0.001$). The use of pethidine was also statistically less in the case group in the same hours after surgery (for all of them, $P < 0.001$).

Conclusion: Rectal indomethacin before laparoscopic cholecystectomy led to lower postoperative nausea and vomiting.

Key Words: Laparoscopic cholecystectomy. Indomethacin. Postoperative. Nausea and vomiting.

INTRODUCTION

Postoperative Nausea and Vomiting (PONV), proposed to be a bothersome experience for patients undergoing surgical procedures since 1991,¹ is one of the most common complications of anesthesia and occurs in about one-third of patients undergoing general anesthesia without prophylactic intervention.² Although it is reported to be much less in laparoscopic procedures,³ the rate of PONV is said to be up to 63 - 73% in some studies.⁴ Various risk factors have also been proposed for it.⁵

Several methods and drugs have been used to reduce this complication, including ondansetron, dexamethasone, etc.,⁶⁻⁸ each having a different mechanism, including anti-inflammatory property of dexamethasone.⁹ Non-Steroid anti-inflammatory drugs (NSAIDs) have also been suggested to have anti-emetic effect with the same

mechanism i.e. inhibition of prostaglandins, which are an effective factor in producing emesis.¹⁰

Previous studies have proven the anti-emetic activity of indomethacin and meloxicam in piglets and described the cyclo-oxygenases (COX) inhibiting effect of NSAIDs as their anti-emetic mechanism.¹⁰ Other studies have investigated the pain-controlling effect of rectal indomethacin and reported decrease in PONV as secondary outcome of indomethacin.^{11,12,13}

As far as PONV is still a challenging issue for patients and surgeons,⁹ studying the effect of indomethacin, which has been proven to be effective in postoperative pain management, on PONV is worthwhile, in order to reduce the overuse of various drugs for patients undergoing surgery.

This study was, therefore, designed with the aim of comparing the efficacy of pre-operatively administered indomethacin suppository with placebo in reducing PONV following laparoscopic cholecystectomy.

METHODOLOGY

This study was a randomized double blind clinical trial, approved by the Ethics Committee of Iran University of Medical Sciences (code 89-04-140-12549). The study population included all candidates of laparoscopic cholecystectomy in Hazrat Rasoul Akram Hospital,

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Tehran, Iran, from February 2010 to September 2012. All patients who were between 20 to 65 years old with a body mass index of less than 30 mg/kg² who had no history of using corticosteroids, NSAIDs, antiemetic agents, or chemical substance abuse, no history of chronic heart, renal or liver disease, active peptic ulcer, gastrointestinal bleeding, or any other contraindication of NSAIDs usage, no current pregnancy or breast feeding entered the trial after signing a written informed consent. A checklist was designed in order to collect data and was filled by a Fellowship candidate in laparoscopy while visiting the patients. Exclusion criteria included patients who had nausea and vomiting pre-operatively and those who required additional analgesic or narcotic before or after surgery.

Based on the pilot study and power of 80, the sample size was calculated at 135 patients for the study. Randomization was generated by the statistician of the study (MP) who was the only person aware of the allocation sequence. The allocation was done based on simple randomization by flipping coin one hour before surgery; the side of the coin (heads: control, tails: cases) determined the assignment of each patient.

One hour before surgery, 100 mg indomethacin suppository (Darupakhsh Co., Tehran, Iran) or placebo suppository (produced by the same company) was administered by one nurse, who did not know about the suppository type, as it has been packed uniformly. The patient also did not know which suppository he/she was receiving. The operative and anesthesia procedure were same for both groups; no anti-emetic was used before, during or after the procedure to be able to assess the pure anti-emetic effect of indomethacin. All the procedures (anesthesia and surgery) were performed by one surgical team and with a uniform standard method, as follows:

All patients received deep venous thrombosis prophylaxis of 5000 IU subcutaneous unfractionated heparin every 12 hours the day before and after surgery. After preparing the patients for operating room, 0.1 mg/kg midazolam hydrochloride and 3 µg/kg fentanyl-citrate were administered intravenously. Induction of anesthesia was performed by 2 - 2.5 mg/kg propofol IV and 0.5 mg/kg atracurium besylate IV. Then the patient was oxygenated and intubated. For anesthesia maintenance 100 µg/kg/minute IV infusions of propofol and 10 mg atracurium besylate IV were administered each half an hour, while the patient's oxygenation and ventilation was continued. All patients were under monitoring during surgery.

All patients underwent laparoscopic cholecystectomy by the same technical procedure (4-trocar technique): two 10-mm-ports in the umbilicus and subxyphoid area (first and second ports), and two 5-mm-ports at 5 cm below

the right 12th rib and right flank (third and fourth ports). A 30° lens was inserted through the first port, hook cautery was inserted through the second port, and grasper was inserted through the third port. Gallbladder fundus was then held up to the patient's upper-right side to visualize the cystic duct. Cystic duct and artery were then clipped and cut by Metzenbaum device and the gallbladder was taken out from the second port. At the end for muscle relaxation reversal 0.5 mg/kg neostigmine and 0.2 mg/kg atropine was administered.

Postoperatively, all patients received pethidine at the patients' request and the amount the patient needed was recorded. However, it was preferable, if any other drug rather than indomethacin could be omitted, in order to be able to investigate its pure effect. Yet, according to the Ethics Committee of the study, it was unethical to leave the patient in pain, and therefore, pethidine was prescribed as co-intervention and compared the needed dose between two groups.

The duration of surgery, intra-operative bleeding, gas passing, acute cholecystitis and omental-visceral adhesions were recorded. After surgery any nausea or vomiting in the first 24 hours postpositively was assessed on hours 1, 6, 12, 24, while being visited by the fellowship of laparoscopy, in which any feeling of nausea or any excretion out of the patients' mouth was considered positive. Visual analog scale (VAS) was used to assess patients' pain at these time intervals.

All the analysis was performed with SPSS version 11.5 for windows (SPSS version 13 Chicago. Inc Chicago, Illinois). Quantitative data are expressed as mean (\pm standard deviation) and qualitative data as frequency (percent). Independent-sample t test was used to assess statistical significant differences in normal-distributed data between case and control groups whereas Mann-Whitney test was used for comparing non-normal distributed data. Also for comparison of qualitative data between two groups, Chi-square or Fisher's exact test was used. Level of statistical significance was set at $P < 0.05$.

RESULTS

One hundred and thirty five patients entered the study, who were randomized to receive indomethacin (n=65) or placebo (n=70). Their mean age was 44.81 ± 16.08 years (45.25 ± 15.03 in indomethacin and 44.40 ± 17.10 in placebo group), The indomethacin and placebo groups were similar regarding demographic data (Table I).

Comparison of operative data, time to start gas passing, and dose of pethidine needed between two groups is shown in Table II. After surgery, compared with the placebo group, mean dosage of pethidine needed by the patients was lower in the indomethacin group 50.0

(25.0 - 50.0) vs. 50.0 (50.0 - 100.0) mg, Mann-Whitney test; $P < 0.001$). The mean duration of gas passing in the indomethacin group was less than that of the placebo group 12.00 (6.00 - 24.00) vs. 24.00 (14.00 - 24.00); Mann-Whitney test; $P < 0.001$).

The results of nausea and vomiting at 1st, 6th, 12th and 24th hour after the operation are presented in Table III. At both 1st and 6th hours, frequency of the patients who experienced nausea and vomiting in placebo group is significantly more than indomethacin group (χ^2 test; for all of them $P < 0.001$). Twelve hours after the operation, more patients in placebo group experienced nausea than the indomethacin group (χ^2 test; $P=0.009$) but they experienced vomiting similar to indomethacin group (χ^2 test; $P=0.624$). At 24th hour, the result revealed no significant differences between two groups in nausea and vomiting.

The results of the visual analogue scale are presented in Table IV; independent-sample t test showed that at all periods after the operation, the mean pain score in the indomethacin group was significantly lower than that of the placebo group (independent-sample t test; $P < 0.001$ for all).

Table I: Patients demographic characteristics.

Variables	Case group (n=65)	Control group (n=70)	P-value
Age, mean \pm SD, years*	45.25 \pm 15.03	44.40 \pm 17.10	0.777
Male : Female, No.**	24:41	20:50	0.301

* Independent-sample t test was used; ** χ^2 test was used.

Table II: Comparison of omental visceral adhesions, acute cholecystitis, duration of operation, time to gas passing, dose of narcotic (pethidine) usage between two groups.

Variables	Control group (n=70)	Case group (n=65)	P-value
Omental visceral adhesions, No.(%)	26 (37.1%)	26 (40.0%)	0.733*
Acute cholecystitis, No. (%)	20 (28.6%)	25 (38.5%)	0.223*
Duration of operation, Median (IQR), hours	60.0 (60.0-90.0)	60.0 (60.0-90.0)	0.204**
Time to gas passing, Median (IQR), hours	12.0 (6.0-24.0)	24.0 (14.0-24.0)	< 0.001 **
Mean dose of narcotic (pethidine) usage, Median (IQR) , mg/mL	50.0 (25.0-50.0)	50.0 (50.0-100.0)	< 0.001 **

* χ^2 test was used; ** Non-parametric t-test (Mann-Whitney U test) was used.

Table III: Comparison of nausea and vomiting at 1st, 6th, 12th, 24th hour after the operation in case and control groups.

Time	Nausea, No.(%)			Vomiting, No. (%)		
	Indomethacin (n=65)	Placebo (n=70)	P-value	Indomethacin (n=65)	Placebo (n=70)	P-value
1 st hour	28 (43.1%)	65 (92.9%)	< 0.001 *	9 (13.8%)	36 (51.4%)	< 0.001 *
6 th hour	13 (20%)	48 (68.6%)	< 0.001 *	0 (0%)	14 (20%)	< 0.001 **
12 th hour	5 (7.7%)	17 (24.3%)	0.009*	3 (4.6%)	3 (4.3%)	0.624**
24 th hour	1 (1.5%)	6 (8.6%)	0.117**	0 (0%)	1 (1.4%)	0.519**

* χ^2 test was used; ** Fisher's exact test was used.

Table IV: Mean of visual analog scales of postoperative pain for patients in placebo.

Time	Indomethacin (n=65)	Placebo (n=70)	P-value*
1 st hour	5.78 \pm 1.74	7.29 \pm 1.24	< 0.001
6 th hour	4.78 \pm 1.74	6.63 \pm 1.38	< 0.001
12 th hour	3.09 \pm 1.42	4.87 \pm 1.58	< 0.001
24 th hour	2.46 \pm 1.26	4.07 \pm 1.48	< 0.001

* Independent sample t test was used.

DISCUSSION

As the results of this study show, fewer patients experienced nausea and vomiting in indomethacin group 1, 6, and 12 hours after the operation. Many studies have investigated prevention of PONV after laparoscopic cholecystectomy, and different drugs have been proposed, including cholinergic, histamine, serotonin, and dopamine antagonists.⁹ Yet, PONV has no established drug prevention, as its mechanism is still unclear and complex.

Girod *et al.* have evaluated the effect of four cyclo-oxygenases (COX) inhibitors on 95 piglets and proven the anti-emetic activity of indomethacin and meloxicam in piglets with indomethacin being the most effective anti-emetic agent, reducing the incidence of acute and delayed phase of emesis by 40 and 60%.¹⁰ They have proposed the role of prostaglandins (an inflammatory substance) in producing emesis, which is inhibited by anti-inflammatory agents, such as cyclo-oxygenase inhibitors, effective in NSAIDs.¹³

Girod's study has proven the anti-emetic effect of indomethacin in the dose of 3 mg/ml IV infusion in piglets, in which emesis was induced by high-dose cisplatin. Although the same effect was seen with indomethacin, 100 mg indomethacin suppository was used in patients after laparoscopy cholecystectomy.

In another study, rectal indomethacin was compared with intra-muscular ketorolac for reduction of post-operative pain after laparoscopic cholecystectomy, in which nausea and vomiting were also reported. They have demonstrated equal efficacy for both drugs on early postoperative pain and nausea/vomiting.¹³ These findings were also confirmed in the study performed by Turner and colleagues.¹¹

Although these two studies have proven that both ketorolac and indomethacin have equal effects in reducing nausea/vomiting, their results are not comparable to this

study, as their first aim was not assessing nausea / vomiting and they had no placebo group. Yet, they confirm the hypothesis that indomethacin can control PONV.

Jangjoo *et al.* have also proven the effect of 100 mg rectal indomethacin on postoperative pain after open appendectomy and have shown a significant reduction in the VAS score of indomethacin group.¹²

The higher VAS score and more pethidine needed by our placebo group also confirms the efficacy of indomethacin on postoperative pain, as previously proven in many studies.^{12,15}

These results also showed significant earlier gas passing in the indomethacin group, which can be related to the effect of indomethacin on postoperative ileus (POI).¹⁶ Other studies have proven the positive effect of other NSAIDs, like ketorolac, on bowel motility and gastrointestinal (GI) transit and, therefore, earlier resolution of POI and decreased PONV.¹⁷ Some other studies have compared the effect of indomethacin and ketorolac on POI in rats and have proven the earlier GI transit in indomethacin group.¹⁸ Regarding the clinical nature of this study, the mechanism of indomethacin in reducing PONV has not been uncovered in this trial. It may be its simultaneous effect on POI that has induced less PONV. Yet, molecular studies are required to assess the exact mechanism.

As far as the authors are concerned, this study is the first randomized trial evaluating the anti-emetic effect of indomethacin after laparoscopic cholecystectomy.

These results clearly showed that administration of rectal indomethacin pre-operatively for patients undergoing laparoscopic cholecystectomy can significantly reduce PONV and, therefore, reduce the patients' need for opioids. It is advised, accordingly, to use rectal indomethacin in patients undergoing laparoscopic cholecystectomy after proper selection of patients regarding contraindication of NSAIDs.

CONCLUSION

The use of rectal indomethacin not only reduced postoperative pain after laparoscopic cholecystectomy, but also decreased postoperative nausea/vomiting in these patients and thus reduced the need for other drugs, including opioids and analgesics.

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