Ketorolac and indomethacin are equally efficacious for the relief of minor postoperative pain

Patricia Morley-Forster FRCPC, Peter T. Newton MD,
Mary-Jo Cook RN

Injectable ketorolac is an effective analgesic in ambulatory surgery patients. However, no studies have compared ketorolac with other NSAIDs in this setting. The analgesic efficacy of intramuscular ketorolac, rectal indomethacin and placebo was compared in healthy women undergoing gynaecological or breast surgery as outpatients. Ninety patients received 30 mg im ketorolac, 100 mg pr indomethacin or placebo in a prospective, randomized, double-blind manner. A standardized anaesthetic protocol was followed. Patients graded their pain on a 10 cm visual analogue scale in the recovery room, twice in the surgical day care unit and during the car ride home. The patients' postoperative fentanyl requirements, time to recovery milestones, and side effects were recorded. The placebo group received more fentanyl in the PACU but did not achieve the same pain relief as either of the NSAID-treated group (ketorolac 44 ± 53 µg, indomethacin 39 ± 55 µg, placebo 87 ± 100 µg, $P < 0.05$). Patients who received an NSAID had less pain at 15 and 90 min ($P < 0.05$). The PACU stay was longer for the placebo group (ketorolac 50 ± 13 min, indomethacin 49 ± 12 min, placebo 62 ± 35 min, $P < 0.05$). Time to ambulation was also longer in the placebo group (ketorolac 117 ± 25 min, indomethacin 121 ± 49 min, placebo 140 ± 51 min, $P < 0.05$). However, no differences were observed between

the two NSAIDs. Side effects were similar in all groups. We conclude that im ketorolac and pr indomethacin are equally effective analgesics in this group of patients.

Le kétorolac injectable est un analgésique efficace en chirurgie ambulatoire. Cependant, aucune étude ne compare le kétorolac avec les AINS utilisés sous les mêmes conditions. Cette étude compare l'efficacité analgésique du kétorolac intramusculaire, de l'indométhacine rectale et d'un placebo chez des patientes ambulatoires non tarées soumises à une chirurgie gynécologique ou mammaire. Au cours d'une étude prospective, randomisée et à double insu, 90 patientes reçoivent du kétorolac 30 mg im, de l'indométhacine 100 mg pr ou un placebo. Un protocole anesthésique standard est utilisé. Les malades évaluent leur douleur sur une échelle visuelle analogue de 10 cm à la salle de réveil, deux fois dans le centre de soins de chirurgie d'un jour et pendant le retour en automobile vers le domicile. Les besoins en fentanyl postopératoire, les incidents du réveil et les effets secondaires sont notés. Les patientes du groupe placebo reçoivent plus de fentanyl à la salle de réveil et sont moins soulagées que les deux groupes traités aux AINS (kétorolac 44 ± 53 µg, indométhacine 39 ± 55 µg, placebo 87 ± 100 µg, $P < 0,05$). Le délai précédant l'ambulation est aussi prolongé dans le groupe placebo (kétorolac 117 ± 25 min, indométhacine 121 ± 49 min, placebo 140 ± 51 min, $P < 0,05$). Toutefois, on ne trouve pas de différence entre les deux groupes AINS. Les effets secondaires sont les mêmes. Nous concluons que le kétorolac im et l'indométhacine pr sont des analgésiques d'une efficacité égale pour notre groupe de patientes.

Key words

ANALGESIA: postoperative;
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indomethacin, ketorolac;
PAIN: postoperative;
SURGERY: ambulatory.

From the Department of Anaesthesia, St. Joseph's Health Centre, University of Western Ontario, London, Ontario, Canada N6A 4V2

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Address correspondence to: Dr. P. Morley-Forster.

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Non-steroidal anti-inflammatory drugs have been used for postoperative analgesia since the early 1970's.¹⁻³ Many anaesthetists first became aware of the efficacy of NSAIDs for postoperative pain relief when injectable ketorolac tromethamine was released on the North American market. Intramuscular ketorolac 30 mg has been shown to be as efficacious as morphine 12 mg and superior to morphine 6 mg im for the relief of moderate to severe postoperative pain.⁴

Indomethacin has been proved to provide effective analgesia postoperatively either as the sole agent⁵ or in conjunction with opioids.^{6,7} The onset time of 20–30 min for an indomethacin suppository⁸ is equivalent to the onset time of *im* ketorolac.⁹

Although there are many studies comparing ketorolac with other opioids, there are very few comparisons of ketorolac with other NSAIDs. In a prospective, randomized, double-blind trial we compared the efficacy of *im* ketorolac and *pr* indomethacin for pain relief after outpatient surgery.

Methods

Approval for this study was granted by the institutional review board. The subjects studied were women aged 18–65 yr, ASA 1–2 undergoing diagnostic laparoscopy, laser conization of cervix for carcinoma *in situ*, or breast biopsy. Exclusion criteria were a history of possible pregnancy, lactation, NSAID sensitivity, coagulopathy, narcotic abuse, or a history of previous peptic ulcer disease.

After written, informed consent had been obtained, subjects were brought to the operating room fasting and unpremedicated. In the operating room, routine monitors were applied and a standard anaesthetic protocol was followed in all patients. Induction consisted of fentanyl $1 \mu\text{g} \cdot \text{kg}^{-1}$, propofol $2\text{--}3 \text{ mg} \cdot \text{kg}^{-1}$. If intubation was planned, d-tubocurarine 3 mg was given as a defasciculant three minutes before succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$. Anaesthesia was maintained with nitrous oxide 50% in oxygen, isoflurane 1–2%, and atracurium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ as needed for muscle relaxation.

After induction, each patient was randomly assigned to one of three groups. The hospital pharmacy prepared the randomization table and all study drugs and placebos beforehand. One group (KET) received 30 mg ketorolac *im* and a placebo suppository; the second group (IND) received 100 mg indomethacin *pr* and a placebo injection; the third group (PLAC) received both a placebo injection and a placebo suppository. At the completion of surgery, neuromuscular blockade was reversed with a standard dose of glycopyrrolate and neostigmine.

Subjects were transferred awake to the Post-anaesthetic Care Unit (PACU). In the PACU, intravenous fentanyl $50 \mu\text{g}$ q 15 min was administered by the research nurse if the patient requested analgesia. Standard visual analogue pain scores were obtained at 15, 60, and 90 min after emergence from anaesthesia as well as during the ride home. The patient marked their degree of pain on an open-ended horizontal 10 cm line with 0 being no pain and 10 being the worst pain imaginable. The first postoperative pain score was obtained before administration of any fentanyl. The patients recorded their subjective feeling of sedation on a visual analogue sedation

TABLE I Demographic data for the three treatment groups

Variable	Ketorolac <i>n</i> = 31	Indomethacin <i>n</i> = 31	Placebo <i>n</i> = 25
Age (yr)	37 ± 14	35 ± 8	35 ± 11
Wt (kg)	62 ± 13	65 ± 13	67 ± 14
OR time (min)	20 ± 14	20 ± 11	18 ± 11
Diagnostic laparoscopy/ cervical conization	24	27	25
Breast surgery	7	4	0
No. intubated	10	10	13

scale with 0 being completely alert and 10 being asleep. The total amount of fentanyl administered in the PACU was recorded.

Patients were discharged from the PACU at the discretion of the nurses using the usual criteria of adequately controlled pain and a post-anaesthetic recovery room (PARR) score greater than 7 out of 10. The PARR score assesses patient colour, respiration, circulation, consciousness, and activity each on a scale of 0–2 giving a maximum possible total of 10. Patients were discharged home from the Surgical Day Care Unit (SDCU) when they were able to walk unassisted and could tolerate oral fluids. The times to these recovery milestones were noted as well as duration of stay in PACU and total postoperative stay. Side effects of nausea or vomiting, drowsiness, dizziness, itching and rectal fullness were recorded.

The pain and sedation scores, PARR scores and recovery milestones were analysed using analysis of variance (ANOVA). The pain scores were subjected to *a priori* contrast of NSAID groups vs placebo. Fentanyl requirements were compared with one-way ANOVA. The incidence of side effects was tested using Chi square analysis with Fisher's exact test where appropriate. Data are presented as means ± SD.

Results

Of 93 women approached regarding this study, 90 agreed to participate. Three patients were excluded from analysis for failure to follow the anaesthetic protocol of the study. This left 31 patients in the ketorolac group, 31 in the indomethacin group and 25 in the placebo group. The groups were similar with regards to age, weight, type and duration of surgery (Table I).

Both of the groups treated with an NSAID required less fentanyl than the placebo group ($P < 0.05$) but there was no difference in postoperative narcotic consumption between the KET and IND groups (KET $44 \pm 53 \mu\text{g}$, IND $39 \pm 55 \mu\text{g}$, PLAC $87 \pm 100 \mu\text{g}$, $P < 0.05$).

Postoperative pain scores were lower at 15 and 90 min in patients who received NSAID ($P < 0.05$) but no different at 60 min or on the way home (Figure 1). Pain

FIGURE 1 Postoperative pain scores. Mean pain scores ($\pm$ SEM) at 15, 60, 90 min postoperatively and on the car ride home. *Placebo group significantly different. $P < 0.05$.

scores were similar in the ketorolac and indomethacin groups at all times.

Sedation analogue scores showed no inter-group differences at any time (Figure 2).

The time spent in recovery room and the time to ambulation were shorter in the NSAID-treated groups ($P < 0.05$, Table II) with no difference between the ketorolac and indomethacin groups. Time to oral intake and total postoperative stay were the same in all three groups.

The overall incidence of side effects was low and showed no differences among groups (Table III).

Discussion

Non-steroidal anti-inflammatory drugs improved outcome in this group of surgical outpatients by reducing postoperative pain and shortening recovery times in comparison with the control group. Their analgesic efficacy is related to their ability to reduce prostaglandin accumulation at the site of surgical trauma.

Cell membrane injury leads to release of bradykinin, histamine, and arachidonic acid. All NSAIDs inhibit cyclooxygenase, the enzyme required to convert arachidonic acid to prostaglandins. Prostaglandins facilitate inflammation by potentiating bradykinin and histamine producing a zone of hyperalgesia to both mechanical and thermal stimuli at the injured site.¹⁰ In addition, prostaglandins stimulate pain receptors to release Substance P, a potent inflammatory mediator, from cell bodies of sensory nerve fibres.¹¹

Indomethacin suppositories 100 mg q8h were reported by Reasbeck *et al.* in 1982 to be an effective adjunct to opioid analgesia for abdominal surgery.⁶ Other studies

FIGURE 2 Postoperative sedation scores. Mean sedation scores ($\pm$ SEM) at 15, 60 and 90 min postoperatively. (NS).

TABLE II Comparison of recovery milestones among the three groups

	Ketorolac	Indomethacin	Placebo
PACU time (min)	50 $\pm$ 13	49 $\pm$ 12	62 $\pm$ 35*
Time to liquids (min)	50 $\pm$ 16	47 $\pm$ 21	57 $\pm$ 33
Time to stand (min)	117 $\pm$ 25	121 $\pm$ 49	140 $\pm$ 51*
Total postop stay (min)	148 $\pm$ 35	151 $\pm$ 46	167 $\pm$ 54

*Statistically significant to $P < 0.05$.

TABLE III Side effects experienced in the three treatment groups

Side effects	Ketorolac n = 31	Indomethacin n = 31	Placebo n = 25
Nausea/vomiting	3	3	5
Drowsiness	2	4	1
Dizziness	1	0	1
Itching	0	0	1
Rectal fullness	1	2	0

No statistical difference in side effects among the three treatment groups.

using different postoperative pain models have confirmed this finding.^{12,13} The dose required for analgesia is higher than that required for anti-inflammatory activity.¹⁴

Ketorolac 30 mg *im* has been shown to be equivalent to 12 mg morphine *im* and 100 mg meperidine *im*.⁹ Suggested reasons for its analgesic potency are that it blocks both cyclooxygenase and lipoxygenase preventing synthesis of both prostaglandins and leukotrienes.¹⁵ Another hypothesis, supported by animal work, is that ketorolac may cause the release of endogenous opioids.¹⁶

We compared ketorolac *im* and indomethacin *pr* be-

cause they share a similar onset time of 20 to 30 min. Both can be given just after induction of anaesthesia and produce reliable postoperative analgesia even for short procedures. Injectable indomethacin is not available in North America for *im* injection.

In this study, surgical incision occurred almost immediately after NSAID administration so that their beneficial postoperative effects can not be attributed to pre-emptive analgesia. Murphy and Medley found, in thoracotomy patients, that the quality of pain relief and reduction in postoperative opioid requirements was the same whether indomethacin was given the night before or at the conclusion of surgery.¹⁷ One of their hypotheses was that the central sensitization to pain outweighed the peripheral effect of prostaglandin inhibition.

Preoperative oral NSAIDs have been used successfully to alleviate pain and reduce discharge times after laparoscopic tubal occlusion.^{18,19} Brown *et al.* have shown that a single oral preoperative dose of 550 mg of naproxen sodium was as effective at one hour postoperatively in gynaecological, orthopaedic and general surgical patients as a single injection of 10 mg of morphine.²⁰ The potential problems with oral, as opposed to parenteral, NSAIDs are a delayed and unpredictable onset, and a higher incidence of gastric irritation when given on an empty stomach.

The incidence of side effects in the NSAID-treated groups was no different from that of the placebo group. However, we excluded patients with a history of previous ulcer disease or coagulopathy.

Ketorolac does not appear to offer any advantage in this postoperative pain model over rectal indomethacin. While and Watcha have pointed out in a recent editorial the need for cost-benefit assessment of new drugs.²¹ Ketorolac, although unquestionably a potent NSAID, may not be required to control pain of minor to moderate severity. Ketorolac should be compared with other NSAIDs at equipotent dosages to allow clinicians to decide on the best postoperative analgesia at the lowest cost.

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