

# INDOMETHACIN AND KETOROLAC GIVEN PREOPERATIVELY ARE EQUALLY EFFECTIVE IN REDUCING EARLY POSTOPERATIVE PAIN AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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**OBJECTIVE:** To evaluate the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) on pain after laparoscopic cholecystectomy.

**DESIGN:** A prospective, randomized, placebo-controlled, double-blind study.

**SETTING:** A university hospital.

**PATIENTS:** Fifty-two patients with cholelithiasis but without known allergy to one of the study drugs, history of bleeding, peptic ulcer disease, known cardiac, lung or renal disease, abnormal liver function or use of opiates or NSAIDs within 2 weeks before operation. Patients were assigned to one of three groups, and treatment was randomized by placing the drugs in sealed, numbered envelopes.

**INTERVENTION:** Administration of the NSAIDs ketorolac, intramuscularly, or indomethacin, rectally, before laparoscopic cholecystectomy.

**MAIN OUTCOME MEASURES:** Postoperative pain scored on a visual analogue scale and by nurse assessment, total dose of fentanyl citrate given, and nausea or emesis.

**RESULTS:** Patients in the placebo group reported significantly more pain than either NSAID group ( $p < 0.05$ ) and were reported as having significantly more pain by the nurses ( $p < 0.05$ ). These patients were subsequently treated with a higher mean postoperative dose of fentanyl citrate than either NSAID group ( $p < 0.05$ ). Furthermore, the placebo group reported more nausea and emesis ( $p < 0.05$ ). There was no significant difference in any of the parameters measured between the ketorolac or indomethacin group.

**CONCLUSIONS:** The data demonstrate that the NSAIDs ketorolac and indomethacin, administered preoperatively, decrease early postoperative pain and nausea after laparoscopic cholecystectomy and are equally efficacious in producing these results.

**OBJECTIF :** Évaluer l'efficacité des anti-inflammatoires non stéroïdiens (AINS) pour le contrôle de la douleur après une cholécystectomie par laparoscopie.

**CONCEPTION :** Étude prospective randomisée à double insu contrôlée par placebo.

**CONTEXTE :** Hôpital universitaire.

**PATIENTS :** Cinquante-deux patients atteints de cholélithiase mais sans allergie connue aux médicaments à l'étude, ni antécédent de saignement, d'ulcère gastro-duodéal, de cardiopathie, de pneumopathie ou de nérophathie connue, de fonction hépatique anormale ou d'utilisation d'opiacés ou d'AINS dans les 2 semaines précédant l'intervention. Les patients ont été répartis en trois groupes et l'on a randomisé le traitement en plaçant les médicaments dans des enveloppes numérotées et scellées.

**INTERVENTION :** Administration d'AINS comme le kétorolac, par voie intramusculaire, ou l'indométhacine, par voie rectale, avant une cholécystectomie par laparoscopie.

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*Accepted for publication Oct. 11, 1995*

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PRINCIPALES MESURES DES RÉSULTATS : Douleur postopératoire évaluée selon une échelle visuelle et par le personnel infirmier, dose totale administrée de citrate de fentanyl et nausées ou vomissements.

RÉSULTATS : Les patients qui ont reçu le placebo ont signalé une douleur beaucoup plus importante que ceux qui ont reçu des AINS ( $p < 0,05$ ) et le personnel infirmier a aussi signalé qu'ils ressentaient plus de douleur ( $p < 0,05$ ). On leur a administré par la suite une dose postopératoire moyenne plus élevée de citrate de fentanyl qu'aux sujets des deux groupes qui avaient reçu des AINS ( $p < 0,05$ ). De plus, les sujets qui ont reçu un placebo ont signalé plus de nausées et de vomissements ( $p < 0,05$ ). Il n'y avait pas d'écart important entre les paramètres mesurés chez les sujets qui ont reçu du kétorolac ou de l'indométhacine.

CONCLUSIONS : Les données démontrent que des AINS comme le kétorolac et l'indométhacine, administrés avant l'intervention, diminuent les premières douleurs et nausées postopératoires après une cholécystectomie par laparoscopie et qu'ils sont aussi efficaces l'un que l'autre.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics and have been advocated for use in minor surgery, including laparoscopic procedures. They have been found to reduce postoperative pain after some laparoscopic gynecologic procedures.<sup>1,2</sup> The majority of cholecystectomies are now performed laparoscopically.<sup>3</sup> However, the effects of different postoperative analgesics have not been thoroughly investigated in patients recovering from laparoscopic cholecystectomy. In this study, the possibility that preoperative NSAIDs might reduce postoperative pain and nausea after laparoscopic cholecystectomy was investigated using a prospective, placebo-controlled and double-blind protocol.

## METHODS

The study was approved by the Queen's University ethics committee and was conducted at the Kingston General Hospital. The inclusion criteria were any American Society of Anesthesiologists (ASA) score I or II patients booked for a simple laparoscopic cholecystectomy by the study surgeon. The exclusion criteria were any allergy to a study drug, a history of prolonged bleeding or peptic ulcer disease, known cardiac, lung or renal disease, abnormal liver function test results and the use of either an opiate or NSAID within 2 weeks of the

surgery. Patients were withdrawn from the study if an open cholecystectomy became necessary. The study was terminated once 60 patients had been enrolled or statistical significance had been determined by an independent observer. Sixty patients were calculated to be the sample size required to give an 80% probability of detecting a difference between treatment groups with a type I error of 0.05.

Patients enrolled in the study signed an informed consent form, and baseline results were obtained for both the visual analogue scale and the postoperative questions. A standard anesthetic was administered to all patients. Induction was achieved with fentanyl citrate (2 µg/kg) and propofol (2 mg/kg), and orotracheal intubation was facilitated with succinylcholine (1 mg/kg). Anesthesia was maintained with a propofol infusion of 100 µg/kg per minute, vecuronium bromide (0.1 mg/kg) and fentanyl citrate boluses. The patients were ventilated with up to 1% isoflurane in 100% oxygen. After induction of anesthesia, the patients were then randomly allocated to one of the three treatment groups; a placebo group, a ketorolac group and an indomethacin group. This was done by the operating room nurse, who removed the study drugs from a sealed and numbered envelope. All patients received both a deltoid intramuscular injection and a rectal suppository. The ketorolac group received the manufacturer's recommended injection of

30 mg of ketorolac and a glycerin suppository; the indomethacin group received an injection of normal saline and the manufacturer's recommended 100 mg indomethacin suppository; the placebo group received an injection of normal saline and a glycerin suppository. The patient, surgeon and researcher were all blinded to the patient's treatment group.

The surgery was a standard four-trocar laparoscopic cholecystectomy. A Veress needle was used to obtain the pneumoperitoneum, and electrocautery was used for dissection. The gallbladder was removed through the infraumbilical incision, which was enlarged with a Kelly forceps. This incision was closed with a single figure-of-eight stitch of 1-0 Vicryl (Ethicon, Peterborough, Ont.) through the fascia. Both 10 mm trocar incisions were closed with three interrupted, inverted subcuticular stitches of 4-0 Vicryl and all four incisions were infiltrated with 5 mL of 0.05% bupivacaine. The patients were transferred to the recovery room, where they immediately received 10 mg of metoclopramide intravenously. All the patients were held in the recovery room for 120 minutes while the data were collected.

Data were collected at 15, 30, 60 and 120 minutes after arrival in the recovery room by the researcher. The patients scored their pain using a vertical 10-cm visual analogue scale arranged such that 0 cm represented no pain and 10 cm represented the

worst pain the patient could imagine. The patients then answered questions about nausea and emesis, breathing, drowsiness, itching, headaches and deltoid or rectal pain. Patients complaining of pain were given 25 µg boluses of fentanyl citrate every 5 minutes until they were comfortable and requested no further analgesia when it was offered by the recovery room nurses. Their nausea or emesis was similarly treated with 25 mg of diphenhydramine hydrochloride. When the patients were finally discharged from the recovery room, the nurses commented on whether the patient had been comfortable or agitated during the initial recovery period. Agitated patients were those who, after the emergence reaction from anaesthesia, continued to be hyperactive, combative, inconsolable and difficult to settle. The anaesthesia record was used to collect data on total operative time, propofol dose, intraoperative and postoperative fentanyl citrate doses and patient agitation.

The data were analysed by a non-parametric analysis of variance for multiple comparisons and the Mann-Whitney test for intergroup comparison; a *p* value of less than 0.05 was considered significant. Data are presented as the means (and standard deviation).

**RESULTS**

The study was terminated after 56 patients had been enrolled because statistical significance was reached. Data were analysed from 52 patients; 4 patients were unable to score the visual analogue scale 15 minutes after admission to the recovery room because of excessive sedation. These four patients were divided among all treatment groups.

There were no statistically significant differences in the patient parameters among the three treatment groups (Table I). Similar results were found for the operative data (Table II). Furthermore, there were no reported cases

of hemorrhage or operative complications in any treatment group.

The results of the visual analogue scale, patient agitation and the total postoperative dose of fentanyl citrate are presented in Table III. The placebo group scored a mean of 7.2 cm at 15 minutes postoperatively whereas the ketorolac and indomethacin groups scored 3.6 cm and 3.7 cm respectively. The difference between the placebo group and the other two groups was significant (*p* < 0.05). The scores on the visual analogue scale for the remainder of the patients' postoperative recovery revealed no significant differences between any of the three groups. Patient agitation revealed a similar trend. In the placebo group, the nurses recorded that 33% of patients were agitated compared with 11% of the patients in the ketorolac group and none of the patients in the indomethacin group (*p* < 0.05).

The total postoperative fentanyl citrate dose reflects treatment based on the patients' request for opiates when offered. The placebo group was administered a mean of 2.0 µg/kg whereas the ketorolac group received only 0.46 µg/kg and the indomethacin group only 0.56 µg/kg (*p* < 0.05).

Results between the ketorolac group and the indomethacin group for visual analogue scale, patient agitation and mean postoperative fen-

**Table I**  
**Age and Sex of Patients in the Three Study Groups**

Sex/age	Treatment group		
	Placebo, <i>n</i> = 18	Ketorolac, <i>n</i> = 17	Indomethacin, <i>n</i> = 17
Male/female	6/12	7/10	7/10
Mean (and SD) age, yr	43.1 (14.4)	49.0 (11.2)	47.8 (14.5)

**Table II**  
**Duration of Anesthesia, Total Dose of Fentanyl Citrate and of Propofol Given During Operation for Patients in the Three Study Groups**

Parameter	Treatment group		
	Placebo, <i>n</i> = 18	Ketorolac, <i>n</i> = 17	Indomethacin, <i>n</i> = 17
Mean (and SD) duration of anesthesia, min	72 (21.9)	80 (17.3)	82 (21.2)
Mean (and SD) total dose of fentanyl citrate, µg/kg per min	0.04 (0.01)	0.03 (0.014)	0.041 (0.014)
Mean (and SD) total dose of propofol, mg/kg per min	114 (28.3)	120 (46.6)	123 (25.3)

tanyl citrate dose revealed no significant differences. Furthermore, there was no significant difference between males and females in all the parameters measured.

With respect to the postoperative questionnaire (Table IV), there were no significant differences between the treatment groups for all the adverse effects except nausea. In the placebo group, 44% of patients reported nausea or emesis, whereas in both the ketorolac and indomethacin groups, only 24% of patients reported these symptoms ( $p < 0.05$ ).

DISCUSSION

When compared with the placebo group, the preoperative use of ketorolac and indomethacin decreased early postoperative pain after laparoscopic

cholecystectomy. Patients in both treatment groups requested less opiate analgesia than those in the placebo group because they experienced less pain within the first 15 minutes in the recovery room. The initial visual analogue scales were higher for the placebo group, and patients in that group requested more fentanyl citrate to achieve the same level of comfort as the NSAID groups. There were no significant differences between the placebo and treatment groups in the visual analogue scales or opiate requirement after the 15-minute measurement. This suggests that the initial difference in the degree of pain experienced by patients in the treatment and placebo groups was overcome by the nurse's successful treatment, in the placebo group, in administering more fentanyl citrate

between the first and second visual analogue measurement. Furthermore, initial postanesthetic agitation was reported to be more frequent in the placebo group, which again may reflect the increased level of pain in those patients during early recovery.

Several other studies<sup>4-9</sup> have reported similar results with both these medications given preoperatively for different operative procedures. NSAIDs are thought to act primarily by inhibiting prostaglandin synthesis from arachidonic acid, thereby blocking the effects of prostaglandins on inflammation and receptor sensitivity. However, NSAIDs have other effects that may influence their analgesic properties, including changes in membrane-associated enzyme activity and anion transport, oxidative phosphorylation and the incorporation of arachidonic acid into macrophage membranes. Research has demonstrated that NSAIDs inhibit neutrophil activation and aggregation and second messenger generation in the absence of effects on prostaglandin synthesis.<sup>10</sup> Furthermore, NSAIDs have been shown to have effects in the spinal cord that mediate the perception of pain. Our dose was administered immediately before surgery and, given that the mean time of the operation was approximately equal to that for the NSAIDs to obtain therapeutic serum levels, it is hard to believe that the NSAIDs could have effected the synthesis and release of inflammatory mediators that would have been initiated at the beginning of the operation. However, if NSAIDs exert their analgesic effect through other mechanisms instead of, or in addition to, their effects on prostaglandin metabolism, a single perioperative dose may be sufficient to alter the patient's perception of pain by these other pathways.

Although there are no studies in

Table III

Measurements of Postoperative Pain for Patients in the Three Study Groups

Parameter	Treatment group		
	Placebo, n = 18	Ketorolac, n = 17	Indomethacin, n = 17
Mean (and SD) score on visual analogue scale at 15 min, cm	7.2 (2.6)	3.6 (2.2)*	3.7 (2.0)*
Agitation, % of patients	33	11*	0*
Mean (and SD) total dose of fentanyl citrate, µg/kg	2.0 (0.58)	0.46 (0.5)*	0.56 (0.6)*

\*p < 0.05 v. placebo

Table IV

Percentage of Patients with Adverse Postoperative Symptoms in the Three Study Groups

Parameter	Treatment group		
	Placebo, n = 18	Ketorolac, n = 17	Indomethacin, n = 17
Nausea or emesis	44	24*	24*
Itching	0	0	0
Headache	11	6	12
Shortness of breath	22	18	12
Rectal/deltoid pain	0	0	0

\*p < 0.05 v. placebo

the literature comparing the direct pharmacologic equivalencies of indomethacin and ketorolac, the dose used for each study drug was that recommended by the manufacturer. We chose to administer the medication following induction of anesthesia to minimize patient discomfort and to guarantee a standard time of administration since most of the patients were ambulatory. Not one patient reported an adverse effect from the deltoid or rectal administration of the drugs. Furthermore, there were no postoperative complications from hemorrhage. There are reports<sup>11,12</sup> of increased blood loss following preoperative administration of NSAIDs, and one study<sup>12</sup> reported an increase in bleeding time, although it was not clinically relevant when compared with the placebo group. Although NSAIDs generally should be avoided before surgery, severe platelet dysfunction is associated primarily with acetylated salicylates; other classes of anti-inflammatory drugs have a negligible effect on platelet function and can be used perioperatively with rare hemorrhagic complications.<sup>13</sup> Furthermore, therapeutic levels were only obtained at the end of surgery, and laparoscopic cholecystectomy usually involves minimal dissection and hemorrhage.

The patients who received NSAIDs preoperatively also reported less nausea or emesis than patients in the placebo group, who had more pain and received approximately four times as much fentanyl citrate postoperatively. The increased frequency of nausea or emesis in the placebo group is likely a reflection of the administration of more opiates, with their adverse effect on gastrointestinal function.

Our data suggest that ketorolac given intramuscularly and indomethacin given rectally are equally ef-

ficacious in reducing early pain after laparoscopic cholecystectomy. Intramuscular ketorolac reaches peak serum levels after an average of 50 minutes, and rectal indomethacin required approximately the same amount of time. Our results reveal no appreciable difference in clinical effect between ketorolac and indomethacin. Therefore, the increased cost of ketorolac does not appear warranted. Our findings are consistent with those of a previous study,<sup>14</sup> which compared these drugs for gynecologic and breast surgery.

In summary, the preoperative use of ketorolac or indomethacin reduces the early postoperative pain and nausea after laparoscopic cholecystectomy, thereby improving the quality of recovery. Further research is required to determine the duration of this effect and, with the introduction of ambulatory laparoscopic cholecystectomy, analgesic regimens that can reduce postoperative pain and nausea may reduce hospital admissions. This research is in progress.

## References

1. Crocker S, Paech M: Preoperative rectal indomethacin for analgesia after laparoscopic sterilisation. *Anaesth Intensive Care* 1992; 20: 337-340
2. Ding Y, White PF: Comparative effects of ketorolac, dezocine, and fentanyl as adjuvants during outpatient anesthesia. *Anesth Analg* 1992; 75: 566-571
3. Steiner CA, Bass EB, Talamini MA et al: Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. *N Engl J Med* 1994; 330: 403-408
4. Pavy T, Medley C, Murphy DE: Effect of indomethacin on pain relief after thoracotomy. *Br J Anaesth* 1990; 65: 624-627
5. Stouten EM, Armbruster S, Houmes RJ et al: Comparison of ketorolac and morphine for postoperative pain after major surgery. *Acta Anaesthesiol Scand* 1992; 36: 716-721
6. Segstro R, Morley-Forster PK: Indomethacin as a postoperative analgesia for total hip arthroplasty. *Can J Anaesth* 1991; 38: 578-581
7. Twiston-Davies CW, Goodwin MS, Baxter PJ: Rectal indomethacin for postoperative pain in orthopaedic surgery. *J Bone Joint Surg [Br]* 1990; 72: 510-511
8. Nissen I, Jensen KA, Ohrstrom JK: Indomethacin in the management of postoperative pain. *Br J Anaesth* 1992; 69: 304-306
9. Murphy DF, Medley C: Preoperative indomethacin for pain after thoracotomy: comparison with postoperative indomethacin. *Br J Anaesth* 1993; 70: 298-300
10. Abramson SB, Weissmann G: The mechanisms of action of nonsteroidal anti-inflammatory drugs. *Arthritis Rheum* 1989; 32: 1-9
11. Engel C, Lund B, Kristensen SS et al: Indomethacin as an analgesic after hysterectomy. *Acta Anaesthesiol Scand* 1989; 33: 498-501
12. McGlew IC, Angliss DB, Gee GJ et al: A comparison of rectal indomethacin with placebo for pain relief following spinal surgery. *Anaesth Intensive Care* 1991; 19: 40-45
13. Miller LG, Pritchard JG: Current issues in NSAID therapy. *Prim Care* 1990; 17: 589-601
14. Morley-Forster P, Newton PT, Cook NJ: Ketorolac and indomethacin are equally efficacious for the relief of minor postoperative pain. *Can J Anaesth* 1993; 40: 1126-1130