ORIGINAL ARTICLE

Efficacy and Safety of Oxymorphone Immediate Release for the Treatment of Mild to Moderate Pain After Ambulatory Orthopedic Surgery: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT. Gimbel JS, Walker D, Ma T, Ahdieh H. Efficacy and safety of oxymorphone immediate release for the treatment of mild to moderate pain after ambulatory orthopedic surgery: results of a randomized, double-blind, placebo-controlled trial. Arch Phys Med Rehabil 2005;86:2284-9.

Objective: To assess the analgesic efficacy and safety of 5mg of oxymorphone immediate release (IR) for mild to moderate pain.

Design: Multicenter, double-blind, randomized, placebo-controlled study.

Setting: Ambulatory surgical centers.

Participants: Outpatients (age, ≥18y) undergoing knee arthroscopy.

Intervention: Randomization to 5mg of oxymorphone IR or placebo hourly as needed for up to 8 hours.

Main Outcome Measure: Sum of pain intensity difference (SPID) from baseline to 8 hours.

Results: Among 122 patients randomized, 70.5% and 28.7% had moderate or mild postsurgical pain at baseline, respectively. The mean SPID score was significantly greater in the oxymorphone IR group, showing greater pain relief, compared with the placebo group (least squares mean difference ± standard error, 76.9±28.09; 95% confidence interval, 21.26–132.59; $P=.007$). More placebo patients (48.4%) required rescue medication than oxymorphone IR patients (16.7%), with median times to use of rescue medication of 6 hours 54 minutes and more than 8 hours, respectively ($P<.001$). More patients (47.4%) rated oxymorphone IR "very good" or "excellent" for pain relief versus placebo (25.0%). No oxymorphone IR–treated patients discontinued because of adverse events (AEs) or experienced serious AEs.

Conclusions: Five milligrams of oxymorphone IR was well tolerated and effective at relieving mild or moderate postsurgical pain after outpatient knee surgery.

Key Words: Analgesia; Oxymorphone; Pain, postoperative; Rehabilitation.

ACUTE POSTSURGICAL PAIN IS among the most common types of pain.[1] Recent evidence suggests that the undertreatment of acute postsurgical pain is much more prevalent than was believed previously.[2-4] In addition to needless suffering, untreated pain may decrease productivity and increase health care expenditures.[1,5] The clinical usefulness of opioids for the treatment of pain has long been recognized, and morphine and its derivatives have been widely used for analgesia in a variety of clinical pain states. Ongoing concerns regarding opioid analgesia, including side effects and the need for frequent dosing, have underscored the need for new agents with proven efficacy, tolerability, and improved pharmacokinetic and pharmacodynamic profiles.

Oxymorphone (14-hydroxydihydromorphinone) is a semisynthetic opioid agonist with a high affinity for the μ-opioid receptor and significantly greater analgesic potency than its parent compound morphine.[6] Although oxymorphone-containing products were first approved by the U.S. Food and Drug Administration (FDA) in 1959, a new drug application for an oxymorphone immediate release (IR) tablet is currently under review by the FDA. The analgesic efficacy of 10, 20, and 30mg of oxymorphone IR has been established in patients with moderate to severe acute pain after orthopedic surgery involving osteotomy.[7]

The analgesic efficacy of 5mg of oxymorphone IR has not been studied previously, and the 5-mg dose level is not envisioned as monotherapy for severe pain. However, 5mg of oxymorphone IR may be useful in a variety of clinical settings, including for use as rescue medication for breakthrough pain or when initiating therapy with opioid-naive patients. Assessing efficacy in these settings is more complex, and we believe a selection of a patient population with mild to moderate pain provides a more straightforward method for testing the analgesic efficacy of 5mg of oxymorphone IR. Therefore, we performed a study to compare the analgesic efficacy and safety of up to 8 doses of 5mg of oxymorphone IR with that of placebo in an outpatient population experiencing mild or moderate pain after knee arthroscopy.

Because same-day outpatient surgery has become common and is accompanied by varying and unpredictable levels of patient pain,[8,9] there is an increasing need for flexible analgesic modalities that can be adjusted according to the level of patient pain. This study provides additional useful information on meeting these treatment goals.

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METHODS

This was a multicenter, double-blind, randomized, placebo-controlled study designed to assess the efficacy and safety of 5mg of oxymorphone IR in patients with mild to moderate pain after outpatient knee arthroscopy. The protocol and informed consent form were reviewed and approved by each site's institutional review board. The study was conducted in accordance with the provisions of the Declaration of Helsinki, FDA, Principles of Good Clinical Practice, and International Conference on Harmonization guidelines. All patients provided written informed consent.

Participants

Patients eligible for inclusion in this study were men and nonpregnant, nonlactating women (≥18y) who had completed outpatient knee arthroscopy (eg, meniscus repair, bone chip removal, exploratory arthroscopy, lateral release, synovial débridement, chondroplasty) and had an initial pain intensity score of between 30 and 70mm on a 100-mm visual analog scale (VAS) and a pain rating of mild or moderate on a categoric scale (ratings of none, mild, moderate, severe).

Patients were excluded if they had a history of allergy or known hypersensitivity to opioids, prior participation in an oxymorphone clinical trial, participation in any clinical trial within the past 30 days, opioid abuse within the past 6 months, or alcohol or substance abuse within the past 3 years. The use of long-acting oral or parenteral analgesics (opioid, nonopioid), cyclooxygenase-2 inhibitors, minor tranquilizers, muscle relaxants, or antihistamines within 24 hours of dosing of study drug was prohibited. Additional exclusion criteria included the use of dextromethorphan-containing medications or St. John's wort (in doses >1000mg/d) within 48 hours of dosing of study drug; use of a monoamine oxidase inhibitor within 2 weeks of dosing of study drug; and failure to be stabilized on tricyclic antidepressants, serotonin reuptake inhibitors, or amphetamines (used for attention-deficit/hyperactivity disorder) for at least 4 weeks before dosing of study medication.

Study Design

After surgery, patients who experienced mild to moderate pain on a categoric scale (none, mild, moderate, severe) and rated their pain intensity between 30 and 70mm on a 100-mm VAS were randomized to receive either oxymorphone IR or placebo for up to 8 hours. Treatment assignments were based on a computer-generated randomization schedule prepared by the sponsor before study initiation. Randomization to treatment assignment was balanced by using permuted blocks; patients were assigned to 1 of 2 treatment groups (5mg of oxymorphone IR, placebo). A randomization identifier was assigned to each bottle of study medication. Randomization identifiers were preprinted onto the labels and assigned as patients qualified for entry into the study. The randomization code was not revealed to patients, investigators, clinical staff, or sponsor monitors until all patients had completed the study and the database had been finalized and closed.

After administration of the first dose of study medication, patients were discharged with a diary, study medication (oxymorphone IR, placebo), and rescue analgesic. Patients were instructed by the investigator or other study personnel to take study medication as needed but not more frequently than every hour for up to 8 hours after the first dose (ie, a maximum of 8 doses). The first dose was administered while the patient was at the study site; thereafter, patients were to self-medicate at home. Patients using a rescue analgesic were discontinued from the study for lack of efficacy. Patients were contacted on the evening of surgery and the morning after surgery by study personnel for an assessment of study medication use and adverse events (AEs). In addition, on the morning after surgery, patients were asked to provide a global assessment of pain relief. All patients returned to the study site within 7 days after surgery for an end-of-study assessment.

The date and time of administration of each dose of study medication were recorded by the patients in diaries. Investigators reviewed diary data to verify compliance with the assigned treatment.

Efficacy Assessments

Patients used diaries to record their pain intensity (VAS) at 30 minutes and hourly through 8 hours after the first dose of medication, time of each dose of study medication, and time of dose of rescue medication (if applicable).

Efficacy variables included pain intensity difference (PID; defined as pain intensity at baseline minus the pain intensity at the time point being analyzed) assessed by VAS scores, time to rescue medication use, patient global assessment of pain relief in response to study medication, and the number of doses of study medication used.

The primary endpoint was the sum of the PID scores (SPID) from baseline to 8 hours. PID was calculated at time 0; 30 minutes postdose; and 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose. Each small area (trapezoid) is formed by the PID scores (heights of the trapezoid) at successive time points and length of the interval (base of the trapezoid). Thus, the SPID is the sum of all the small areas from time 0 to 8 hours and is the area under the curve.

At the morning-after-procedure telephone contact (or premature discontinuation, if the patient was still in the clinic), patients were asked to answer 1 question regarding overall pain. In response to the question "How do you rate the pain relief you obtained from the study medication?", the response choices were "excellent" (4), "very good" (3), "good" (2), "fair" (1), or "poor" (0).

Safety Assessments

Throughout the study and within 7 days of study end, AEs were recorded in the patient's clinical report form whether or not they were considered treatment related. An AE was defined as an unfavorable or unintended change in body structure (signs), body function (symptoms), or laboratory result (eg, chemistry profile, electrocardiogram, radiograph) or a worsening of a preexisting condition associated temporarily with use of study medication, whether or not considered related to study medication. All AEs were recorded with regard to intensity (mild, moderate, severe), relationship to study drug (probably, possibly, unlikely), and outcome. Any AE that was ongoing at the completion of the study was followed up until resolution or for 30 days.

Statistical Analyses

Efficacy analyses for the intent-to-treat (ITT) population were performed up to the 8-hour evaluation or time of rescue medication use (if applicable). All tests were 2 sided at a significance level of .05. The ITT population included all randomized patients who received at least 1 dose of study medication, did not violate protocol by vomiting within the first hour of the initial dose, and were properly consented to the study. For efficacy analyses, the last observation carried forward (LOCF) method was used. For the primary endpoint, the baseline observation carried forward method was used to confirm the results of the LOCF analyses.

The primary efficacy endpoint was the 8-hour SPID (VAS). This endpoint was analyzed by using an analysis of covariance (ANCOVA) model with treatment and center as effects and baseline pain intensity as the covariate. The ANCOVA model was prospectively specified in the protocol before the study was conducted. At the end of the analysis, the *P* value for the covariate was found to be .083. Because this is less than .10, the inclusion of baseline pain intensity in the model was deemed appropriate. Least squares means and the 95% confidence interval of the differences between treatment groups were calculated.

The mean difference for the primary efficacy endpoint (0–8h SPID VAS) between the oxymorphone IR and placebo groups was 79. The pooled standard deviation was 157.48. With a sample size of 57 for the oxymorphone IR group and 62 for the placebo group, this study had a power of 77% at a .05 significance level (2-sided test) to detect the treatment difference of 79. As noted earlier, the LOCF method was used to analyze the primary endpoint so that for patients discontinuing because of lack of efficacy or AEs, the last pain assessment before discontinuing was carried forward to 8 hours. Missing data at other time points were interpolated linearly, when possible.

Time to use of rescue medication was estimated by using the Kaplan-Meier method and analyzed by using the log-rank test.[10] Global evaluation of pain relief was summarized and analyzed by using the Wilcoxon rank-sum test, stratified by center. The frequency of the study medication doses and the duration of exposure were summarized descriptively.

Safety analyses were conducted on all treated patients and were based on the incidence of AEs, AEs resulting in discontinuation, and serious AEs. The number and percentage of patients experiencing AEs were summarized by System Organ Class (Medical Dictionary for Regulatory Activities) and preferred term.

RESULTS

Participants

One hundred seventy-two candidates were screened, and 122 were enrolled at 8 centers located in Utah, Arizona, and Alabama (4, 2, and 2 centers each, respectively). The distribution of enrolled patients among centers is outlined in table 1. Most of the 50 patients not enrolled either failed to meet inclusion and/or exclusion criteria or did not consent to participate. All patients who were enrolled were randomized (60 to treatment with 5mg of oxymorphone IR, 62 to placebo). All of the 122 patients received at least 1 dose of study medication and were included in the safety analysis; 119 were included in the ITT population. (Three patients were excluded from the efficacy analysis because of protocol violation [n=2] or improper consent [n=1].) A total of 48 (80.0%) patients who received 5mg of oxymorphone IR completed the study, compared with 29 (46.8%) patients who received placebo (fig 1). As expected, the most common reason for attrition from the study was lack of efficacy. Of the 12 patients in the 5mg of oxymorphone IR group who withdrew, 10 (16.7%) did so because of lack of efficacy and 2 (3.3%) because of protocol violation. Of the 33 patients in the placebo group who withdrew, 30 (48.4%) did so because of lack of efficacy, 2 (3.2%) because of an AE, and 1 (1.6%) patient was lost to follow-up.

Table 1: Distribution of Enrolled Patients Among 8 Clinical Trial Centers (N=122)

Center	n	%
001	6	4.92
002	7	5.74
003	24	19.67
004	1	0.82
005	7	5.74
006	50	40.98
008	9	7.38
009	18	14.75

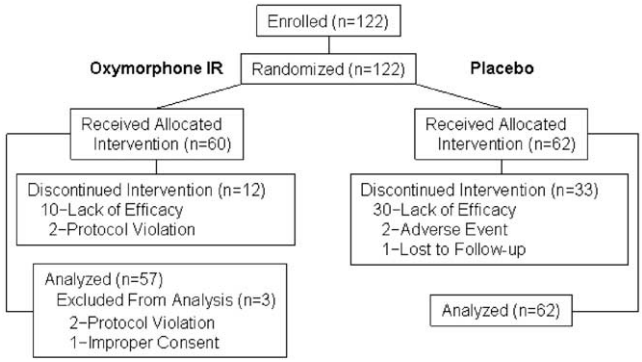

Fig 1. Patient disposition.

Demographics and baseline characteristics of randomized patients are shown in table 2. The mean age of enrolled patients was 45 years. Approximately 47% of patients in the 5mg of oxymorphone IR group and 68% of those in the placebo group were men. Most patients (87% of those in the 5mg of oxymorphone IR group, 81% of those in the placebo group) were white. The majority of patients (68% of those in the 5mg of oxymorphone IR group, 73% of those in the placebo group) had a baseline pain intensity rated as moderate.

Efficacy

Mean SPID scores at 0 to 8 hours. As shown in table 3, oxymorphone IR was significantly better than placebo for the primary efficacy endpoint. The mean SPID scores at 0 to 8

Table 2: Demographics and Baseline Patient Characteristics (N=122)

Characteristics	Treatment Groups: 5mg Oxymorphone IR (n=60)	Treatment Groups: Placebo (n=62)
Mean age ± SD (y)	44.8±14.48	45.0±13.78
Sex, n (%)		
Women	32 (53.3)	20 (32.3)
Men	28 (46.7)	42 (67.7)
Ethnic group, n (%)		
Black	3 (5.0)	3 (4.8)
White	52 (86.7)	50 (80.6)
Hispanic	3 (5.0)	8 (12.9)
Pacific Islander	1 (1.7)	1 (1.6)
Other	1 (1.7)	0 (0.0)
Pain intensity at baseline, n (%)		
Mild	18 (30.0)	17 (27.4)
Moderate	41 (68.3)	45 (72.6)
Severe	1 (1.7)	0 (0.0)

Abbreviation: SD, standard deviation.

Table 3: Analgesic Efficacy for ITT Patients

Variable, Mean	5mg Oxymorphone IR (n=57)	Placebo (n=62)	LS Mean Difference	Statistical Results*		
				95% CI	SE	*P*
SPID VAS: 0–8 hours	74.8	−4.2	76.9	21.26–132.59	28.09	.007

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error.
*Pairwise comparison statistical results are between oxymorphone IR and placebo. ANCOVA model included main effects for treatment and center and baseline pain intensity (VAS) as covariate in the model. Results of the analysis were confirmed with the baseline observation carried forward method: the least squares mean difference ± SE was 55.0±24.25 (P=.025).

hours were significantly greater (ie, showing greater pain relief) in the oxymorphone IR group compared with the placebo group. Oxymorphone IR showed a significantly ($P<.05$) greater reduction in pain intensity from baseline to all time points postbaseline (except 7h) compared with placebo (fig 2).

Pain intensity at 0 to 8 hours. Mean pain intensity (VAS) scores at 0 to 8 hours for ITT patients with moderate pain at baseline are depicted in figure 3. Compared with patients who received placebo, those treated with oxymorphone IR experienced a statistically significant reduction in pain intensity at all time points throughout the 8-hour postdose period, except for a marginally nonsignificant reduction in pain at 4 hours postdose. From 5 to 8 hours, the reductions in mean pain were also clinically meaningful in the oxymorphone IR group. A similar analysis for the small number of patients with mild baseline pain failed to reveal statistical or clinical improvements in the oxymorphone IR group (data not shown).

Rescue medication use. Only 16.7% of oxymorphone IR–treated patients used rescue medication, compared with approximately 50% of those who received placebo (fig 4). The median time to rescue medication use for the oxymorphone IR group was significantly longer (>8h) than that in the placebo group (6h 54min; $P<.001$). After a patient used rescue medication, he/she was withdrawn from the study, and additional data pertaining to amount and type of rescue medications used were not captured.

Patients' global satisfaction with treatment. Approximately half (47.4%) of the patients in the oxymorphone IR group rated their pain relief as "excellent" or "very good," compared with 25.0% of those in the placebo group (P=.009) (table 4).

Dosing. The mean number of doses taken by patients was similar in each group (placebo group, 3.9 doses; oxymorphone IR group, 4.6 doses). The mean dosing interval was slightly longer in the oxymorphone IR group (1.92h) compared with the placebo group (1.63h).

Safety

Although the study was not powered for safety analysis and statistical tests of differences between groups were not performed, the percentage of patients reporting at least 1 AE appeared similar for the oxymorphone IR and placebo groups: 32 (53.3%) patients treated with oxymorphone IR and 28 (45.2%) patients who received placebo experienced treatment-emergent AEs. The most common AEs in both groups were nausea, headache, and vomiting (table 5). None of the patients in the oxymorphone IR group withdrew because of an AE, and none experienced a serious AE. In the placebo group, 2 patients (3.2%) withdrew because of AEs, and 1 patient had a serious AE.

DISCUSSION

In this study in patients with mild to moderate pain after ambulatory arthroscopic knee surgery, 1 to 8 doses of 5mg of oxymorphone IR was statistically and clinically superior to placebo for all measures of pain control. The study achieved its primary endpoint with a power of 77%. The primary efficacy variable assessed in this study—mean SPID over 0 to 8 hours—was significantly (P=.007) greater in the oxymorphone IR group than in the placebo group. Considerably more patients in the placebo group than in the oxymorphone IR group (48%

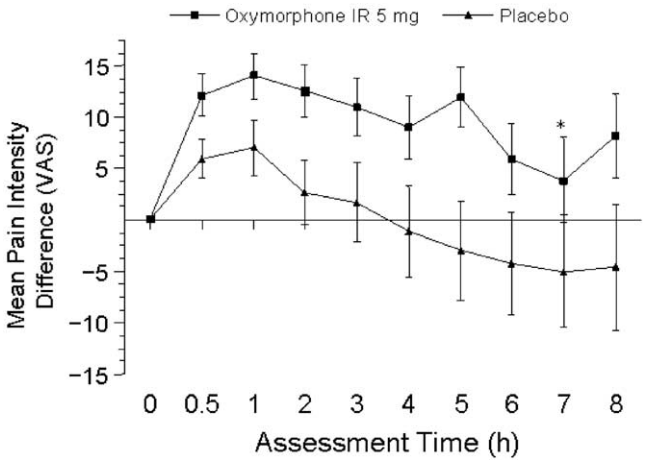

Fig 2. Mean pain intensity difference ± standard error of the mean (SEM) at 0 to 8 hours for ITT patients. *$P<.05$ at all time points except at 7 hours.

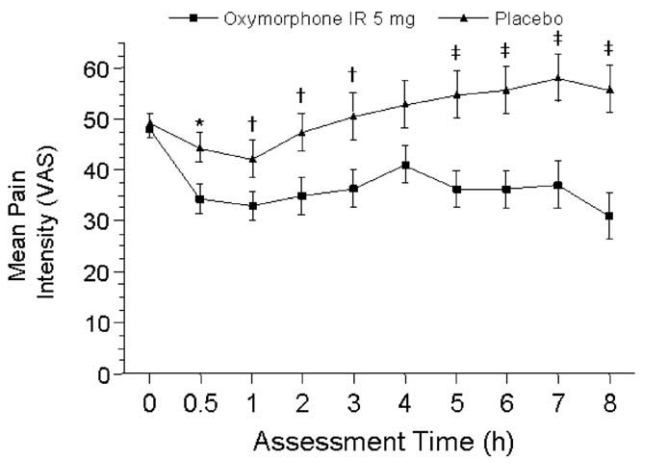

Fig 3. Mean pain intensity (VAS) ± SEM at 0 to 8 hours for ITT patients with moderate pain at baseline. *$P<.01$; †$P<.05$; ‡$P<.001$.

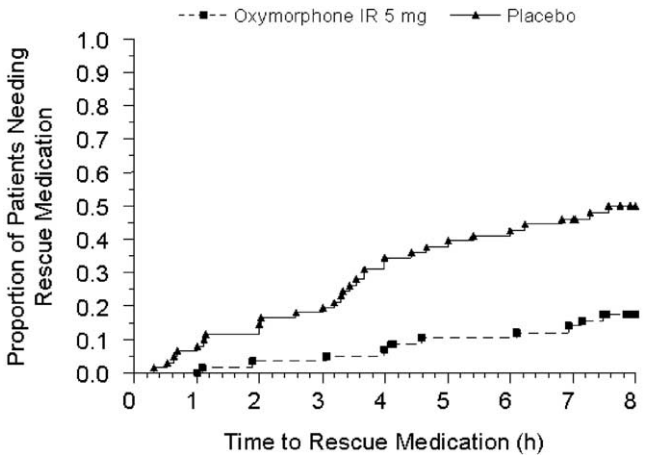

Fig 4. Time to use of rescue medication for ITT patients.

vs 17%) discontinued early from the study because of lack of efficacy. Most (>80%) oxymorphone IR–treated patients used no rescue medication, whereas about half of the patients who received placebo did use rescue medication. Moreover, the median time to rescue medication use was shorter in the placebo group than in the oxymorphone IR group. Substantially more oxymorphone IR–treated patients (47.4%) than placebo-treated patients (25.0%) rated their pain relief as "excellent" or "very good." Five milligrams of oxymorphone IR was generally safe and well tolerated.

Patients in the oxymorphone IR group took slightly more doses of study medication than did those in the placebo group, but this difference may be attributable to the larger percentage of patients in the oxymorphone IR group who completed the study compared with the placebo group. When only the patients completing the study are examined, 35% (10/29) of the placebo group received the maximum number of doses of study medication, whereas only 23% (11/48) of the oxymorphone IR group received 8 doses of study medication.

In the current study, the mean dosing interval was slightly longer in the oxymorphone IR group (1.92h) compared with the placebo group (1.63h). Although it might be expected that the analgesic ineffectiveness of placebo would result in much shorter dosing intervals, patients also had the option of discontinuing and receiving rescue medication, and almost half the placebo group chose to discontinue. In addition, the presence of "placebo responders" who completed the study likely contributed to the similarity in mean dosing interval.

Because this study included patients with either mild or moderate pain at baseline, it is conceivable that the efficacy observed for the total population was limited to 1 subgroup. As shown in figure 3, the group of patients with moderate pain at baseline who received oxymorphone IR clearly achieved better pain control than the placebo-treated subgroup with moderate baseline pain. Similar results were not observed with patients reporting mild pain at baseline. This observation must be interpreted cautiously, however, because the group with mild pain had fewer patients, and the study was not designed to separately assess efficacy in mild and moderate pain groups.

It is also important to note that the current study was not designed to establish the dosing interval of oxymorphone IR but rather to show that a 5-mg dose can be used to titrate to efficacious analgesia with good tolerability. In addition, the present study was designed to evaluate the efficacy of multiple 5-mg doses of oxymorphone IR; no conclusions can be drawn regarding the efficacy of a single 5-mg dose.

Most previous studies using the ambulatory arthroscopic knee surgery setting have assessed the efficacy of analgesic medications when used preemptively. These include studies of sufentanil or sufentanil plus methylprednisolone[11]; intra-articular bupivacaine with epinephrine or placebo plus epinephrine[9]; and intra-articular ketorolac, morphine, or bupivacaine administered during ambulatory knee arthroscopic meniscectomy.[12] Unlike these previous studies, we believe the design used in the current study is more sensitive than the preemptive investigations of intra-articular agents because only patients with confirmed pain were eligible for enrollment.

These recent studies underscore the increased use of ambulatory surgery and the need for appropriate analgesic modalities to ensure safe and adequate relief of acute postsurgical pain. Prior investigation has shown that either oxymorphone IR at 10 to 30mg or oxymorphone extended release at 20mg provides effective analgesia for patients who experience

Table 4: Patients' Global Assessment of Pain Relief*

Result	Placebo (n=56)†	5mg Oxymorphone IR (n=57)
Excellent or very good	14 (25.0)	27 (47.4)
Good	19 (33.9)	18 (31.6)
Fair or poor	23 (41.1)	12 (21.0)

NOTE. Values are n (%).
*P=.009 for treatment effect.
†Fifty-six of the 62 patients who received placebo were evaluable for global assessment of pain relief.

Table 5: Treatment-Emergent AEs

AEs	5mg Oxymorphone IR (n=60)	Placebo (n=62)
Patients with at least 1 AE	32 (53.3)	28 (45.2)
Nausea	17 (28.3)	12 (19.4)
Headache	10 (16.7)	5 (8.1)
Vomiting	8 (13.3)	8 (12.9)
Dizziness	4 (6.7)	1 (1.6)
Constipation	2 (3.3)	1 (1.6)
Dry mouth	2 (3.3)	1 (1.6)
Burning sensation	1 (1.7)	0 (0.0)
Diarrhea	1 (1.7)	2 (3.2)
Dysuria	1 (1.7)	0 (0.0)
Fatigue	1 (1.7)	0 (0.0)
Joint swelling	1 (1.7)	1 (1.6)
Laryngitis	1 (1.7)	0 (0.0)
Muscle twitching	1 (1.7)	0 (0.0)
Pruritus	1 (1.7)	3 (4.8)
Somnolence	1 (1.7)	1 (1.6)
Sweating increased	1 (1.7)	0 (0.0)
Syncope	1 (1.7)	0 (0.0)
Tinnitus	1 (1.7)	0 (0.0)
Bacterial arthritis	0 (0.0)	1 (1.6)
Bradycardia	0 (0.0)	1 (1.6)
Dyspepsia	0 (0.0)	1 (1.6)
Hypotension	0 (0.0)	1 (1.6)
Insomnia	0 (0.0)	1 (1.6)
Migraine	0 (0.0)	1 (1.6)
Neck pain	0 (0.0)	1 (1.6)
Pain in extremity	0 (0.0)	1 (1.6)

NOTE. Values are n (%).

moderate to severe postoperative pain after major orthopedic procedures.[7,13] The current study establishes that 5mg of oxymorphone IR is a generally safe and well-tolerated dose that can be effectively titrated to relieve mild to moderate postsurgical pain. As with other low-dose opioids, the 5-mg oxymorphone IR dose may also be useful as an initial dose to begin titration in opioid-naive patients, as rescue medication for breakthrough pain, during dose titration or opioid conversion, and as a complement to sustained-release formulations of the same opioid. Further study of these and other uses of low-dose oxymorphone IR will help elucidate its clinical potential.

CONCLUSIONS

In patients who underwent outpatient knee surgery, 5mg of oxymorphone IR was statistically and clinically superior to placebo for all measures of pain control. Five milligrams of oxymorphone IR was well tolerated, with a mean consumption of 4.6 doses within the 8-hour treatment period. Most patients receiving oxymorphone IR appeared to be able to effectively and safely self-dose to satisfactory pain control in a manner similar to that of patient-controlled analgesia, except that low-dose oral opioids were used. However, the study was not designed to assess satisfactory analgesia as the primary endpoint. Additional studies are warranted to assess whether low-dose oral opioids are an appropriate treatment option for ambulatory surgical patients.

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