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A Novel Injectable Formulation of Diclofenac Compared with Intravenous Ketorolac or Placebo for Acute Moderate-to-Severe Pain After Abdominal or Pelvic Surgery: A Multicenter, Double-Blind, Randomized, Multiple-Dose Study

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BACKGROUND: Injectable formulations of diclofenac have long been available in Europe and other countries. These formulations use a default dose of 75 mg of diclofenac delivered IV over 30 to 120 minutes or as an IM injection. A novel formulation of injectable diclofenac sodium, Dyloject® , is solubilized with hydroxypropyl β-cyclodextrin (HPβCD) so that it can be given IV or IM in a small volume bolus. In this multicenter, multiple-dose, multiple-day, randomized, double-blind, parallel-group phase 3 study, we investigated whether lower doses of HPβCD diclofenac delivered as a small volume bolus would be effective for the management of acute pain after abdominal or pelvic surgery.
METHODS: Adults with moderate and severe pain, defined as ≥50 mm on a 0 to 100 mm visual analog scale, within 6 hours after surgery were randomly assigned (1:1:1:1 ratio) to receive HPβCD diclofenac, 18.75 mg or 37.5 mg; ketorolac tromethamine 30 mg; or placebo. Patients in all treatment arms received a bolus IV injection every 6 hours until discharged. They were observed for at least 48 h, and for up to 5 days. Rescue IV morphine was available any time, up to a total of 7.5 mg over a 3-hour period. The primary efficacy measure was the sum of pain intensity differences from 0 to 48 hours after study drug initiation.
RESULTS: Three hundred thirty-one patients received ≥1 dose of study drug. Over the first 48 hours, both IV HPβCD diclofenac doses, as well as ketorolac, produced significant reductions in pain intensity over placebo (all $P < 0.05$), as well as significant reductions in the need for rescue morphine administration. Both doses of HPβCD diclofenac, as well as ketorolac, significantly reduced rescue morphine dosages, as compared to placebo ($P \leq 0.0001$), and time to rescue morphine administration was significantly increased by treatment with 18.75 mg diclofenac and ketorolac. The overall incidence of treatment-related adverse events was 20.2%. No treatment-related serious adverse events were reported in either diclofenac dose group, whereas only 1 was reported in the ketorolac group.
CONCLUSIONS: For patients with acute moderate and severe pain after abdominal or pelvic surgery, repeated 18.75 mg and 37.5 mg doses of HPβCD diclofenac provided significant analgesic efficacy, as compared to placebo. Significant analgesic efficacy was also provided by the active comparator ketorolac. Both HPβCD diclofenac and ketorolac significantly reduced the need for opioids. (Anesth Analg 2012;115:1212–20)

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In recent decades, multimodal analgesia has become standard clinical practice for the control of moderate and severe acute postoperative pain.[1–3] Adding nonselective nonsteroidal antiinflammatory drugs (NSAIDs) to opioids results in better analgesia, less opioid consumption, and consequent decreases in postoperative nausea, vomiting, and sedation.[4,5] Parenteral NSAIDs are often preferred when patients cannot tolerate or are unable to take oral medications and when they require rapid onset of analgesia.[6] Although combining NSAIDs with opioids is generally beneficial, the effectiveness of NSAIDs as monotherapy for moderate or severe pain has been infrequently studied.

First introduced in Europe in 1973, diclofenac is classified as an NSAID with analgesic, antiinflammatory,

and antipyretic activity, and is highly effective and well tolerated in the treatment of acute pain.[7,8] Its mechanism of action involves both cyclooxygenase (COX)-1 and COX-2 antagonism, and on a milligram basis, it is one of the most potent COX inhibitors clinically available.[9] Additional effects of diclofenac include opening of KCNQ2/3 potassium channels,[10,11] *N*-methyl-D-aspartate receptor inhibition, and stimulation of endorphinergic neural pathways.[12]

An injectable formulation of diclofenac is the most commonly used non-narcotic injectable analgesic in the world (data on file for 2010 U sales, IMS Health, Westport, CT). Because the diclofenac molecule is poorly soluble, the original injectable formulations (e.g., Voltarol®, Novartis Pharmaceuticals UK Ltd., Surrey, UK) contain propylene glycol and benzyl alcohol. To lessen venous irritation when given IV, these formulations require preparation for each IV dose (dilution and buffering with 100 to 500 mL of diluent) and slow infusion over 30 to 120 minutes.[a] This need for prolonged infusion could slow the onset of analgesia and require the availability of additional IV access sites for concurrent administration of other agents that are incompatible. A recent approach to reducing the duration of administration of IV diclofenac and increasing its tolerability is to solubilize it with a cyclic carbohydrate derivative, hydroxypropyl β-cyclodextrin (HPβCD), thus allowing therapeutic doses of diclofenac to be quickly injected as a small volume (≤1 mL) bolus.

A single-dose study of HPβCD diclofenac 75 mg for pain after third molar extraction demonstrated a significantly faster onset of action than the original injectable formulation of diclofenac.[13] Subsequently, a single 37.5-mg dose of HPβCD diclofenac was shown to produce a maximal analgesic effect in a molar extraction trial evaluating doses ranging from 3.75 through 75 mg.[14] The current study was designed to test the hypothesis that repeated doses of HPβCD diclofenac (18.75 and 37.5 mg, given every 6 hours) would provide superior analgesic efficacy versus placebo for the treatment of acute moderate-to-severe pain after abdominal or pelvic surgery. The primary efficacy endpoint was the sum of pain intensity differences (SPID) over 48 hours. A standard 30 mg dose of ketorolac tromethamine, the only other injectable nonopioid analgesic available at the time of the study, was used as an active comparator with regard to efficacy and safety.

METHODS

The study was registered on March 13, 2007 at ClinicalTrials.gov (identifier NCT00448110). The protocol was approved by each site's IRB, and all patients provided written, IRB-approved informed consent.

Patients

At 16 US sites, adults 18 to 65 years old were screened if they were scheduled for abdominal or pelvic surgery within 2 weeks. Key inclusion criteria were moderate-to-severe postoperative pain, defined as intensity ≥50 mm on a 0 to 100 mm visual analog scale (VAS) within 6 hours after surgery, and weight >50 kg. Exclusion criteria were applied to the preoperative, intraoperative, and postoperative periods. Key preoperative exclusion criteria were a history of chronic disease or severe asthma, a recent (≤6 months) cardiovascular event or clinically significant abnormal electrocardiogram (ECG) at screening, consumption of aspirin (except ≤325 mg/day for antiplatelet cardiac protection), opioids, other NSAIDs, other common analgesics, major and minor tranquilizers, or antihistamines ≤24 hours before study drug initiation (except if administered during surgery), consumption of a monoamine oxidase inhibitor, tryptophan, carbamazepine, or valproate ≤2 weeks before baseline, any clinically significant laboratory abnormality, and previous or present peptic ulceration, gastrointestinal bleeding, or any bleeding diathesis. In addition, long-acting NSAIDs or COX-2 inhibitors were to be discontinued 3 days before surgery. Subjects were also excluded in the event of a known allergy to diclofenac, NSAIDs, morphine, anesthetics, or any excipient of the study preparation, receipt of any other investigational medication within 3 months before administration of the study drug, known or suspected alcohol or drug abuse, and unwillingness to remain in the clinical research center for 2 nights or return within 5 to 9 days for a safety follow-up visit. Female subjects with a positive pregnancy test within 24 hours of surgery or who were lactating at screening were also excluded. Intraoperative exclusion criteria were subcostal incision during surgery and concomitant use of NSAIDs or acetaminophen (other intraoperative medications were not restricted). Subjects with abnormal postoperative baseline ECG were excluded from study participation. In addition, patient-controlled analgesia was not permitted before or during study drug dosing. Nitrous oxide and very short-acting barbiturates or benzodiazepines were allowed, provided that there was a ≥1.5-hour washout period before study drug administration to avoid residual effects on pain intensity assessments. If insufficient washout time (<1.5 hours) preceded scheduled study drug dosage, the patient was not enrolled in the study and did not receive the study drug. Postoperative regional anesthesia was not allowed.

Study Design

This was a multicenter, multiple-dose, multiple-day, randomized, double-blind, active- and placebo-controlled, parallel-group phase 3 study. Within 6 hours of completing surgery, patients who reported a VAS pain score ≥50 mm and met all other eligibility requirements were randomly assigned to 1 of 4 treatment groups (1:1:1:1 ratio): HPβCD diclofenac 18.75 mg or 37.5 mg; ketorolac tromethamine 30 mg; or placebo. Assignments were made according to a computer-generated random number code, and clinical staff and patients were blinded to study drug assignment. The first dose of study medication (1 mL IV bolus) was received by patients in all treatment arms within this first 6-hour period (Table 1). Administration of the first dose of study drug was taken as time 0, and all subsequent dosing and evaluation time points were in relation to time of first study drug dose. Subsequent injections were received every 6 hours until discharge or until patient withdrawal/discontinuation from the study, due either to an adverse

[a] Novartis Pharmaceuticals UK Ltd. Voltarol® ampoules. Summary of product characteristics. Available at: http://www.medicines.org.uk/emc/document.aspx?documentid=1339. Accessed January 16, 2012.

Table 1. Baseline Demographic and Clinical Characteristics[a]

Variable, n = 331	Placebo (n = 76) n (%)	Ketorolac 30 mg (n = 82) n (%)	Diclofenac 18.75 mg (n = 86) n (%)	Diclofenac 37.5 mg (n = 87) n (%)
Age, years				
Mean (SD)	42.8 (9.66)	42.9 (11.42)	42.6 (11)	43.3 (10.83)
Gender				
Male	15 (19.7%)	15 (18.3%)	13 (15.1%)	19 (21.8%)
Female	61 (80.3%)	67 (81.7%)	73 (84.9%)	68 (78.2%)
Ethnicity				
Caucasian	62 (81.6%)	60 (73.2%)	68 (79.1%)	65 (74.7%)
Asian	0%	2 (2.4%)	0%	2 (2.3%)
Hispanic	8 (10.5%)	10 (12.2%)	10 (11.6%)	10 (11.5%)
African-American	6 (7.9%)	10 (12.2%)	6 (7.0%)	9 (10.3%)
Other	0%	0%	2 (2.3%)	1 (1.1%)
Height, cm				
Mean (SD)	166.6 (8.13)	167.6 (9.76)	165.5 (10.3)	167.2 (9.62)
Weight, kg				
Mean (SD)	82.6 (19.29)	84.2 (23.9)	83.4 (18.3)	83.9 (18.67)
Range	46–142	41–157	47–150	53–155
Time to first dose, min				
Mean (SD)	132.8 (101.5)	123.3 (96.2)	128.2 (93.8)	136.2 (110.1)
Median	93.5	85.0	89.0	92.0
Range	5–417	7–373	5–376	12–371
Surgical procedure[b]				
Abdominal hysterectomy	25 (18 [72.0%], 7 [28.0%])	20 (17 [85.0%], 3 [15.0%])	29 (22 [75.9%), 7 [24.1%])	18 (15 [83.3%], 3 [16.7%])
Vaginal hysterectomy	9 (0 [0.0%], 6 [66.7%])	15 (0 [0.0%], 10 [66.7%])	13 (0 [0.0%], 6 [46.2%])	20 (0 [0.0%], 13 [65.0%])
Abdominal surgery	14 (3 [21.4%], 11 [78.6%])	12 (2 [16.7%], 10 [83.3%])	12 (2 [16.7%], 10 [83.3%])	12 (4 [33.3%], 8 [66.7%])
Inguinal hernia repair	9 (8 [88.9%], 1 [11.1%])	14 (13 [92.9%], 1 [7.1%])	10 (9 [90.0%], 1 [10.0%])	11 (10 [90.9%], 1 [9.1%])
Myomectomy	3 (3 [100.0%], 0 [0.0%])	5 (5 [100.0%], 0 [0.0%])	3 (3 [100.0%], 0 [0.0%])	6 (6 [100.0%], 0 [0.0%])
Partial colectomy	3 (2 [66.7%], 1 [33.3%])	3 (3 [100.0%], 0 [0.0%])	1 (0 [0.0%], 1 [100.0%])	2 (0 [0.0%], 2 [100.0%])
Pelvic surgery	4 (1 [25.0%], 3 [75.0%])	5 (1 [20.0%], 4 [80.0%])	6 (0 [0.0%], 6 [100.0%])	6 (0 [0.0%], 6 [100.0%])
Salpingo-oophorectomy	2 (0 [0.0%], 2 [100.0%])	3 (2 [66.7%], 1 [33.3%])	5 (3 [60.0%], 2 [40.0%])	2 (2 [100.0%], 0 [0.0%])
Ventral hernia repair	1 (1 [100.0%], 0 [0.0%])	1 (1 [100.0%], 0 [0.0%])	3 (3 [100.0%], 0 [0.0%])	3 (2 [66.7%], 1 [33.3%])
Other	6 (2 [33.3%], 4 [66.7%])	4 (2 [50.0%], 2 [50.0%])	4 (3 [75.0%], 1 [25.0%])	7 (3 [42.9%], 4 [57.1%])
Baseline pain intensity, VAS				
n[c]	76	80	85	86
Mean (SD)	67.7 (14.12)	67.8 (13.81)	67.0 (12.58)	70.8 (15.64)
Median	65.5	65.0	65.0	69.0
Range	50–98	50–99	50–100	50–100

VAS = visual analog scale (0–100 mm).

[a] Number of patients per study center ranged from 1–80, with 10 centers providing 1–20 subjects, 4 centers providing 21–40 subjects, and 2 centers providing >40 subjects.

[b] Total (n open procedures [% of total], n laparoscopic procedures [% of total]); note that for some patients, open vs. laparoscopic was not specified.

[c] Four randomized subjects did not have baseline pain intensity values and were not included in this assessment.

event (AE), inadequate pain control, noncompliance with the study protocol, or at the investigator's discretion. Patients were observed for at least 48 h from baseline (study drug initiation), unless discharged earlier, and for up to 5 days.

Rescue medication (bolus IV morphine 5 mg, titrated up to 7.5 mg after 30 min if analgesia was inadequate) was available upon patient request, up to once every 3 hours any time after administration of the initial dose of study drug, but patients were encouraged to wait at least 1 hour after study medication injection. Patients were not denied rescue medication and if adequate analgesia was not achieved with morphine, the patient was withdrawn from the study and given pain medication in accordance with the investigator's usual practice.

Outcome Measures and Assessments

Pain intensity was assessed at rest and recorded by subjects on a 0 to 100 mm VAS (0 = "no pain"; 100 = "worst pain imaginable") at specified time points (5, 10, 15, 30, and 45 minutes, and 1, 2, 3, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 hours; timeline, Fig. 1) over the 48 hours after the first dose of study medication. Patients remaining at the site longer had their pain assessed every 6 hours until discharge. The primary efficacy measure was SPID (in mm·hours) over the 0- to 48-hour time interval after the first dose of study drug. Assessments were reported by patients and scored using standardized tools. Pain intensity difference (PID) was calculated at each time point by subtracting recorded pain intensity from baseline pain intensity. SPID was calculated as the area under the curve of the PID scores. Secondary efficacy measures were

- SPID over 0 to 24 hours;
- total pain relief (area under the pain relief curve) for the 0- to 24- and 0- to 48-hour intervals (0 to 72, 0 to 96, and 0 to 120 hours as well, if data permitted); pain relief was recorded using a 0 to 100 mm VAS (0 = "no relief"; 100 = "complete pain relief") at the same time

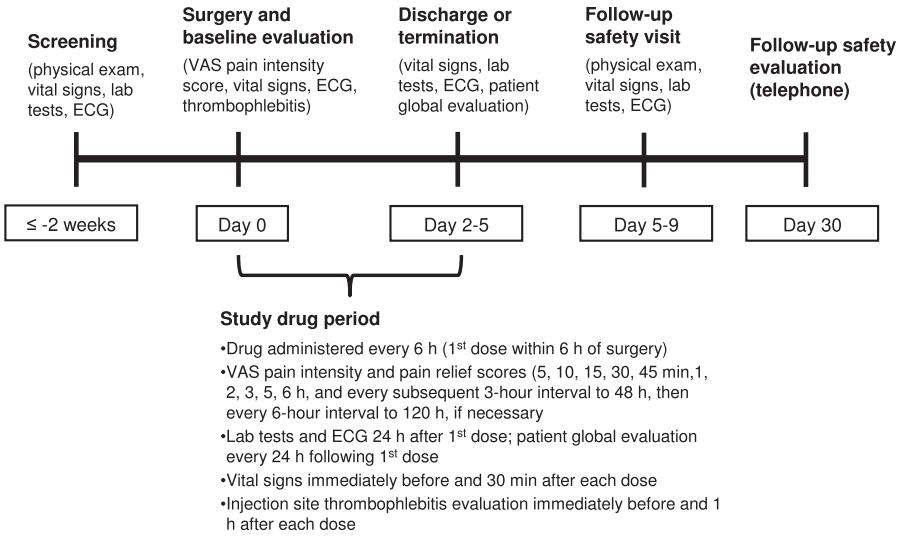

Figure 1. Study timeline. Upon meeting screening and baseline qualifying criteria, patients were to receive study drug for 2 to 5 days. Key efficacy assessment and safety evaluation time points are indicated. VAS = visual analog scale; ECG = electrocardiogram.

Table 2. Injection Site Thrombophlebitis Scale (Adapted From Dinley[15])

Grade/scale	Severity/description
0	No reaction
1	Tenderness along vein
2	Continuous tenderness or pain with redness
3	Palpable swelling or thrombosis within the length of cannula
4	Palpable swelling or thrombosis beyond the length of the cannula
5	As for Grade 4, with overt infection

points at which pain intensity was recorded (excluding baseline);
- proportion of patients with clinically meaningful (≥30%) reduction in pain intensity (vs baseline, using 0 to 100 mm VAS);
- PID at each scheduled assessment;
- time from administration of study drug to administration of rescue medication;
- frequency and amount of rescue medication; and
- patient-reported global evaluation of the study drug at 24 and 48 hours on a 5-point categorical scale ("excellent," "very good," "good," "fair," and "poor").[13]

Patients returned for a safety follow-up 5 to 9 days after baseline and received a follow-up telephone call 30 days postbaseline. Safety assessments included physical examinations, laboratory testing, vital signs, 12-lead ECG, and evaluation of thrombophlebitis at the site of study drug injection using a 6-point scale[15] (Table 2 and Fig. 1). AEs were recorded throughout the study.

Statistical Analysis

Study sample size was based on the calculation that 80 patients in the intent-to-treat (ITT) population per treatment group would provide 80% power to detect a PID of 540 mm·hours between placebo and diclofenac groups over a 48-hour period. This calculation was based on an estimated SD of 1200 mm·hours projected from a prior study by the sponsor.[14]

Efficacy analyses were conducted using Statistical Analysis Software® and unless otherwise noted refer to the ITT population. SPID efficacy measures and pain relief scores were calculated using the trapezoidal rule. For SPID calculations, evaluations after administration of rescue medication or after withdrawal due to AEs or lack of efficacy were imputed in accordance with prespecified rules. If rescue medication was required, pain intensity and relief assessments were obtained before rescue analgesic administration. If rescue medication was administered within 3 hours of the next scheduled assessment, the worst assessment over the preceding 6 hours was carried forward. If the assessments necessary to do this were unavailable, assessments were imputed with the baseline score. For patients discontinuing because of AEs or lack of efficacy, baseline scores were carried forward. The same rules were applied to pain relief assessments.

PID, amount of rescue medication, and patient global evaluation were analyzed using analysis of covariance models with treatment and center as factors and baseline pain intensity as a covariate. Differences between active treatments and placebo were tested with linear contrasts. Comparisons with respect to the primary efficacy measure were performed as follows: diclofenac 37.5 mg versus placebo at the 0.05 level of significance; if the result was significant, diclofenac 18.75 mg was tested versus placebo at the 0.05 level of significance. Ketorolac was used as an active comparator to confirm assay sensitivity. Comparisons between the diclofenac and ketorolac groups were not performed because the study was not powered to discern significant differences between active treatments.

The proportion of patients reporting ≥30% reduction from baseline in pain intensity was analyzed with the Cochran-Mantel-Haenszel test with center as a stratification variable. Time to meaningful (≥30%) reduction in pain intensity and time to administration of rescue medication were analyzed with Kaplan-Meier survival analysis techniques. Descriptive statistics were used for AEs, laboratory test results, vital signs, thrombophlebitis, and ECG results. Logistic regression was used to estimate the relative risk of cardiovascular events.

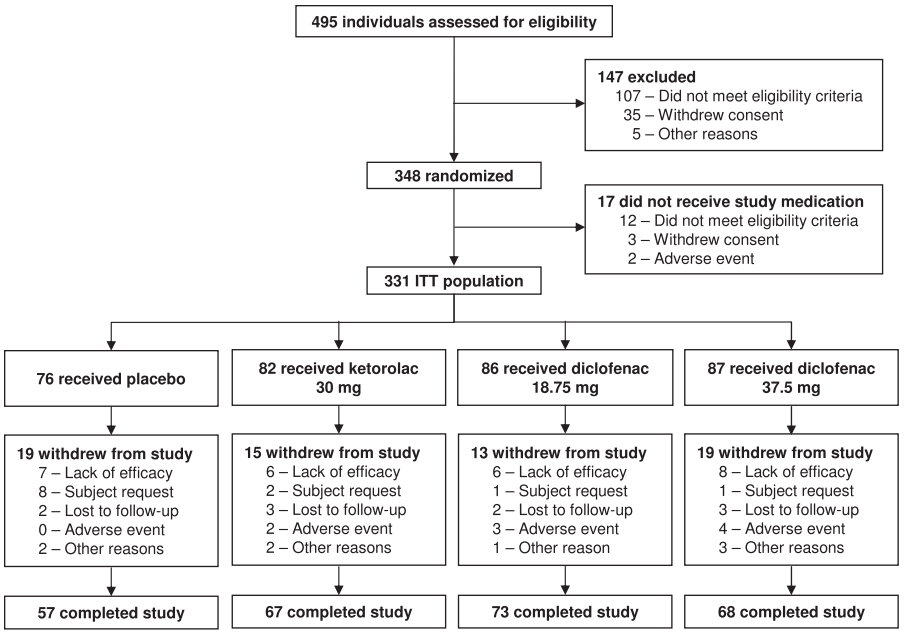

Figure 2. Distribution of patients in study groups and reasons for study withdrawal. A total of 331 patients received at least 1 dose of study drug and were included in the analysis. Overall, 80% of patients completed the study (placebo, 75%; ketorolac 30 mg, 81.7%; diclofenac 18.75 mg, 84.9%; diclofenac 37.5 mg, 78.2%).

RESULTS

Three hundred forty-eight patients were randomly assigned to a treatment arm after surgery (≥85 subjects per treatment group) and 331 received ≥1 dose of study drug (Fig. 2). Of the 17 subjects who were randomized but did not receive study drug, the main reason for exclusion was a failure to meet eligibility criteria, as outlined above (12/17 subjects [70.6%]). Of these 12 subjects, insufficient pain on the VAS scale was the predominant reason for exclusion (9/12 [75%]). All 331 patients receiving ≥1 treatment dose were included in the ITT population and were assessed for demographics, efficacy, and safety. Distribution of the ITT population among treatment groups was as follows: placebo, n = 76; diclofenac 18.75 mg, n = 86; diclofenac 37.5 mg, n = 87; and ketorolac, n = 82. The majority of patients (80.1%, n = 265) completed the study. The median number of doses received across treatment groups was 8 (range, 1 to 13). Forty-nine patients (14.8%) received study drug for 1 day, 267 (80.6%) for 2 days, and 15 (4.5%) for 3 days.

Most patients were female (81%) and Caucasian (77%; Table 1). The mean age in each treatment group was 43 years, and mean subject body weight was 84 kg. There were no significant differences across treatment groups for any baseline characteristic (all $P > 0.05$). The aggregate mean baseline pain intensity was 68.4 mm, within the moderate-to-severe range. At baseline, 60% of patients had moderate pain (50 < VAS <70) and 40% had severe pain (VAS >70). Pain intensity at baseline was not significantly different among treatment groups.

Efficacy

Primary Efficacy Measure

Over the first 48 hours after study drug initiation, mean SPID was significantly greater for both doses of HPβCD diclofenac (18.75 mg, P = 0.032; 37.5 mg, P = 0.0001), and for ketorolac (P < 0.0001), than for placebo (Fig. 3). These results were consistent regardless of baseline pain intensity.

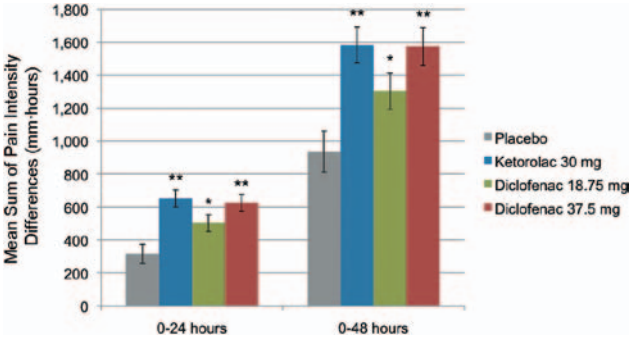

Figure 3. Sum of pain intensity differences (SPID) from 0 to 24 h and 0 to 48 h. Visual analog scale pain intensity was assessed at baseline and at specified intervals in the 48 h subsequent to first drug dose. Pain intensity difference was calculated as the baseline pain intensity minus pain intensity at each scheduled assessment (larger numbers indicate greater pain relief). SPID is shown for the 0 to 24 and 0 to 48 h time periods for placebo, ketorolac 30 mg, diclofenac 18.75 mg, and diclofenac 37.5 mg (error bars indicate SE). There were no significant differences in SPID among active treatments. *P < 0.05, **P ≤ 0.0001 vs placebo.

There were no statistically significant differences in efficacy among the 3 active treatment groups.

Secondary Efficacy Measures

Similar to the 0- to 48-hour interval, SPID over the 0- to 24-hour interval was significantly greater than placebo for both HPβCD diclofenac doses (18.75 mg, p = 0.015; 37.5 mg, P < 0.0001) and ketorolac (P < 0.0001) (Fig. 3). For the 0- to 72-hour period, 18.75 mg diclofenac did not lead to a significantly greater SPID than placebo (P = 0.08), but 37.5 mg diclofenac (P = 0.0010) and ketorolac (P = 0.0018) did significantly improve SPID. Mean PID was consistently greater with the active treatments than with placebo over the first 45 hours, with the exception of the 6-hour and 30-hour assessments.

The criterion for meaningful pain relief (≥30% reduction) was based on the threshold previously reported as

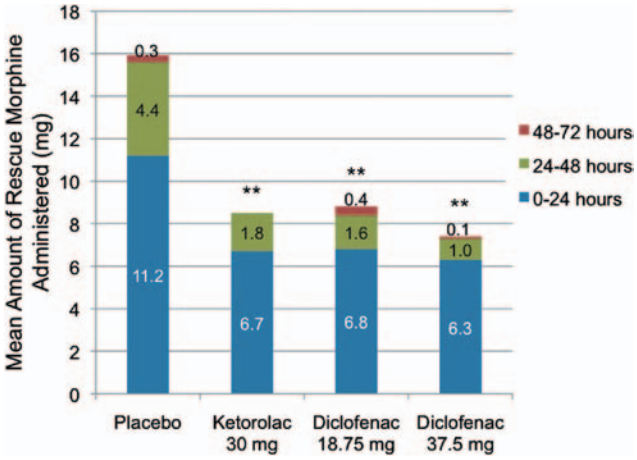

Figure 4. Mean amount of rescue morphine administered. Rescue medication (IV morphine) was available any time after the initial dose of study drug. Subjects, however, were encouraged to wait at least 1 h after the initial study drug dosing. Mean rescue morphine administered per day postsurgery is shown for days 1 (0 to 24 h), 2 (24 to 48 h), and 3 (48 to 72 h). The total cumulative dose received postsurgery (0 to 72 h) was 15.9 mg for placebo, 8.5 mg for ketorolac (30 mg), 8.8 mg for the 18.75 mg dose of diclofenac, and 7.4 mg for the 37.5 mg dose of diclofenac. $^{**}P \leq 0.0001$ vs placebo for 0 to 24, 0 to 48, and 0 to 72 h intervals.

meaningful for acute pain in the postoperative setting.[16] During the first 6-hour dosing period, 55.3% (n = 42) of patients receiving placebo had a ≥30% reduction in pain intensity, whereas 76.8% (n = 63) of patients receiving ketorolac, 64.3% (n = 54) of patients receiving 18.75 mg HPβCD diclofenac, and 69.8% (n = 60) of patients receiving 37.5 mg HPβCD diclofenac reported a ≥30% reduction. The mean time to ≥30% pain intensity reduction among subjects reporting this decline within 6 hours after first study drug dose was rapid across all treatment groups (27 to 33 minutes for the modified ITT population). Median times to ≥30% pain intensity reduction did not differ among any of the active treatment groups and placebo (all $P > 0.05$).

Total pain relief was significantly greater with active treatment than with placebo over the 0- to 24- and 0- to 48-hour time intervals (p = 0.0002 and 0.0008, respectively). Use of both 18.75 mg and 37.5 mg diclofenac resulted in significantly greater mean total pain relief than placebo (18.75 mg: P = 0.037 for the 0- to 24-hour interval and 0.038 for the 0- to 48-hour interval; 37.5 mg: P = 0.0018 for the 0- to 24- and 0- to 48-hour intervals), as did use of 30 mg ketorolac ($P < 0.0001$ for the 0- to 24-hour interval and P = 0.0001 for the 0- to 48-hour interval). There were no significant differences among active treatments.

Table 3. Summary of Adverse Events

AE (n = 331 total subjects)	Placebo (n = 76) n (%)	Ketorolac 30 mg (n = 82) n (%)	Diclofenac 18.75 mg (n = 86) n (%)	Diclofenac, 37.5 mg (n = 87) n (%)	Total Diclofenac (n = 173) n (%)
Nausea	29 (38.2%)	22 (26.8%)	26 (30.2%)	22 (25.3%)	48 (27.7%)
Flatulence	19 (25.0%)	22 (26.8%)	22 (25.6%)	12 (13.8%)	34 (19.7%)
Injection site pain, irritation	5 (6.6%)	17 (20.7%)	19 (22.1%)	14 (16.1%)	33 (19.1%)
Constipation	11 (14.5%)	8 (9.8%)	17 (19.8%)	16 (18.4%)	33 (19.1%)
Headache	15 (19.7%)	14 (17.1%)	9 (10.5%)	7 (8.0%)	16 (9.2%)
Insomnia	9 (11.8%)	7 (8.5%)	9 (10.5%)	7 (8.0%)	16 (9.2%)
Vomiting	11 (14.5%)	7 (8.5%)	7 (8.1%)	5 (5.7%)	12 (6.9%)
Blood CPK*b* increased	3 (3.9%)	12 (14.6%)	7 (8.1%)	6 (6.9%)	13 (7.5%)
Pyrexia	8 (10.5%)	9 (11.0%)	2 (2.3%)	6 (6.9%)	8 (4.6%)
Thrombophlebitis	9 (11.8%)	6 (7.3%)	6 (7.0%)	3 (3.4%)	9 (5.2%)
Pruritus	5 (6.6%)	3 (3.7%)	4 (4.7%)	6 (6.9%)	10 (5.8%)
Tachycardia	5 (6.6%)	4 (4.9%)	2 (2.3%)	2 (2.3%)	4 (2.3%)
Diarrhea	3 (3.9%)	6 (7.3%)	2 (2.3%)	0 (0.0%)	2 (1.2%)
Number of patients experiencing ≥1 AE	62 (81.6%)	72 (87.8%)	73 (84.9%)	73 (83.9%)	146 (84.4%)

AE = adverse event; CPK = creatine phosphokinase.

Table 4. Bleeding- and Wound-Healing-Related Adverse Events

Patients n = 331 total	Placebo (n = 76) n (%)	Ketorolac 30 mg (n = 82) n (%)	Diclofenac 18.75 mg (n = 86) n (%)	Diclofenac 37.5 mg (n = 87) n (%)	Total Diclofenac (n = 173) n (%)
Patients on concomitant anticoagulants	47 (62%)	49 (60%)	55 (64%)	50 (58%)	105 (61%)
Type of bleeding-related AE					
Anemia	3 (3.9%)	2 (2.4%)	0 (0.0%)	4 (4.6%)	4 (2.3%)
Rectal hemorrhage	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (0.6%)
Vaginal hemorrhage	1 (1.3%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (0.6%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.6%)
Abdominal hematoma	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Incision site complication	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound complication	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound dehiscence	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total patients with ≥1 bleeding-related AE	5 (6.6%)	5 (6.1%)	2 (2.3%)	5 (5.7%)	7 (4.0%)
Total patients on concomitant					
Anticoagulants with ≥1 bleeding-related AE	4 (8.5%)	3 (6.1%)	2 (3.6%)	2 (4.0%)	4 (3.8%)

AE = adverse event.

Median time to rescue morphine administration in the ITT population was 2:07 (hours:minutes) (95% CI, 1:15 to 2:40) for placebo but was significantly longer with 18.75 mg diclofenac (3:14; 95% CI, 2:10 to 5:05; $P = 0.014$ vs placebo) and ketorolac (4:15; 95% CI: 3:05, not estimable; $P = 0.0007$ vs placebo). Time to rescue morphine administration did not meet statistical significance versus placebo with 37.5 mg diclofenac. (2:24; 95% CI, 1:50 to 4:23; $P = 0.0574$).

Active treatment decreased the frequency of rescue morphine administration, and for all time intervals studied, patients receiving active treatments required significantly less morphine compared with the placebo group (Fig. 4). For the 0- to 24-h interval, patients receiving 18.75 mg diclofenac, 37.5 mg diclofenac, or 30 mg ketorolac experienced 39%, 44%, and 40% reductions in rescue morphine dosage, respectively, as compared to those treated with placebo (all $P \leq 0.0001$). All active treatments led to a significant reduction in morphine dosage over the 0- to 48- and 0- to 72-hour intervals, as well (all $P \leq 0.0001$).

Patient global evaluations in each of the active treatment groups were significantly superior to placebo ($P < 0.001$) at both 24 and 48 hours, with no significant differences among active treatment groups. Altogether, 83%–87% of patients in the active treatment groups assessed their study drug as "good," "very good," or "excellent" at 48 hours.

Safety

Overall, 84.6% (280/331) of patients experienced ≥1 AE. Most events were mild-to-moderate in severity. Nausea, flatulence, and injection site pain/irritation were the most commonly reported AEs among patients receiving active treatments (Table 3). Moderate-to-severe pain has been shown to be a risk factor for postoperative nausea and vomiting,[17] both of which were most commonly reported in the placebo group (Table 3).

Sixty-seven patients (20.2%) across the entire study population experienced at least 1 AE considered treatment-related by the investigator. The incidence of treatment-related AEs was 23.2% (19/82) in the ketorolac 30 mg group, 19.8% (17/86) in the diclofenac 18.75 mg group, 19.7% (15/76) in the placebo group, and 18.4% (16/87) in the diclofenac 37.5 mg group. One serious AE (SAE, abdominal hematoma) occurred in the ketorolac group and was considered possibly treatment-related. Of 9 AEs that prompted withdrawal from the study, 1 (moderate peripheral edema, in the diclofenac 18.75 mg group) was suspected of being treatment-related. There were no deaths.

The incidence of cardiovascular AEs was 5.4% (18/331) overall, 9.2% (7/76) in the placebo group, 6.1% (5/82) in the ketorolac group, 4.6% (4/87) in the diclofenac 37.5 mg group, and 2.3% (2/86) in the diclofenac 18.75 mg group. No cardiovascular AE was considered treatment-related. Blinded third-party analysis of ECGs revealed no clinically meaningful findings. Injection site pain/irritation was more common in active treatment groups than with placebo (Table 3). Mild-to-moderate borderline increases of liver enzymes were reported for 2%–5% of patients across all four groups. There were no reported hepatic or renal-related AEs or acute hepatic or renal impairment.

The incidence of bleeding-related AEs was 6.6% (5/76) in the placebo group, 6.1% (5/82), in the ketorolac group, 5.7% (5/87) in the diclofenac 37.5 mg group, and 2.3% (2/86) in the diclofenac 18.75 mg group (Table 4). There were no declines in hemoglobin or platelets between baseline and follow-up in any treatment group. Among subjects receiving anticoagulants or medications with anticoagulant properties, post hoc analysis revealed that 4/105 (3.8%) subjects receiving either dose of diclofenac reported ≥1 bleeding-related AE, while 3/49 (6.1%) and 4/47 (8.5%) from the ketorolac and placebo groups, respectively, had bleeding-related AEs.

DISCUSSION

The results of this study establish the analgesic efficacy of multiple-dose injectable HPβCD diclofenac for the treatment of acute postoperative pain, confirming and extending data from 2 randomized, double-blind trials establishing the efficacy of single-dose HPβCD diclofenac after third-molar extraction.[13,14] Leeson et al.[13] found that both HPβCD diclofenac 75 mg and the original injectable 75 mg diclofenac formulations were superior to placebo regarding the primary endpoint of total pain relief over 4 hours and demonstrated similar AE profiles. In a second study,[14] in which patients were eligible only if they had a baseline VAS-rated pain intensity of moderate-to-severe, HPβCD diclofenac was superior to placebo for total pain relief over 6 hours for 4 of 5 doses tested (75, 37.5, 18.75, and 9.4 mg). In addition, the 37.5 mg and 75 mg HPβCD diclofenac doses were superior to placebo at the earliest assessment of pain relief (5 minutes), whereas a standard 30-mg dose of ketorolac was not.

Injectable diclofenac formulations containing propylene glycol and benzyl alcohol, the form heretofore available outside the United States for the prevention or treatment of postoperative pain, require slow infusion over a period of 30 to 120 minutes. The current study demonstrates that small IV bolus delivery of HPβCD diclofenac without an initial loading dose is effective for the treatment of acute moderate-to-severe pain after abdominal or pelvic surgery. Delivery of 18.75 mg or 37.5 mg dosages every 6 hours provided significant analgesic efficacy over placebo. Analgesic efficacy was also significant in subjects receiving a standard dose of 30 mg ketorolac. All 3 active drugs were significantly more effective than placebo as measured by the SPID, total pain relief, and average amount of rescue morphine. Although the current phase 3 trial was not powered as a safety study, we report the incidence of treatment-emergent and treatment-related AEs for all study groups. No treatment-related SAEs were reported in either diclofenac dose group, whereas 1 SAE (abdominal hematoma) reported in the ketorolac group was suspected of being treatment related. Neither diclofenac nor ketorolac was associated with an increased incidence of bleeding-related AEs.

Confirming long-standing clinical experience, the frequency and amount of rescue medication were both greatest in the first 24 hours postoperatively. The opioid-sparing effect of the active treatments, compared with placebo, was 40% during every time interval studied, a key finding given that meta-analysis reveals that morphine reduction of this magnitude significantly decreases the incidence of postoperative vomiting and sedation.[4–5,18] Significant

opioid-sparing effects were previously noted with injectable diclofenac in a study that compared a single dose of IV diclofenac 75 mg with IV ketorolac 60 mg and placebo in 102 patients undergoing orthopedic surgery.[19] NSAIDs reduced morphine requirements versus placebo by up to 29% over 24 hours and significantly reduced postoperative nausea, vomiting, and pruritus.

The vast majority of literature on NSAID use for multimodal acute postoperative pain control describes NSAIDs as generally useful for mild-to-moderate, but not severe pain.[20] In this study, however, bolus IV injection of diclofenac (and the active comparator ketorolac) proved effective for severe, as well as moderate pain, thereby extending the clinical applicability of NSAIDs to a pain intensity not previously thought to be routinely controllable with an NSAID plus minimal amounts of rescue opioid medication. In addition, the ability to administer this formulation by bolus as opposed to a prolonged infusion offers the opportunity for a more rapid onset of pain relief, as well as reduced time that the IV line cannot be used to deliver concomitant, potentially incompatible drugs.

Like any phase 3 trial, the current study is limited in its generalizability owing to the application of strict inclusion and exclusion criteria, including restrictions on comorbid medical conditions. Other recent studies of HPβCD diclofenac imposed fewer restrictions. In an orthopedic pain setting, HPβCD diclofenac was safe and effective when evaluated with a methodology similar to that used here but with fewer constraints on patient age, weight, or preoperative renal or hepatic impairment.[b] Another phase 3 trial demonstrated the safety of postoperative HPβCD diclofenac in hundreds of patients with known NSAID risk factors, including advanced age, renal or hepatic impairment, and postoperative anticoagulation.[c]

The current study has important implications now that most operations are ambulatory or performed on a short-stay basis.[1] Unrelieved pain may delay patient discharge and is a common reason for unplanned admissions and readmissions.[1,21] Excessive reliance on opioids for postoperative analgesia may increase morbidity, not just because of dose-related side effects but also because of the potential for rapid development of acute tolerance and hyperalgesia.[22]

In conclusion, this study demonstrates that a novel IV formulation of diclofenac, a well-established NSAID with a known safety profile, provides a high degree of efficacy for the treatment of acute moderate and severe pain after abdominal or pelvic surgery. Within the patient population studied, both HPβCD diclofenac doses (18.75 mg and 37.5 mg) provided significantly greater analgesic efficacy than placebo, as did the active comparator ketorolac. For pain management, as with pharmacotherapy in general, it is recommended that clinicians use the lowest effective dose for the shortest necessary time. The current study, however, was not powered to discern significant differences among active treatment groups, with respect to primary or secondary efficacy endpoints, and as a result, optimal HPβCD diclofenac dosage remains to be determined through more comprehensive assessment. HPβCD diclofenac's ability to be used as a primary analgesic option for patients arriving in the postanesthesia care unit with moderate or severe pain, as demonstrated in the current study, may offer advantages over other parenteral non-narcotic analgesic formulations, particularly when exposure to high dosages of NSAIDs and/or opioids pose significant risk to the patient.

[b] Carr D, Hamilton D, Lang E, Melson T, Daniels S. Safety and efficacy of Dyloject®, a novel parenteral diclofenac formulation, after orthopedic surgery: superiority over ketorolac for analgesia and opioid-sparing. Presented at the International Association for the Study of Pain 13th World Congress on Pain, Montreal, QC, Canada, August 29–September 2, 2010.

[c] Chelly J, Hamilton D, Lang E, Melson T, Singla S, Carr D. Safety profile of Dyloject®, a novel parenteral diclofenac formulation, in 971 postoperative patients including older, renally or hepatically impaired, and anticoagulated. Presented at the International Association for the Study of Pain 13th World Congress on Pain, Montreal, QC, Canada, August 29–September 2, 2010.

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