CMRO

Current Medical Research & Opinion Vol. 26, No. 8, 2010, 1915–1923

0300-7995
doi:10.1185/03007995.2010.495564

Article 5313/495564

Original article

Intranasal ketorolac for acute postoperative pain

Neil Singla
Lotus Clinical Research/Huntington Hospital, Pasadena, CA, USA

Sonia Singla
Glendale Adventist Medical Center, Glendale, CA, USA

Harold S. Minkowitz
Memorial Hermann Memorial City Medical Center, Houston, TX, USA

John Moodie
Colin Brown
Waikato Clinical Research, Hamilton, New Zealand

Address for correspondence:
Neil Singla, MD, Lotus Clinical Research, Inc., 100 West California Boulevard, Unit 25, Pasadena, CA 91105, USA.
Tel.: +1 877 568 8727; Fax: 626-628-3422; Neil@lotuscr.com

Key words:
Balanced COX1/COX2 inhibitor – Intranasal NSAID – Opioid sparing – Postoperative analgesia

Accepted: 20 May 2010; published online: 17 June 2010
Citation: Curr Med Res Opin 2010; 26:1915–23

Abstract

Background:
Efficacy and tolerability of intranasal ketorolac (SPRIX®) was assessed in abdominal surgery patients.

Methods:
Adult patients were randomly assigned to receive ketorolac 31.5 mg ($n=214$) or placebo ($n=107$) every 6 hr after surgery for 48 hr, then up to 4 times/day for up to 5 days. Morphine sulfate via patient controlled analgesia was available in both groups as needed.

Results:
Least square mean 6 hr summed pain intensity difference scores were significantly greater in the ketorolac group indicating better analgesic efficacy compared to placebo (117.4 vs. 89.9, $p=0.032$; difference 27.6, 95% CI 2.5–52.7). Pain intensity difference indicated significantly better pain relief in the ketorolac group at 20 min after the first dose ($p=0.01$). Morphine use over 48 hr decreased 26% in the ketorolac group compared to placebo ($p=0.004$). Day 1 global pain control scores were significantly higher in the ketorolac group compared to placebo ($p=0.009$). Quality of analgesia was rated significantly higher ($p=0.009$) in the ketorolac group by 20 min after first dose. Adverse event and serious adverse event incidences were similar in both groups. Rhinalgia and nasal irritation, generally mild and transient in nature, occurred more frequently in the ketorolac group.

Conclusion:
Intranasal ketorolac was well tolerated and provided effective pain relief within 20 minutes with reduced opioid analgesia use. While IN ketorolac was assessed in an inpatient, conventional surgery setting in this study, IN ketorolac use may have more relevance for use in outpatient settings and ambulatory surgery or fast-track surgical procedures.

Introduction

Effective management of acute postoperative pain often involves a multimodal approach incorporating the use of nonopioid analgesics in order to optimize analgesic efficacy and reduce opioid-related side effects. Nonopioid analgesics are often preferred in ambulatory surgeries to allow patients to return to normal functioning more quickly. Ketorolac is a nonopioid, balanced COX1/2 inhibitor used for the short-term management of moderate-to-severe acute pain in patients undergoing inpatient and ambulatory procedures[1,2]. The analgesic efficacy of intravenous and intramuscular ketorolac formulations provide efficacy similar to morphine sulfate and meperidine in patients who have had major surgery, including abdominal procedures[2]. An intranasal formulation of ketorolac (SPRIX®) has recently been approved for the short-term (up to 5 days) management of acute moderate to moderately severe pain in adults who require analgesia at the opioid level. Intranasal ketorolac is a patient-administered alternative to injectable ketorolac and opioids for pain management that will allow continuity of pain medication used immediately after surgery and on an

outpatient basis. Intranasal delivery has the advantage of achieving peak plasma concentrations with similar kinetics as intramuscular (IM) injection in a formulation that patients can self-administer. This may have utility in ambulatory patients, and can provide continuity of pain management as patients transition to home. Intranasal delivery also is an attractive option for patients not able to take medications orally, or who are experiencing nausea or vomiting.

The pharmacokinetics of intranasal ketorolac delivery are similar to those reported following intramuscular administration[3]. Local tolerance and systemic toxicology studies performed in rats and rabbits showed that intranasal administration of ketorolac exhibits toxicity similar to that of other routes of administration and does not result in adverse effects on the nasal passage or upper and lower respiratory tracts[4]. Intranasal ketorolac (10 and 31.5 mg administered via disposable, multidose, metered-spray device) has been evaluated in placebo-controlled studies in patients following major surgery[5,6] with both single and multiple doses in combination with opioid analgesia and dental impaction surgery[7] following a single dose. Patients who received 31.5 mg intranasal ketorolac in single or multiple doses had significant reductions in mean morphine sulfate use, significantly lower pain intensity scores, and superior quality of analgesia ratings compared to placebo[5–7]. Single and multiple doses of intranasal ketorolac are well tolerated[3,5–7]. The primary adverse event in healthy volunteers and surgery patients is mild nasal irritation. Intranasal ketorolac use is also associated with a reduction in the incidence of side effects typically observed following opioid use, including pruritis, pyrexia and constipation.

The objectives of the present phase 3, randomized, double-blind, placebo-controlled study were to evaluate the analgesic efficacy and tolerability of intranasal ketorolac use after abdominal surgery in patients permitted to use opioid analgesia.

Methods

Patients

Men or women age 18–64 years undergoing major open abdominal surgery under general anesthesia at six sites in the US and New Zealand were eligible for the study if expected to remain in the hospital for at least 48 hours with the possibility of remaining for up to five days. The protocol (ROX-2005-01) was approved by an institutional review board and all patients provided signed, informed consent. Patients were enrolled between December 2005 and February 2007.

Screening physical examinations, complete blood counts, and serum chemistries were obtained before patients were assigned to treatment groups. Exclusion criteria included active or recent peptic ulcer disease; history of clinically significant gastrointestinal bleeding; allergy or sensitivity to any of the study medications; current upper respiratory tract infection that could interfere with the absorption of the nasal spray or with the assessment of adverse events; the use of any intranasal product within 24 hours prior to study entry; pregnancy; and breastfeeding. Neuraxial opioids and the use of nonsteroidal anti-inflammatory drugs other than the study drug were prohibited.

Patients satisfying inclusion and exclusion criteria were randomly assigned in a 2:1 ratio using a blocked randomization schedule to receive intranasal ketorolac 31.5 mg or matching placebo every six hours for the first 48 hours following surgery, then up to four times per day. A randomized list of kit numbers in blocks of three (i.e. 1,1,2; 2,1,1; 1,2,1, where 1 = active and 2 = placebo) was generated in SAS and the randomization schedule was stratified by study site. The number of ketorolac kits was twice the number of placebo kits in this scheme. Kits were numbered and shipped to sites as needed in multiples of three keeping each block of three intact. Kits were assigned in numerical order (lowest to highest, i.e., sequentially) as subjects qualified to enter the study at the site. Patients and all study site personnel were blinded to treatment assignments. Compliance was established by accountability of returned study drug at the end of the treatment period.

After surgery, intravenous opioid was administered at the discretion of the investigator until patients were comfortable. Once comfortable, patients recorded pain intensity (PI) ratings using a visual analog scale (VAS) of 0 to 100 mm where 0 represents no pain and 100 is the worst pain imaginable. When PI ratings equaled at least 40 on the VAS, patients received intranasal ketorolac or placebo. Once study medication was initiated, patients in both the ketorolac and placebo groups had access to morphine sulfate by intravenous patient controlled analgesia (PCA) through at least 48 hr for pain not controlled by study drug. When PCA was no longer required, oral analgesia such as hydrocodone/acetaminophen was permitted for pain not controlled by study treatment. The dosing scheme is summarized in the dashed-line box in Figure 1.

Ketorolac (15% w/w) and placebo solutions were contained in matching, specially designed metered-pump spray devices. All study doses were administered as one spray (100 μL) into each nostril. Each patient received a kit containing five devices, each containing a calendar day's supply of drug.

Data collection and efficacy endpoints

All subjects who received at least one dose of study drug were included in the efficacy and safety analyses

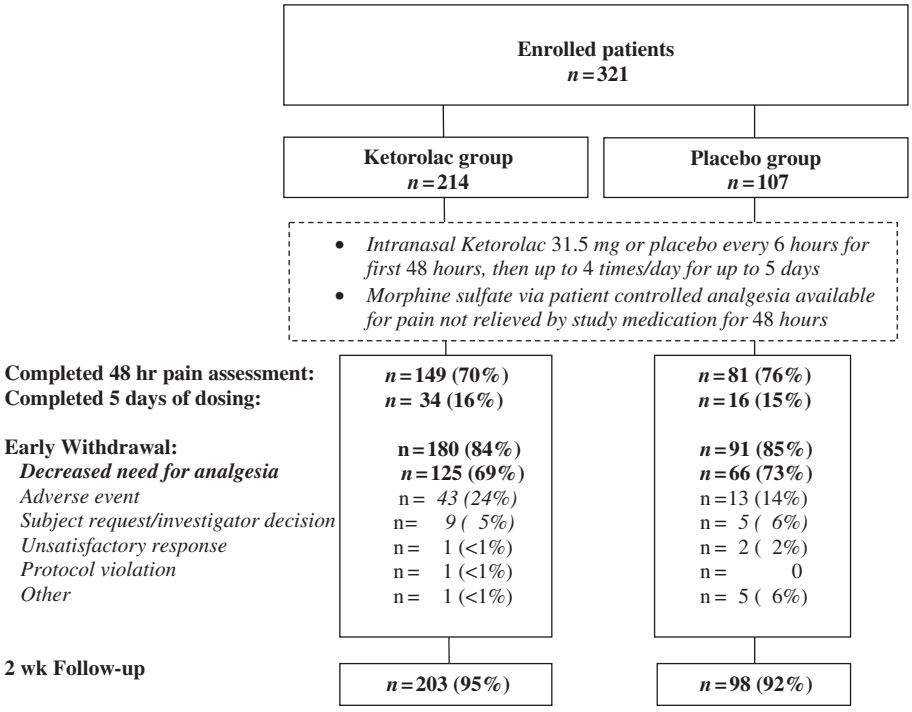

Figure 1. Progression of patients in the study.

(intent-to-treat, ITT population). Patients recorded pain intensity using the VAS before receiving the study drug, at 20, 40, and 60 minutes, and 2, 3, 4, 5, 6, 12, 18, 24, 30, 36, 42, and 48 hours after the first dose.

Following the 48 hour dose on postoperative Day 2, and for all doses given up to the 72 hour time point on postoperative Day 3, assessments were made immediately before each dose. When patients no longer required study drug for analgesia, all pain assessments stopped. Post treatment pain intensity difference (PID) scores were calculated by subtracting the post treatment VAS score from the baseline VAS score. The primary efficacy measure was the 6-hour summed pain intensity difference (SPID6).

Secondary efficacy measures included morphine use through 72 hours collected and tabulated at 2-hour intervals for the first 12 hours and at 6-hour intervals for the remainder of the first 72 hours. Morphine use in mg was calculated by adding all PCA morphine use and morphine equivalents for other analgesic medications administered for that time period. Morphine equivalents were calculated using American Pain Society guidelines[8]. Other secondary efficacy endpoints were 4-hour SPID, peak relief scores (defined as maximum PID), quality of pain relief, and global assessment of pain control. Quality of pain relief was reported by patients on a 5-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent) and was collected at the same time points as pain intensity assessments. Patients also recorded global assessment of pain control (measured on a 5-point categorical scale where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent) once each day.

Safety

All patients who received at least one dose of study medication were evaluated for safety by assessing spontaneously reported adverse events and clinical signs, hematology and clinical chemistry throughout the treatment period and at a 14 day follow-up visit. Cardiovascular and nasal evaluations were made at the end of the treatment period and at the 14 day follow-up visit.

Statistical analysis

Sample size determinations were based on power computations from results of previous randomized, controlled studies with IN ketorolac[4,5] where a two-group *t*-test with 0.05 two-sided significance level will have 90% power to detect a difference in means of 34–46, assuming that the pooled or common standard deviation is between 86 and 112 when the sample sizes in the two groups are 100 and 200 (total sample size of 300).

For the SPID6 and post treatment pain evaluations, the 'last observation carried forward' (LOCF) method for handling missing data was used, whereby missing responses were replaced with the last available observation. Missing data between time points were linearly interpolated. To examine the sensitivity of the results to the

LOCF method of extrapolation, two alternative methods of analysis were examined. Pain intensity ratings were extrapolated using the LOCF following the first use of supplemental or backup medication or concomitant medication prohibited by the protocol. Hourly PI ratings were not extrapolated following use of PCA morphine. The first alternative method used BOCF following the first use of supplemental or backup medication or early withdrawal for other reasons as specified in the analysis plan. The second method used observed cases. No extrapolation following the first use of supplemental or backup medication or early withdrawal for other reasons was performed.

PID, SPID and Peak Relief scores were analyzed using the two-way analysis of covariance with the baseline PI score made prior to study drug administration as the covariate. Factors in the analysis included study center, treatment, and center-by-treatment interaction. Results were presented as the adjusted means (i.e., least square means) for each treatment group, the difference in means between groups, the associated 95% confidence interval, and *p* value. The PI ratings and morphine sulfate use were analyzed using two-way analysis of variance (ANOVA). The quality of analgesia data and the once-daily global evaluation of analgesia were analyzed using the Cochran–Mantel–Haenszel row mean score test stratified by study center.

Results

Demography and patient progression

Three hundred twenty-one patients were enrolled and assigned to treatment, 214 in the ketorolac group and 107 in the placebo group. The majority of patients (230/321, 72%) completed pain assessments for the first 48 hours, 149 in the ketorolac group and 81 in the placebo group. Sixteen percent (50/321) of patients completed 5 days of dosing. The main reason for not completing 5 days of dosing was the decreased need for analgesia, which occurred in 70% (191/271) of patients. Decreased need for analgesia occurred in similar proportions of patients in the placebo and ketorolac groups. The majority of patients (301/321, 94%) completed the 2-week follow-up assessment. Twenty-four percent (43/214) of patients in the ketorolac group and 14% (13/107) of patients in the placebo group withdrew from the study due to an adverse event. A flow diagram of patient participation in the study that includes other reasons for withdrawal from the study is shown in Figure 1.

The number of doses of study medication received did not differ between the placebo and ketorolac groups. The median number of doses for all patients was eight in both the placebo and ketorolac groups, and ranged from one to 18 doses. The majority of patients (60%, 194/321) in both groups received between 6–10 doses, and 19% (62/321) received from 11–15 doses.

Table 1. Demographic and baseline characteristics of patients.

	Ketorolac Group $N=214$	Placebo Group $N=107$
Mean Age, yr ± SE	46 ± 1	46 ± 1
(range)	(22–64)	(28–70)
Sex [no. (%)]		
Female	206 (96)	103 (96)
Male	8 (4)	4 (4)
Weight, kg (mean ± SE)	77.0 (1.3)	79.7 (1.7)
Race [no. (%)]		
Caucasian	154 (72)	76 (71)
Black	23 (11)	11 (10)
Other	37 (17)	20 (19)
Baseline Characteristics		
Day 0, (Mean ± SE)		
Vital Signs		
Systolic blood pressure (mmHg)	126.1 ± 1.3	126.6 ± 1.7
Diastolic blood pressure (mmHg)	73.1 ± 0.8	72.4 ± 1.3
Pulse (beats per min)	78.3 ± 0.9	75.2 ± 1.1
Respiration (breaths per min)	36.7 ± 0.03	36.6 ± 0.04
Temperature (degree Celsius)	17.1 ± 0.2	16.7 ± 0.2
Predose pain intensity, VAS score	62.5 ± 1.6	60.8 ± 1.1

Patient characteristics and vital signs following surgery on Day 0 were clinically similar in the two groups and are shown in Table 1. The majority of patients were white (72%) and female (96%) with a mean age of 46 years. The majority of procedures were hysterectomies with or without oophrectomy (223/321, 69.5%). Other procedures included oophrectomy (26/321, 8.7%), myomectomy (32/321, 9.7%), bowel resection, ileostomy, colectomy or colostomy (18/321, 5.6%), cystectomy, hernia repair, or omentectomy (14/321, 4.9%), prostectomy (6/321, 1.9%), and cesarean section (2/321, 0.6%). The majority of patients had general anesthesia (317/321, 99%); epidural anesthesia was used in three patients and spinal anesthesia in one patient.

Efficacy assessments

Pain intensity

SPID6 score for the ketorolac group was significantly higher compared to the placebo group (least square means ± SE were 117.4 ± 7.7 vs. 89.9 ± 10.6, respectively, $p=0.032$; difference in means 27.6, 95% CI 2.5–52.7) indicating better analgesic efficacy with intranasal ketorolac. Mean pain intensity VAS scores decreased over time in both groups and were significantly lower in the IN ketorolac group compared to placebo at 20 minutes (55.4 ± 1.9 vs. 60.5 ± 1.3, $p=0.014$, 60 minutes (47.0 ± 1.5 vs. 53.5 ± 2.1, $p=0.008$), 2 hours (43.3 ± 1.6 vs. 49 ± 2.2, $p=0.026$), 3 hours (36.5 ± 1.5 vs. 44.2 ± 2.2, $p=0.002$), 6 hours (29.8 ± 1.4 vs. 34.5 ± 2.2, $p=0.038$), 18 hours (29.0 ± 1.5 vs. 32.3 ± 2.3, $p=0.016$), 24 hours

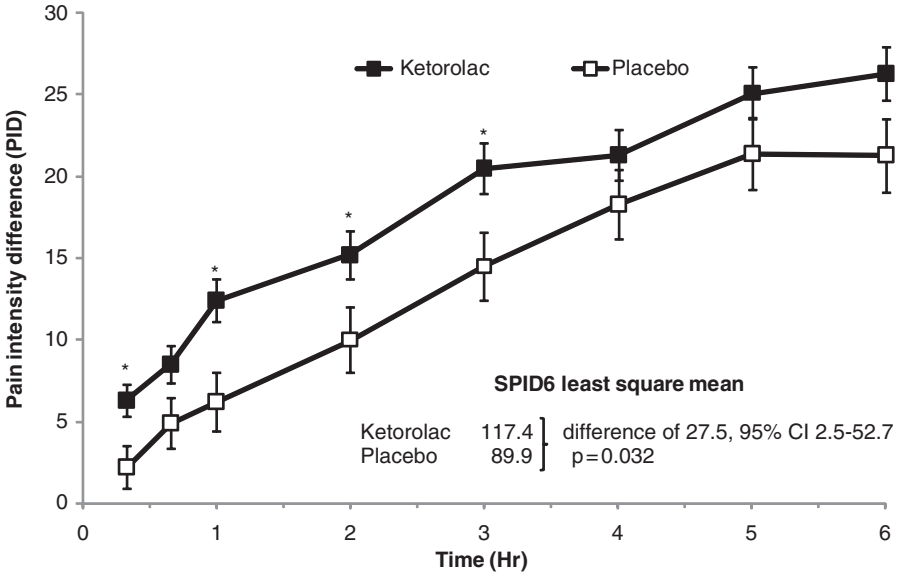

Figure 2. Least square mean pain intensity difference (PID) scores ± SE for patients following a single dose of intranasal ketorolac (31.5 mg) or placebo on Day 1 after surgery. The summed PID at 6 hours (SPID6) is shown inset. *Significantly different from placebo, $p < 0.05$.

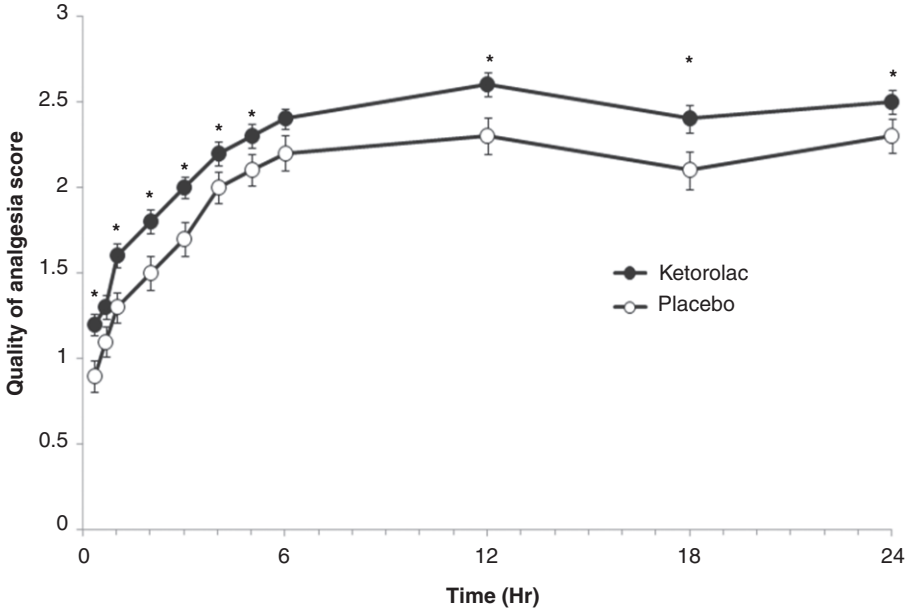

Figure 3. Patient rating of quality of analgesia in the first 24 hours after surgery using a scale where 0 = Poor, 1 = Fair, 2 = Good, 3 = Very Good, 4 = Excellent. Values represent the mean scores at each time point ± SEM. *Significantly different from placebo, $p < 0.05$.

(26.4 ± 1.5 vs. 32.3 ± 2.3, $p = 0.016$), and 30 hours (24.3 ± 1.5 vs. 29.5 ± 2.2, $p = 0.037$). After 30 hours, there were no statistically significant differences between treatment groups. Mean PID scores through the initial 6 hours after the first dose of study medication increased in both groups as shown in Figure 2. At every time point, PID scores were higher for subjects in the ketorolac group compared to those for the placebo group and were statistically significantly higher for the ketorolac group at 20 minutes ($p = 0.010$), 1 hour ($p = 0.005$), 2 hours ($p = 0.034$), and 3 hours ($p = 0.017$).

For both alternative analyses where the sensitivity of the LOCF method of extrapolation was tested, treatment group differences for the primary endpoint, SPID6, were statistically significant in favor of ketorolac ($p = 0.048$ for BOCF; $p = 0.037$ for the observed cases analysis).

SPID4 least square mean values were 66.1 ± 4.9 and 47.2 ± 6.8 for the 31.5 mg intranasal ketorolac and placebo

groups, respectively ($p = 0.021$). Peak relief scores for the intranasal ketorolac and placebo groups (least square mean values 32.7 ± 1.5 and 30.0 ± 2.1, respectively) were not statistically significantly different.

Quality of analgesia

The quality of analgesia was rated by patients (where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent) as statistically significantly better in the intranasal ketorolac group compared to the placebo group at all time points (Figure 3) from 20 minutes (1.2 ± 0.06 versus 0.9 ± 0.09, $p = 0.009$) to 24 hours (2.5 ± 0.07 versus 2.3 ± 0.1, $p = 0.04$), except for the 40-minute and 6-hour time points.

Global assessment of pain control

The global assessment of pain control was significantly better in the intranasal ketorolac group compared to the placebo group (mean ± SE scores where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent: 2.6 ± 0.06 vs. 2.4 ± 0.09, $p = 0.009$) on Day 1. Differences between groups were not significantly different on Days 2, 3 and 4.

Morphine use

Rescue medication for pain not relieved by study drug included PCA morphine sulfate and oral analgesics such as hydrocodone/acetaminophen. The mean total amount of morphine equivalents used from 0 to 24 hours was 42 mg in the intranasal ketorolac group vs. 54 mg in the placebo group ($p = 0.003$) and 23 mg in the intranasal ketorolac group vs. 31 mg ($p = 0.041$) in the placebo group for 0–48 hours. Morphine use was decreased by 34% in the intranasal ketorolac compared to the placebo group for 0–72 hours (82 mg vs. 121 mg), but the difference was not statistically significant. There were very small numbers of patients in the assessment of 0–72 hour (10 in the intranasal ketorolac group and 13 in the placebo group) due to the decreased need for analgesia. The decrease in morphine use in the ketorolac group for the first 48 hours is shown in Figure 4.

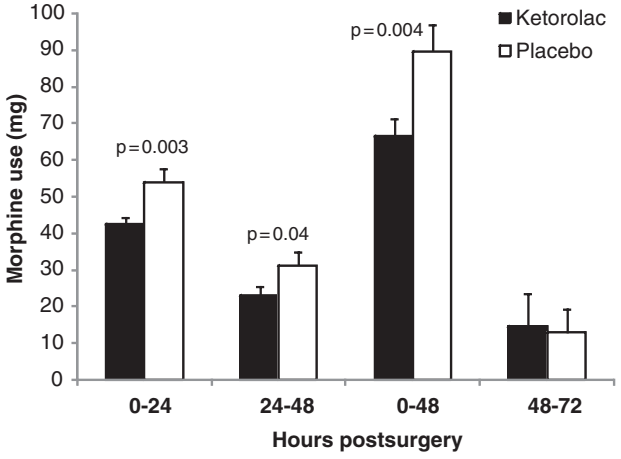

Figure 4. The mean reduction in morphine use by patients in the intranasal ketorolac and placebo groups during the first 24 hours after surgery, 24–48 hours after surgery, the first 48 hours after surgery, and 48–72 hours after surgery. *P* values for significant differences are shown above the bars.

Table 2. The most commonly reported (≥10%) adverse events in the ketorolac and placebo treatment groups.

Adverse event	Number of patients (%)	
	Ketorolac Group $n = 214$	Placebo Group $n = 107$
Nausea	122 (57)	66 (62)
Constipation	59 (28)	35 (33)
Vomiting	51 (24)	24 (22)
Headache	47 (22)	25 (23)
Flatulence	39 (18)	23 (22)
Rhinalgia	43 (20)	0 (0)
Pyrexia	34 (16)	36 (34)
Pruritis	31 (15)	19 (18)
Anemia	33 (15)	11 (10)
Insomnia	30 (14)	16 (15)
Epistaxis	29 (14)	17 (16)
Nasal discomfort	24 (11)	3 (3)
Hypotension	22 (10)	6 (6)
Tachycardia	20 (9)	15 (14)

Safety and tolerability

The percentage of patients with at least one adverse event were similar in the two treatment groups (ketorolac: 93%, 198/214; placebo: 96%, 103/107). The majority of patients (265/321, 83%) had events considered mild, and the proportion was similar in the ketorolac and placebo groups (84% vs. 79%).

Adverse events were characteristic of those following major abdominal surgery and receiving morphine PCA. The most frequent events (≥10%) are listed in Table 2. Common adverse events in both groups were nausea, constipation, vomiting, and headache. There was a trend (≥5% difference) for reduced incidences of nausea, constipation, pyrexia and tachycardia in the ketorolac group compared to placebo.

Although the overall proportion of patients withdrawing from the study was similar in both groups, more patients in the ketorolac group compared to placebo withdrew due to adverse events [43/207 (24%) vs. 13/98 (14%), respectively]. Within the early withdrawals due to adverse events, the most frequent reasons for withdrawals were similar in both groups and were classified as GI disorders (17% vs. 15% in the ketorolac and placebo groups, respectively), nervous system disorders (15% vs. 31%, respectively), respiratory/thoracic/mediastinal disorders, which included nasal discomfort or irritation (30% vs. 31%, respectively) or renal/urinary tract disorders (6% vs.

8%, respectively), or infections/infestations (4% vs. 8%, respectively). The excess withdrawals in the ketorolac group resulted from seven withdrawals due to disorders of the blood/lymphatic, cardiac, eye, immune, skin, general, or reproductive systems and six withdrawals due to a vascular, procedural, or investigational event. There were no withdrawals due to these events in the placebo group.

Rhinalgia, nasal discomfort, and anemia occurred more frequently in the ketorolac group. None of the anemia events were considered related to study medication. Most events related to nasal irritation were mild, transient, and did not increase in severity with repeated dosing. Results of nasal examinations at the end of the study after the last dose of medication showed that 8% of ketorolac patients and 5% of placebo patients had findings considered by the investigator to be clinically significant. The difference between the groups was not statistically significant, ($p = 0.47$). The majority of the findings were described as 'mild' or 'small' changes. The 14-day follow-up assessment captured reports by patients in the 2 weeks following end of treatment. Nasal event rates for the 31.5 mg intranasal ketorolac and placebo groups were 17% and 9%, respectively and the difference between groups was not statistically significant ($p = 0.09$). Investigators evaluated patient reports and noted 'clinically significant' findings regardless of relationship to medication use in 50% of the events reported by patients in the ketorolac group and 46% of events in the placebo group.

Eighteen patients reported 28 serious adverse events. The rates of serious events were identical in the two groups: 6% (12/214 patients) in the ketorolac group and 6% (6/107 patients) in the placebo group. The majority of serious adverse events were related to gastrointestinal tract disorders ($n = 7$ including ileus, nausea, and vomiting), post-procedural complications ($n = 6$), and infections ($n = 3$). Twenty-five of the 28 (89%) serious events were considered probably not related to study drug. No patients had gastrointestinal bleeding, surgical bleeding, or renal insufficiency considered related to study medication. Three events in the same patient in the intranasal ketorolac group were considered possibly related to study drug and were nausea, vomiting and upper abdominal pain, all of which resolved without sequelae.

There were no clinically relevant differences between the treatment groups regarding vital signs, hematology, or clinical chemistry measurements. No deaths occurred during the study.

There was no difference between groups in percentage of patients with treatment-emergent cardiac adverse events (including irregular heart beat/palpitations, rapid heartbeat, shortness of breath, chest pain, and changes in blood pressure) assessed at the end of the study: 23/214, 11% in the ketorolac group and 10/107, 9% in the placebo group. The percent of patients reporting cardiovascular-related adverse events during the 2 weeks after the end of treatment were similar in the two groups: 15% and 16%, respectively in the ketorolac and placebo groups ($p = 0.74$).

Discussion

The efficacy and tolerability of the intranasal formulation of ketorolac self-administered by patients every 6 hr for 48 hr then up to four times a day for up to 5 days was evaluated. The patients in this study had moderate-to-severe baseline pain levels following major open abdominal surgeries. The majority of patients completed 48 hours of pain assessments, but very few completed 5 days of dosing, primarily due to decreased need for pain medication (70% of patients). Even though all patients had access to PCA morphine sulfate, intranasal ketorolac 31.5 mg every 6 hr for 48 hr had statistically and clinically significant benefits compared to placebo in acute pain control and resulted in significantly less use of opioid analgesia. Patients in the intranasal ketorolac group required 21% less opioid in the first 24 hr and 26% less in the first 48 hr than patients in the placebo group. Intranasal ketorolac was associated with a rapid onset of analgesia: patients in the intranasal ketorolac group had significantly lower pain scores and reported a better quality of analgesia at the earliest measurement of 20 minutes after study drug administration.

These results confirm the findings of previous phase 2 and phase 3 trials in which superior analgesia as well as opioid-sparing properties were demonstrated for intranasal ketorolac 31.5 mg versus placebo administered every 8 hr for the first 48 hr daily[5–7]. In a previous phase 3 study, a reduction in opioid use of 34% was observed for patients undergoing abdominal or orthopedic procedures who received intranasal ketorolac[5]. The four times per day regimen in the present study was selected in order to assess tolerability using the maximum allowed dosing regimen currently prescribed for the intramuscular ketorolac formulation.

The results support previous findings that administration of parenteral ketorolac formulations following major surgery reduces opioid use[9,10]. The lower rates of nausea, constipation and other opioid-related side effects in the ketorolac group likely reflect the decreased morphine use by patients in that group. Reductions in opioid-related side effects were also reported in previous intranasal ketorolac clinical trials[5–7], and with other parenteral formulations of ketorolac[9,11–14]. The lower rate of pyrexia observed in the ketorolac group is likely due to antipyretic effects associated with COX1/2 inhibitors and has been previously reported in ketorolac-treated patients[6,15].

Rates of adverse events and serious events in the ketorolac and placebo groups were similar and were typical of a patient population undergoing major abdominal surgical

procedures and receiving opioid analgesics. There were no reports of treatment-related gastrointestinal bleeding or renal insufficiency. Anemia occurred in both groups and was numerically greater in the ketorolac group (15% versus 10% in the placebo group). These events did not persist at the 2-week follow-up assessment. There were no reports of postoperative bleeding associated with ketorolac administration. Ketorolac is known to inhibit platelet aggregation and thromboxane production[18]. The risks of hematological abnormalities with ketorolac use are not reported to be increased unless ketorolac is used at high doses, is administered beyond 5 days, or is administered to high-risk patients[19]. Cardiovascular events are a cause of concern with the use of COX2 inhibitors and some mixed COX1/2 inhibitors, but this has not been the case with the short-term use of ketorolac. There were no treatment-emergent cardiovascular events in the intranasal ketorolac group during the study. The proportion of patients reporting cardiovascular events in the 2 weeks following the study were similar in the ketorolac and placebo groups.

Local nasal symptoms, including rhinalgia and nasal discomfort, were the only events occurring considerably more frequently in the ketorolac group compared to the placebo group during treatment. Nasal irritation events were typically categorized as mild, were transient, and did not increase in severity with increasing ketorolac use. Similar proportions of patients in the ketorolac and placebo groups withdrew from the study due to nasal irritation. Similar proportions of patients in each group also reported nasal mucosal changes in the 2 weeks after the end of treatment. Nasal irritation is not considered serious and is a frequent side effect of intranasal administration of drugs, including intranasal corticosteroids and antihistamines[20].

Clinical practice guidelines advocate multimodal analgesia with opioid and nonopioid drugs for management of postoperative pain[21,22]. Ketorolac has the advantage of being highly soluble, which enabled ketorolac to be developed for intranasal delivery. Parenteral ketorolac is widely used for pain management within the immediate postoperative period for patients undergoing inpatient and ambulatory procedures[13,23,24]. Ketorolac can be part of an analgesic regimen that promotes return to normal activities and reduces costs[25,26] and may be useful in patients with opioid tolerance, or in settings where use of regulated analgesics is not appropriate. As an alternative to ketorolac injection and IV administration, IN ketorolac could help achieve recommended recovery goals for ambulatory and fast-track surgery patients[27]. Clinical studies demonstrate that IN ketorolac provides pain control when used alone or when combined with opioids. When used as part of a multi-drug regimen that includes opioids, IN ketorolac allows patients to reduce their opioid dose and achieve better pain relief than that provided by opioids alone. IN ketorolac achieves peak blood levels as rapidly as an IM injection and provides a patient-administered alternative to injectable ketorolac that will allow continuity of pain medication used immediately after surgery and on an outpatient basis. The IN formulation is also an option for patients who have difficulty swallowing oral analgesic medications, or who experience nausea and vomiting.

Limitations

While analgesic strategies for postoperative pain management are frequently tested using analgesic consumption (and opioid-sparing) as an outcome measure, a recognized limitation of the study is that this measure has not been evaluated rigorously, hence we have not used it as a primary outcome measure. This may account for the ranges in reduction in opioid use and concomitant reduction in opioid-related side effects observed across clinical trials[16,17]. A limitation of the study is that IN ketorolac was assessed in an inpatient, conventional surgery setting when in fact, IN ketorolac use may have more relevance for use in outpatient settings and ambulatory surgery or fast-track surgical procedures.

Conclusion

Intranasal ketorolac is currently indicated for management of acute pain for up to 5 days in adults with moderate to moderately severe pain. In this study, intranasal ketorolac 31.5 mg self-administered four times a day for up to 5 days was effective and well tolerated in treating acute pain in surgery patients and resulted in reduced opioid use and improved quality of analgesia. There were no cardiovascular-related adverse events during the study or during the 2 weeks following treatment.

Transparency

Declaration of funding
Financial support for the study was provided by ROXRO PHARMA.

Declaration of financial/other relationships
All authors were study investigators and report no financial relationships.

Acknowledgment
Patrice Ferriola, PhD provided writing and editorial support in preparation of the manuscript, which was funded by ROXRO PHARMA.

Data in this paper were previously presented in part as an abstract accepted as an Excellence and Innovation Oral and Poster Presentation at the scientific session of the Society for

Ambulatory Anesthesia, 23rd Annual Meeting, May 1–4, 2008, Baltimore, MD, USA.

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