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A comparison of ketorolac and fentanyl for controlling postoperative uterine cramping pain in ambulatory surgery patients

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the pain of dysmenorrhea by inhibiting the synthesis of prostaglandins that cause the uterus to contract. Studies have not been undertaken previously to determine the effectiveness of NSAIDs in controlling uterine pain resulting from gynecological surgery. This study compares the NSAID ketorolac tromethamine to fentanyl, a commonly used opioid, in 100 women undergoing gynecological surgery in an ambulatory setting. Subjects were randomly assigned to receive either fentanyl or ketorolac IM at the end of the surgical procedure. Uterine cramp pain and non-uterine pain were rated on separate verbal analog scales in the recovery room. Incidence of nausea and vomiting and need for postoperative opioid analgesics were also compared between the two study groups. No significant differences were found between the two groups in the severity of uterine cramp pain, in the need for supplemental analgesia or in the incidence of nausea or vomiting. Both drugs appeared to provide reasonable patient comfort, but in the sub-group of patients who required postoperative opioid, the ketorolac group had lower non-uterine pain scores in the late postoperative period than did the fentanyl group. The absence of clear superiority of the NSAID may indicate that a biochemical pathway other than the prostaglandin mechanism is involved in the production of postoperative uterine cramping pain. Copyright © 1996 Elsevier Science B.V.

Keywords: Fentanyl; Ketorolac; Uterine pain; Ambulatory anesthesia; Postoperative analgesia; Prostaglandins

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce menstrual uterine cramping by inhibiting the synthesis of prostaglandins which cause the uterus to contract [1–3]. Gynecological surgery such as laparoscopy with uterine instrumentation and hysteroscopy can also produce uterine cramping pain postoperatively. Because NSAIDs are thought to be more effective than opioids in relieving menstrual cramps, it has been reasoned that they may also be more successful in controlling postoperative uterine pain. Several studies have compared NSAIDs and opioids as analgesics after outpatient laparoscopic surgery, however, none of these studies distinguished uterine cramping pain from other postoperative pain [4–7]. The results of several of these studies appear to be in conflict, but the inconsistencies may be due to differences in experimental protocol such as dose, method, and time of drug administration.

Studies comparing analgesics after cesarean section and vaginal delivery have looked specifically at uterine cramp pain [8–10]. These studies, in contrast to the dysmenorrhea literature, have not consistently shown NSAIDs to be superior to opioids in analgesic performance. The question of whether NSAIDs are effective analgesics for uterine cramp pain resulting from gynecological surgery remains open.

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Ketorolac tromethamine is the first injectable NSAID available in the United States. It inhibits prostaglandin synthesis and is an effective analgesic for pain resulting from a variety of surgical procedures [4]. Studies indicate that its analgesic properties are comparable or superior to opioids such as meperidine, morphine and fentanyl when equivalent doses are compared [5,11–13]. It has been shown to reduce the pain of dysmenorrhea as well as postpartum uterine cramping [14,15]. The present study compares ketorolac tromethamine to fentanyl, a commonly used opioid, for analgesic performance in women undergoing gynecological surgery in an ambulatory setting. The drugs' performances are analyzed specifically for effectiveness in relieving uterine cramp pain. Control of other pain resulting from the surgical procedure and the incidence of nausea and vomiting are also compared.

2. Materials and methods

One-hundred healthy women (ASA physical status I or II) scheduled to undergo laparoscopy, hysteroscopy or dilatation and curettage (D and C) were enrolled in this study. This protocol was approved by our Institutional Review Board and informed consent was obtained from each patient. Candidates were excluded from the study if they had taken any NSAID within 24 h of surgery or if they were allergic to or had other contraindications to ketorolac, fentanyl or aspirin. Patients were not asked to participate if they were minors, over 65 years of age, pregnant, or if their weight did not fall between 41–100 kg. Subjects were stratified by whether or not laparoscopy was a likely part of the surgical procedure. Computer generated randomization sequences were used to assign subjects of each stratum to one of two study groups: those given ketorolac (0.86 mg/kg, maximum dose 60 mg) and those given fentanyl (1 μg/kg). Patients who underwent laparoscopy after being assigned to the non-laparoscopy group were transferred to the appropriate laparoscopy group. We subsequently found no differences between laparoscopy and non-laparoscopy patients, and for purposes of analysis created two study groups, ketorolac and fentanyl.

The study design was double-blinded. Anesthesia, surgery, and nursing staff involved in the patient's care were unaware of which drug the patient received, as were the patient and the research specialist who conducted the postoperative interviews.

A standard anesthesia protocol was followed. Subjects were given no premedication. Anesthesia was induced with thiopental (4–6 mg/kg) and maintained with a combination of nitrous oxide, isoflurane and oxygen. Succinylcholine was administered for relaxation during intubation only. Study drug was prepared by an investigator not otherwise involved in caring for the patient. The anesthesiologist injected the solution into the deltoid muscle at the end of the surgical procedure. End of procedure was defined as the time at which the endoscope or the uterine curette was removed, whichever came first. At the end of laparoscopy procedures, 5 ml of 0.25% bupivacaine was infiltrated at incision/puncture sites. Any breaks in the anesthesia protocol resulted in the subject's removal from the study.

Upon arrival in the recovery room, patients were asked by a research specialist to rate their uterine cramping pain on a verbal numerical scale [16] ranging from 0 to 10, with 0 being no pain and 10 being the worst pain possible. Patients were then asked to rate any other pain that they were experiencing on the same scale. They were also asked if they were feeling nauseated. This evaluation was repeated at 0.5 h intervals for 3 h or until the patient was discharged, whichever came first. Incidents of retching and vomiting were recorded as they occurred. The clinical judgment of the attending anesthesiologist and the recovery room nurses (all blinded to the study drug administered) determined the need for additional analgesic medication postoperatively. This determination was not dependent on the verbal analog pain score. Patients requiring additional analgesia were given meperidine in 12.5 mg i.v. doses repeated as necessary. Patients requiring an antiemetic were given prochlorperazine in 2.5 mg i.v. doses. Time of administration and total dose of meperidine and incidence of prochlorperazine administration were recorded. Upon discharge, the length of the recovery room stay was recorded. The criteria for discharge were the absence of severe pain or nausea, the ability to sit up in a chair, ambulate, void, and verbalize understanding of discharge instructions.

Patients were telephoned the day after their surgery and asked if they had experienced nausea or retching/vomiting after leaving the hospital the previous day. They were also asked if they had taken any medication

Table 1
Distribution of surgical procedures between study groups

Surgical procedure	Fentanyl group ($n = 50$)	Ketorolac group ($n = 50$)
D and C	1	2
Hysteroscopy	2	4
D and C/ and hysteroscopy	5	5
Laparoscopy		
Tubal coagulation	2	4
Diagnostic	11	8
Laser ablation/lysis	8	8
+ hysteroscopy and/or D and C	21	19

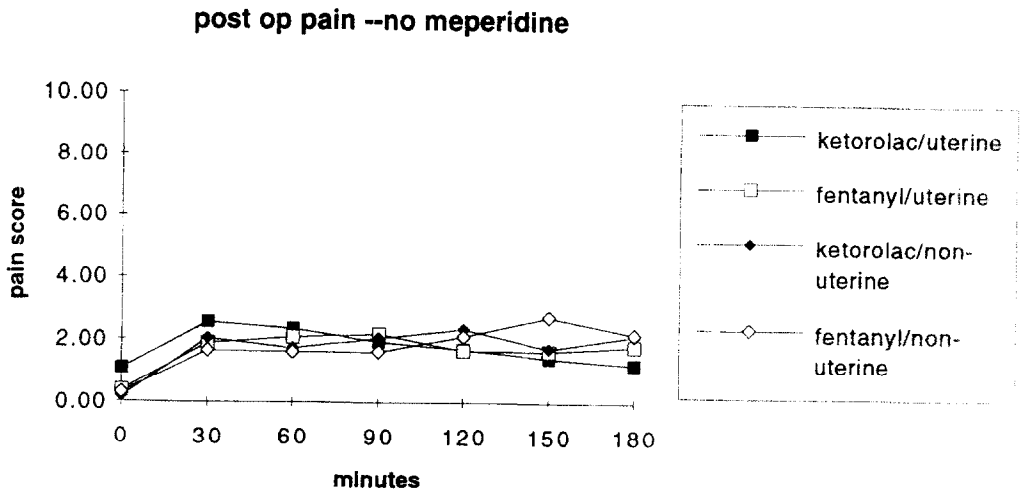

Fig. 1. Mean pain ratings for uterine cramping pain and non-uterine pain in patients not requiring postoperative opioid.

Table 2
Postoperative pain scores (patients requiring no supplemental analgesia)

		Uterine							Non-uterine						
		Time (min) after admission to recovery room							Time (min) after admission to recovery room						
		0	30	60	90	120	150	180	0	30	60	90	120	150	180
Ketorolac	*n*	30	29	30	27	21	14	7	30	29	30	27	21	14	7
	Mean	1.07	2.53	2.33	1.93	1.69	1.43	1.21	0.17	2.02	1.73	2.04	2.33	1.17	2.14
	SD	2.38	2.73	2.68	2.61	2.11	1.87	1.58	0.91	2.76	2.66	2.87	2.76	2.06	1.65
Fentanyl	*n*	28	27	29	28	23	18	8	28	27	29	28	23	18	8
	Mean	0.38	1.87	2.07	2.18	1.65	1.64	1.81	0.30	1.63	1.60	1.61	2.11	2.72	2.19
	SD	1.11	2.72	2.51	2.38	2.37	2.34	2.62	1.61	2.32	2.13	2.18	2.28	2.41	1.44

There is no significant difference between the Ketorolac group and Fentanyl group pain scores at any time period.

on the day of their surgery after being discharged. Incidence of nausea, retching/vomiting and use of analgesics during this post-discharge period were recorded.

The significance of differences in pain scores between the ketorolac and fentanyl groups was determined by repeated measures analysis of variance (ANOVA) or *t*-tests where appropriate. Demographic variables were tested for differences with one-way ANOVA and variables with discrete values were tested for significant differences by Chi-square analysis. A value of $P < 0.05$ was used as the criterion for significance in all statistical analyses.

3. Results

There were no significant differences between the two study groups in age, weight, ASA physical status, or length of surgery. The weights and ages of the study population ranged between 44–96 kg and 22–62 years, respectively. Each study group consisted of 50 women. Two patients, one from each group, were lost to telephone follow-up. Table 1 shows the distribution of procedures between the two groups. Three patients, one in the fentanyl group and two in the ketorolac group, were admitted to the hospital overnight. The reasons for the three admissions were (1) unresolved nausea, (2) possible surgical perforation of the uterus, and (3) unavailability of a person to be with the patient at home. All three admissions were thought to be unrelated to the study. Post-discharge data were collected as though the patient had been discharged after 3 h in the recovery room.

The mean time between administration of the study drug and the initial pain assessment was 32.7 min. This time was occupied with closing laparotomy puncture sites, treating minor bleeding points, cleaning prep solution from the patient, positioning the patient on a litter, and transport to the recovery room.

Sixty-one patients (31 fentanyl, 30 ketorolac) did not require supplemental analgesia in the recovery room. In these patients, there was no difference between the study groups in either uterine cramping or non-uterine pain scores at any time in the postoperative period (Fig. 1, Table 2).

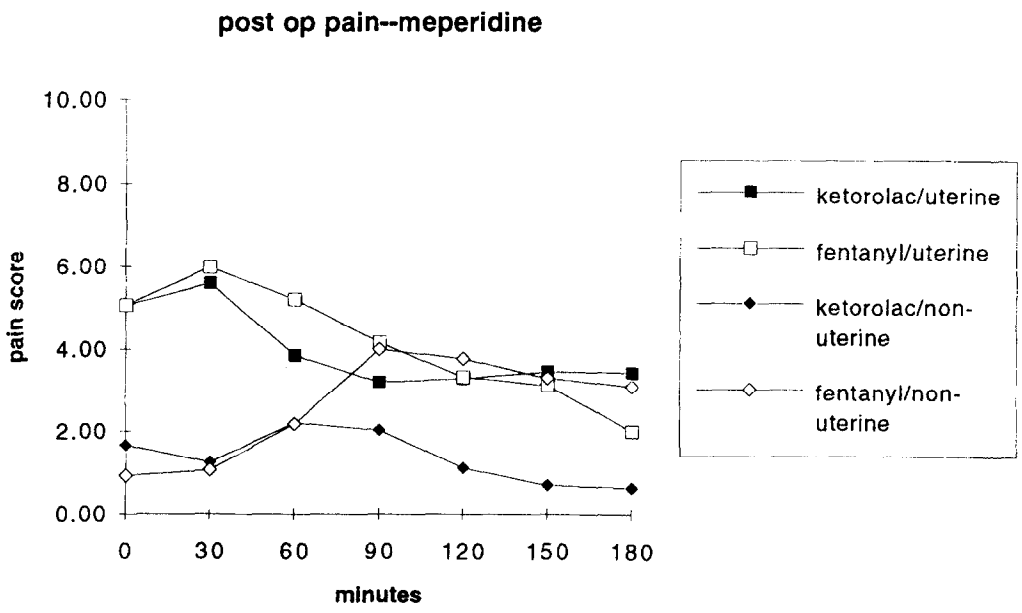

Fig. 2. Mean pain ratings for uterine cramping pain and non-uterine pain in patients requiring postoperative opioid.

Table 3
Postoperative pain scores (patients requiring supplemental analgesia)

		Uterine							Non-uterine						
		Time (min) after admission to recovery room							Time (min) after admission to recovery room						
		0	30	60	90	120	150	180	0	30	60	90	120	150	180
Ketorolac	*n*	20	19	20	20	16	12	8	20	19	20	20	16	23	8
	Mean	5.05	5.58	3.85	3.20	3.28	3.46	3.44	1.65	1.24	2.20	2.03	1.09	0.69	0.63
	SD	3.74	3.35	3.34	3.45	3.25	3.07	1.99	3.10	2.74	3.09	2.77	2.60	1.25	1.06
Fentanyl	*n*	16	18	18	19	17	12	11	16	19	18	19	17	12	11
	Mean	5.06	5.97	5.19	4.16	3.32	3.13	2.00	0.91	1.05	2.17	4.00	3.76*	3.29**	3.09*
	SD	3.91	3.19	3.32	2.93	2.55	2.45	2.38	2.49	2.63	3.00	3.51	3.43	3.24	2.67

*Significantly different from Ketoralac group ($P<0.01$).
**Significantly different from Ketorolac group ($P<0.02$). There are no other significant pain score differences between the ketorolac group and the fentanyl group.

Thirty-nine patients required meperidine in the recovery room (19 fentanyl group, 20 ketorolac group). These patients were separated from the remainder of the study group for further pain analysis.

Average time from recovery room admission to first dose of meperidine was: fentanyl patients, 47 ± 32 min (SD); ketorolac patients, 34 ± 32 min (SD) ($P = 0.25$).

In the meperidine-requiring patients, there was no difference between the ketorolac group and the fentanyl group in uterine pain scores. However, non-uterine pain was significantly less at 120, 150 and 180 min in patients who had received ketorolac (Fig. 2, Table 3).

The ketorolac and fentanyl groups did not differ significantly in the mean duration of recovery room stay (2.6 versus 2.7 h). Table 4 shows the incidence of nausea and vomiting for each group in the recovery room and during the post-discharge period. There were no statistically significant differences between the two groups in the incidence of nausea or retching/vomiting throughout the course of the study. The two groups did not differ significantly in the number of subjects requiring prochlorperazine or meperidine, the number of doses of meperidine required, or the incidence of analgesic use after discharge (Table 5).

4. Discussion

We found no difference between ketorolac and fentanyl in relief of either uterine cramping pain or non-uterine pain at any point in the study in patients who did not require supplemental analgesia. Late in the recovery room stay (120–180 min) patients who had received ketorolac and meperidine rated their non-uterine pain as less severe than did patients who had received fentanyl and meperidine. This is not surprising

Table 4
Number of subjects experiencing gastrointestinal effects

	Recovery room nausea	Recovery room retching/vomiting	Post-discharge nausea	Post-discharge retching/vomiting
Fentanyl group	35	25	29	15
Ketorolac group	33	16	24	13

There were no statistically significant differences between the groups.

since fentanyl has a faster onset than ketorolac, but a shorter duration of action [17,18].

Previous studies have suggested that ketorolac may not provide any significant advantage over opioids in reducing nausea and vomiting following gynecological as well as other types of surgery [18–20]. Our results lend further support to these findings, as we found no difference in the incidence of nausea and vomiting between the two study groups. The contribution of postoperative analgesics to total length of stay is controversial. Ding [5] found no difference between ketorolac and fentanyl. Lysak [7] demonstrated more rapid discharge for patients receiving ketorolac, but that study was confounded by the administration of postoperative morphine to more than half of the patients. Our data, including patients who received supplemental opioid, do not demonstrate a difference between ketorolac and fentanyl in discharge times.

We attempted to identify factors associated with the need for meperidine. The most obvious possibility is more extensive or more painful surgery (laparoscopy with lysis of adhesions or laser ablation of endometriosis). There was no correlation between type of operation and need for meperidine. There was no statistically significant difference in the need for meperidine between the fentanyl and ketorolac groups regardless of the extent of the operation. Patients with a preoperative diagnosis of pain (pelvic pain, dysmenorrhea, dyspareunia) might be more prone to postoperative pain needing opioid therapy. No statistical relationship could be demonstrated.

We identified several clinical sources of potential error or confusion. First, it may have been difficult for patients to distinguish between uterine cramp pain and more generalized abdominal pain. On several occasions, subjects said that they believed they had mislocated their pain earlier in the study, i.e., they originally said they were experiencing uterine cramping pain when in retrospect they believed they had been feeling incisional or abdominal pain or vice versa. In such cases, pain ratings were left as they had originally been reported. Analysis of the pain scores of patients requiring meperidine suggests that patients can distinguish between uterine and other pain. Uterine pain scores were significantly ($P < 0.01$) higher than non-uterine pain scores in both ketorolac and fentanyl patients at the initial evaluation and 30 min later (Fig. 2). This may have been the result of local anesthesia infiltration in the surgical wound sites. Intrauterine pressure monitoring might offer a more objective measure of uterine cramping in the postoperative setting but may also act to stimulate uterine contractions. Such intrauterine monitoring has been used in the study of dysmenorrhea [3,21] and to investigate patients' ability to localize uterine cramp pain [22].

Table 5
Postoperative medication

Medication	Fentanyl group	Ketorolac group
Required prochlorperazine	8	9
Required meperidine	19	20
Average number of meperidine doses	1.5	1.6
Used analgesic after discharge from hospital	31	23

There were no statistically significant differences between the groups.

For the majority of patients, either ketorolac or fentanyl provided adequate postoperative analgesia. Demand for supplemental analgesia was not particularly associated with either study drug. Among patients who required meperidine in the recovery room, those who had received ketorolac had significantly less non-uterine pain at 120, 150, and 180 min.

The biochemical mechanism involved in postoperative uterine cramping pain may differ from the mechanism of menstrual (dysmenorrheic) cramps. Several substances in addition to prostaglandins are known to have effects on uterine contractility. These include leukotrienes, estrogen, progesterone, oxytocin and vasopressin [2,23–25]. About 20% of dysmenorrheic women do not respond to NSAID therapy. In these women, it is thought that cramping is not due to elevated levels of prostaglandins but rather to an excess of leukotriene. Postpartum uterine cramping can be significantly relieved by aspirin [8,15], which is the only NSAID that is ineffective against menstrual uterine cramping [1].

Prostaglandin production may be the primary factor in most cases of dysmenorrhea but not necessarily in

postpartum and postoperative uterine cramping pain. NSAIDs may provide superior analgesia only for a subset of patients in whom the prostaglandin pathway is primarily responsible for uterine cramping pain. We found no significant difference between ketorolac and fentanyl in relieving postoperative uterine cramp pain, and infer that factors other than, or in addition to prostaglandins, are involved.

Acknowledgements

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