Original Article

Analgesic Efficacy and Safety of a Novel Injectable Formulation of Diclofenac Compared With Intravenous Ketorolac and Placebo After Orthopedic Surgery

A Multicenter, Randomized, Double-blinded, Multiple-dose Trial

Stephen Daniels, DO,* Timothy Melson, MD,† Douglas A. Hamilton, BS, MBA,‡ Eric Lang, MD,‡ and Daniel B. Carr, MD‡

Objectives: A novel injectable formulation of diclofenac, Dylloject, utilizes hydroxypropyl-β-cyclodextrin (HPβCD) as a solubilizing agent, allowing dosing as a small-volume intravenous bolus for postoperative pain. In this test of the efficacy and safety of HPβCD diclofenac, we hypothesized that HPβCD diclofenac would relieve moderate and severe pain after orthopedic surgery.

Patients and Methods: Adults 18 to 85 years old with moderate and severe pain within 6 hours after surgery were randomized to HPβCD diclofenac, ketorolac tromethamine, or placebo, and stratified by risk cohort. The HPβCD diclofenac non-high-risk cohort dose was 37.5 mg, the high-risk cohort received 18.75 mg, and patients ≥ 95 kg received 50 mg. The ketorolac dose was 30 mg in the non-high-risk and high-weight cohorts and 15 mg in the high-risk cohort. Rescue intravenous morphine was given for pain as needed. Efficacy was measured by the sum of pain intensity differences (SPID).

Results: Mean SPID scores of 277 patients were significantly better with HPβCD diclofenac and ketorolac than with placebo (P < 0.0001), across all risk cohorts (P < 0.05). HPβCD diclofenac was associated with better SPID scores, faster onset of analgesia, and significantly lower opioid requirement (P < 0.008) than ketorolac. In patients more than or equal to 65 years, HPβCD diclofenac was associated with significantly better analgesic efficacy (P = 0.05), and lower opioid requirement versus ketorolac. The incidence of treatment-related adverse events was similar across groups.

Discussion: HPβCD diclofenac is safe and efficacious for acute moderate and severe pain after orthopedic surgery and significantly spares morphine use.

Key Words: diclofenac, postoperative pain, NSAID, Dylloject

Evidence-based guidelines hold that nonsteroidal anti-inflammatory drugs (NSAIDs) are integral to the management of acute postoperative pain.1,2 Particularly in the context of “fast-track” surgery, multimodal anesthesia is important to accelerate discharge and reduce opioid-related side effects.3 A recent systematic review concluded that NSAIDs and ketamine decrease postoperative pain intensity while reducing concurrent opioid requirements.4

Not all NSAIDs are efficacious for moderate or severe pain,5 or achieve clinically meaningful reductions in opioid utilization.6 In addition, some formulations of acetaminophen5 and NSAIDs6,7 require prolonged infusion, making administration time consuming and possibly delaying pain relief. Ketorolac, although efficacious as a single agent given by intravenous (IV) bolus, interferes with platelet aggregation8 and increases the risk of bleeding9 to such extents that dosage reductions are mandatory in at-risk populations such as the elderly.10

Diclofenac sodium, a nonselective NSAID, has been established for over 30 years to be highly effective and well-tolerated for the management of numerous painful conditions.11,12 A novel formulation of IV diclofenac, Dylloject (Hospira Inc.), is under development for the US market that will allow it to be administered as small-volume IV boluses every 6 hours versus slower infusions of higher dosages over 30 to 120 minutes. In this formulation, hydroxypropyl-β-cyclodextrin (HPβCD) is used as an inert solubilizing agent that releases diclofenac immediately upon injection.13

In the development program for HPβCD diclofenac, a single 37.5 mg dose was significantly more efficacious than placebo in a molar-extraction pain model.14 Subsequently, a randomized, multiple-dose trial demonstrated the safety and superior efficacy, relative to placebo, of HPβCD diclofenac 18.75 and 37.5 mg when used for acute moderate and severe pain after major abdominal or pelvic surgery.15

The objective of the current trial was to investigate HPβCD diclofenac for treatment of moderate and severe pain after elective orthopedic surgery. Three important subsets of patients were identified a priori on the basis of anticipated risk (Fig. 1). As a positive, active control, the only other NSAID available for parenteral use at the time in the United States, IV ketorolac, was included. We evaluated whether HPβCD diclofenac offered superior pain relief as compared with placebo and ketorolac, and whether the amount of opioid rescue medication decreased with HPβCD diclofenac. We also examined whether HPβCD diclofenac offered effective pain relief to specific subgroups of patients for whom pain management may be difficult, such as high-risk patients or the elderly. In addition, we monitored the occurrence of adverse events (AEs) with HPβCD diclofenac as compared with ketorolac or placebo.
MATERIALS AND METHODS

Patients

The study was registered in July 2007 at ClinicalTrials.gov (NCT00507026). After Institutional Review Board approval and Institutional Review Board–approved written informed consent, patients were screened at 12 study sites. Key inclusion criteria included age 18 to 85 years, weight 36 to 136 kg, and expectation of moderate to severe postsurgical pain requiring continuous IV analgesia after elective orthopedic surgery. Key exclusion criteria included dehydration in the elderly, recent history of cardiovascular events, history of gastric ulcers, severe renal or hepatic impairment, and recent use of other analgesics (Table 1).

Study Design

This was a multicenter, multiple-dose, multiple-day, randomized, double-blind, active-controlled and placebo-controlled, parallel-group study. Patients with moderate or severe pain within 6 hours postoperatively, defined as pain intensity of ≥50 mm on a 0 to 100 mm visual analog scale (VAS), were randomly assigned to IV HPβCD diclofenac, ketorolac, or placebo (2:1:1 ratio). Assignments were made according to a computer-generated random number code.

Dehydrated and age >65 y
Recent history (≤6 mo) of a cardiovascular event (eg, myocardial infarction, stroke)
History of uncontrolled conditions, such as gastric erosion/ulceration or bleeding diathesis, renal impairment, or cardiac failure that required hospitalization in the month before screening or in the opinion of the investigator made participation in the study inadvisable
Recent use (≤2 wk) of a monoamine oxidase inhibitor, tryptophan, carbamazepine, or valproate
Recent use (≤24 h) of aspirin (except 325 mg or less of cardiac-protective daily dosing), other NSAIDs, or other common analgesics; centrally acting analgesic adjuvants; tranquilizers; or antihistamines, except medications administered during surgery. All opioids, long-acting NSAIDs or cyclooxygenase-2 inhibitors must have been discontinued ≤3 d before surgery
Hepatic dysfunction determined by Child-Pugh score > 9
Screening serum creatinine > 3 mg/dL
Intra-articular corticosteroid injection within the last 3 months unless the operation was to replace a single injected joint; then the exclusion was within the last month

TABLE 1. Exclusion Criteria

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FIGURE 1. Distribution of patients randomized. A total of 277 patients received at least 1 dose of study drug and composed the intent-to-treat and safety populations. Overall, 239 (86%) patients completed the study (51/72 on placebo, 71%; 56/60 on ketorolac, 93%; 132/145 on diclofenac, 91%).

TABLE 1. Exclusion Criteria

Dehydrated and age >65 y
Recent history (≤6 mo) of a cardiovascular event (eg, myocardial infarction, stroke)
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Hepatic dysfunction determined by Child-Pugh score > 9
Screening serum creatinine > 3 mg/dL
Intra-articular corticosteroid injection within the last 3 months unless the operation was to replace a single injected joint; then the exclusion was within the last month
Randomization was also stratified by risk cohort [high-risk, non–high-risk, or high-weight (≥ 95 kg)] at baseline (Fig. 1), and by anticipated long stay (> 24 h) versus shorter stay, resulting in 6 strata within the randomization schedule. “High-risk” patients were defined as those who weighed < 50 kg, were more than or equal to 65 years, and by anticipated long stay (> 24 h) versus shorter stay, resulting in 6 strata within the randomization schedule. “High-risk” patients were defined as those who weighed ≤ 50 kg, were more than or equal to 65 years, and by anticipated long stay (>24 h) versus shorter stay, resulting in 6 strata within the randomization schedule. Patients who weighed more than 95 kg and lacked any high-risk characteristics were assigned to the high-weight cohort, and received 50 mg of HPβCD diclofenac or 30 mg of ketorolac. Patients who weighed more than 95 kg and had any risk factor received 18.75 mg of HPβCD diclofenac or 15 mg of ketorolac. Patients in all treatment groups received a 15 second bolus IV injection every 6 hours until discharge. Patients were observed for at least 24 hours from baseline (study drug initiation) and for up to 5 days. All study drugs were blinded to the investigator and the patient; dose levels of the individual study treatments were not blinded.

Rescue IV morphine was available if the primary study drug did not provide relief and was given as needed in 2.5 mg increments and not exceeding a total of 7.5 mg every 24 hours after the start of dosing and at completion/early termination.

Patients assessed their pain at baseline and at specified time points through the next 24 hours (5, 10, 15, 30, 45 min and 1, 2, 3, 5, 6, 9, 12, 15, 18, 21, 24 h after the first dose). Those who remained at the site longer assessed their pain every 3 hours until discharged. Safety assessments included physical examinations, laboratory testing, vital signs, 12-lead electrocardiography, evaluation of thrombophlebitis at injection site, and a prospective investigator-administered wound-healing questionnaire. AEs were recorded between surgery and randomization, not just after baseline, to distinguish treatment-emergent AEs. In addition to physical examinations, bleeding-related AEs were assessed by noting any decreases for hemoglobin, hematocrit, and red blood cell values from preoperative screening through the first 24 postoperative hours.

**Statistical Analysis**

A sample of 120 patients on HPβCD diclofenac (including both doses) and 60 patients on placebo were needed to provide 95% power to detect a clinically significant difference for each time interval in the primary efficacy measure. This calculation was based on an estimated SD of 468 for the 0 to 24-hour interval obtained from a randomized, placebo-controlled pivotal trial the sponsor conducted in an orthopedic surgical population.

Efficacy analyses were conducted using Statistical Analysis Software, and unless otherwise noted refer to the intent-to-treat population. The analysis of SPID, PID, total pain relief, patient global evaluation, and amount of rescue medication were based on analysis of covariance (ANCOVA) models, with treatment and center as factors and baseline pain as a covariate. The presence of a treatment-by-center interaction was also tested with an ANCOVA model. If this analysis detected a significant treatment-by-center interaction, a sensitivity analysis was performed to explore the interaction. Confidence intervals were based on the pooled SD obtained from an ANCOVA model. Treatment differences were tested with linear contrasts.

All testing of statistical significance was 2-sided unless the test performed was inherently 1-sided. Interaction P-values < 0.1 were considered significant; otherwise, P-values < 0.05 were considered significant. For SPID, comparisons between HPβCD diclofenac and placebo were performed in the following order: 0 to 24, 0 to 48, 0 to 72, 0 to 96, and 0 to 120 hours. If any of the comparisons failed to demonstrate statistical significance, no further comparisons were made. Total pain relief was analyzed similarly. The proportion of patients attaining at least 30% reduction in pain intensity and the frequency of rescue medication use were analyzed with Cochran-Mantel-Haenszel tests, with center as a stratification variable.

For summed calculations, evaluations after the administration of rescue medication or after withdrawal because of AEs or lack of efficacy were imputed in accordance with prespecified rules. For subgroup analyses of pain intensity, a more conservative and simplified set of imputation rules was applied.

**RESULTS**

**Patients**

A total of 277 patients were randomized and received ≥ 1 dose of study drug (Fig. 1). Altogether, 239 patients (86%) completed the study. The most frequent reason for withdrawal was lack of efficacy (31 patients, 11%), which was most common in the placebo group and the long-stay population. Most study participants were female (178 patients, 64%) and white (255 patients, 92%) (Table 2). The mean age was 55 years, and 82 patients (30%) were more than or equal to 65 years. Six patients (2%) were < 50 kg and 66 (24%) were > 95 kg.

There were no significant differences across treatment groups for any baseline characteristic, either overall or within any risk cohort, in duration of surgery, duration of anesthesia, or time from end of surgery until study dose initiation. Most of the patients received study drug for ≤ 3 days (≤ 1 d, 153 patients, 55%; ≤ 2 d, 169 patients, 61%;...
Of the 277 patients, 169 (61%) had 1 to 8 doses, 83 (30%) had 9 to 12 doses, and 25 (9%) had >13 doses. The overall mean pain intensity on VAS was 69 mm at baseline (Table 2), and did not differ across treatment groups or risk cohorts. Altogether, 157 (57%) of the 277 patients had moderate pain (50 mm < VAS < 70 mm) and 118 (43%) had severe pain (VAS ≥ 70 mm). Eleven patients were assigned to the wrong risk cohort at baseline, and in 4 cases the dosage was adjusted. The subgroup analyses presented here are based on dose levels received.

### Efficacy

In all time intervals, the mean SPID was significantly greater for diclofenac and ketorolac than for placebo \((P < 0.0001)\) (Fig. 2). These results were consistent across baseline pain intensities. There were no significant differences in SPID values based on length of stay. The treatment-by-center interactions were not significant for the mean SPID scores over the 0 to 24, 0 to 48, 0 to 72, 0 to 96, and 0 to 120-hour time intervals, indicating consistency of treatment effects across study centers and baseline pain intensities.

Total pain relief over 0 to 24, 0 to 48, 0 to 72, 0 to 96, and 0 to 120 hours was significantly better with HPβCD diclofenac and ketorolac than with placebo \((P < 0.0001)\). In the subgroup of 118 (43%) of 277 patients who had severe pain at baseline, total pain relief over all time intervals was significantly better with HPβCD diclofenac and ketorolac than with placebo \((P < 0.05)\). Clinically meaningful pain reduction (≥30% reduction in intensity) was achieved by 117 (81%) of the 145 patients on HPβCD diclofenac and 45 (75%) of the 60 patients on ketorolac, compared with 31 (43%) of the 72 patients on placebo. The proportion of patients who had meaningful pain reduction with HPβCD diclofenac was significantly superior to the proportion with ketorolac at 10 minutes, 42, 48, and 60 hours \((P \leq 0.05\) for all comparisons).

HPβCD diclofenac evidenced a faster onset of analgesia as measured by PID. HPβCD diclofenac was significantly greater than placebo at 10 minutes \((P = 0.03)\), whereas ketorolac required 30 minutes \((P = 0.006)\). For active treatments, statistical separation from placebo was maintained for 120 hours. Patient global evaluations for the active treatments were significantly higher than for placebo \((P < 0.0001)\) (Fig. 3).

### TABLE 2. Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HPβCD Diclofenac (N = 145)</th>
<th>Ketorolac (N = 60)</th>
<th>Placebo (N = 72)</th>
<th>Total (N = 277)</th>
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<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 53 (36.6)</td>
<td>20 (33.3)</td>
<td>26 (36.1)</td>
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<td>Female 92 (63.4)</td>
<td>40 (66.7)</td>
<td>46 (63.9)</td>
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<td>Age (y)</td>
<td>Mean (SD) 55.9 (14.35)</td>
<td>54.9 (15.77)</td>
<td>54.5 (15.67)</td>
<td>55.3 (14.97)</td>
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<td>Weight (kg)</td>
<td>Mean (SD) 88.86 (21.79)</td>
<td>87.42 (18.89)</td>
<td>87.12 (22.99)</td>
<td>88.10 (21.45)</td>
</tr>
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<td>Range</td>
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<td>53.2-136.4</td>
<td>47.7-138.3</td>
<td>45.0-143.2</td>
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<td>Risk cohort, n (%)</td>
<td>Non–high-risk 63 (43.4)</td>
<td>28 (46.7)</td>
<td>32 (44.4)</td>
<td>123 (44.4)</td>
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<td>High-risk 46 (31.7)</td>
<td>18 (30.0)</td>
<td>24 (33.3)</td>
<td>88 (31.8)</td>
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<td>High-weight 36 (24.8)</td>
<td>14 (23.3)</td>
<td>16 (22.2)</td>
<td>66 (23.8)</td>
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<td>Risk category, n (%)</td>
<td>Age ≥ 65y 42 (29.0)</td>
<td>17 (28.3)</td>
<td>23 (31.9)</td>
<td>82 (29.6)</td>
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<td>Weight &lt; 50 kg 5 (3.4)</td>
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<td>1 (1.4)</td>
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<td>Hepatic impairment 3 (2.1)</td>
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<td>Ulcer history 0</td>
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<td>1 (0.4)</td>
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<td>Length of stay, n (%)</td>
<td>Short stay (&lt;24h) 62 (42.8)</td>
<td>28 (46.7)</td>
<td>32 (44.4)</td>
<td>122 (44.0)</td>
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<td>Long stay (&gt;24h) 83 (57.2)</td>
<td>32 (53.3)</td>
<td>40 (55.6)</td>
<td>155 (56.0)</td>
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<td>Surgical procedure, n (%)</td>
<td>Bunionectomy, foot other 46 (31.7)</td>
<td>20 (33.3)</td>
<td>23 (31.9)</td>
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<td>Knee replacement 38 (26.2)</td>
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<td>Knee surgery other 23 (15.9)</td>
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<td>6 (8.3)</td>
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<td>Hip replacement 19 (13.1)</td>
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<td>Lower extremity soft tissue excision or repair 6 (4.1)</td>
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<td>3 (4.2)</td>
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<td>2 (2.8)</td>
<td>10 (3.6)</td>
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<td>Ankle surgery 3 (2.1)</td>
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<td>2 (2.8)</td>
<td>7 (2.5)</td>
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<td>Baseline pain intensity, VAS</td>
<td>Mean (SD) 69.54 (14.23)</td>
<td>72.17 (15.19)</td>
<td>66.83 (13.12)</td>
<td>69.40 (14.25)</td>
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<td>Median 66.00</td>
<td>71.00</td>
<td>64.00</td>
<td>66.00</td>
</tr>
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<td></td>
<td>Range 50-100</td>
<td>50-100</td>
<td>50-100</td>
<td>50-100</td>
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<tr>
<td>Severity, n (%)</td>
<td>Moderate (≥50-70mm VAS) 84 (57.9)</td>
<td>29 (48.3)</td>
<td>46 (63.9)</td>
<td>159 (57.4)</td>
</tr>
<tr>
<td></td>
<td>Severe (≥70mm VAS) 61 (42.1)</td>
<td>31 (51.7)</td>
<td>26 (36.1)</td>
<td>118 (42.6)</td>
</tr>
</tbody>
</table>

There were no significant differences between groups.

HPβCD indicates hydroxypropyl-β-cyclodextrin; NSAID, nonsteroidal anti-inflammatory drug; VAS, 0 to 100 mm visual analog scale.

≤3d, 252 patients, 91%; ≤5d, 277 patients, 100%. Of the 277 patients, 169 (61%) had 1 to 8 doses, 83 (30%) had 9 to 12 doses, and 25 (9%) had ≥13 doses.

The overall mean pain intensity on VAS was 69 mm at baseline (Table 2), and did not differ across treatment groups or risk cohorts. Altogether, 157 (57%) of the 277 patients had moderate pain (50 mm ≤ VAS < 70 mm) and 118 (43%) had severe pain (VAS ≥ 70 mm). Eleven patients were assigned to the wrong risk cohort at baseline, and in 4 cases the dosage was adjusted. The subgroup analyses presented here are based on dose levels received.
Rescue

HPβCD diclofenac-treated patients required significantly less morphine than the placebo control group ($P < 0.0001$) (Fig. 4). Over the 5 days of treatment, patients on HPβCD diclofenac also used significantly less morphine than those receiving ketorolac (11.8 vs. 18.1 mg, 35% reduction vs. ketorolac, $P = 0.008$) (Fig. 5). The median time from administration of study drug to administration of rescue medication ($tm$) was greatest for HPβCD diclofenac ($tm = 220.0 \text{ min}$, $P < 0.0001$ compared with placebo) followed by ketorolac ($tm = 137.0 \text{ min}$, $P < 0.0001$ compared with placebo) and placebo ($tm = 51.0 \text{ min}$).

Risk Cohorts

SPIID scores for HPβCD diclofenac were significantly higher than placebo across risk and weight cohorts, and significantly higher than ketorolac in the high-risk cohort at the 0 to 24 and 0 to 48-hour intervals (Fig. 6). One subgroup of high-risk patients, those more than or equal to 65 years ($n = 80$), who received low-dose HPβCD diclofenac had a greater response rate than those receiving low-dose ketorolac or placebo, as defined by 30% reduction in pain intensity (Fig. 7A). Elderly HPβCD diclofenac-treated patients needed less rescue medication than those given ketorolac or placebo ($P = 0.05$), and less frequently (Fig. 7B).

Safety

No deaths were reported. Overall, 216 (78%) of the 277 patients studied reported 1 or more AEs, with a similar incidence in the active treatment groups (Table 3), and risk cohorts. Most AEs (92%) were mild to moderate in severity. Nausea was the most common AE overall and in each risk cohort. Within the high-weight cohort, use of HPβCD diclofenac 50 mg did not increase the risk of an AE compared with placebo. Forty-seven (17%) of the 277 patients reported 1 or more AEs thought to be treatment related (Table 3). This included 7 (8%) of the 88 patients in the high-risk cohort, 27 (22%) of the 123 patients in the non–high-risk cohort, and 13 (20%) of the 66 patients in the high-weight cohort.
Five patients had serious cardiovascular events: 3 (2.1%) of the 145 patients on HPβCD diclofenac developed deep vein thrombosis (2 of these patients were >95 kg), 1 (1.7%) of the 60 patients on ketorolac developed congestive heart failure, and 1 (1.4%) of the 72 patients on placebo developed hypotension. None of these events was considered treatment related.

The incidence of bleeding-related AEs was similar in the active treatment groups (HPβCD diclofenac, 23/145 patients, 16%; ketorolac, 13/60 patients, 22%) and not significantly greater than in the placebo group (12/72 patients, 17%). Likewise, in the subset of patients who received anticoagulants (n = 197), there were no clinically meaningful differences in bleeding-related AEs across treatment groups. There were no major differences in renal or liver function tests between the active treatment groups and placebo.

DISCUSSION

This study establishes the safety and efficacy of IV HPβCD diclofenac for managing acute moderate and severe pain alone or in combination with opioids in patients recovering from orthopedic surgery. HPβCD diclofenac 18.75, 37.5, or 50 mg every 6 hours was found to provide superior analgesia to those receiving placebo and rescue morphine and greater effects than ketorolac beginning at 0 to 48 hours, although the difference did not reach statistical significance. During the trial, all treatment groups, including placebo, could receive supplemental morphine as needed to help manage pain. HPβCD diclofenac-treated patients required 35% less rescue morphine than those treated with ketorolac (P = 0.008). When rescue morphine was needed, the median time until administered was 220 minutes for HPβCD diclofenac, more than 4 times longer than placebo (51 min) and 83 minutes longer than in those receiving ketorolac (137 min).

Elderly patients receiving low-dose HPβCD diclofenac (18.75 mg) had statistically significant better outcomes than those receiving low-dose ketorolac (15 mg). This included a higher likelihood of analgesic response, better analgesic efficacy, and lower overall opioid requirements than those receiving ketorolac. These are important findings given that the elderly are at greater risk of opioid-induced and NSAID-induced side effects and lower dosages are warranted of each to minimize their exposure and risk.

In the perioperative period, side effects of particular concern with NSAIDs are renal impairment and increased risk of bleeding.2 Safety data were consistent with what has been demonstrated in a randomized, multidose trial of HPβCD diclofenac after major abdominal or pelvic surgery.

FIGURE 4. Cumulative amount of rescue medication administered. The total morphine requirement over the first 5 days was 42% lower with hydroxypropyl-β-cyclodextrin (HPβCD) diclofenac than with placebo (11.8 vs. 20.5 mg morphine), and in every time interval the opioid-sparing effect was ≥ 40% with HPβCD diclofenac compared with placebo. *P < 0.0001 versus placebo; #P < 0.05 versus ketorolac.

FIGURE 5. Cumulative proportions of patients in each treatment group who required rescue medication. Of the patients who required rescue morphine, more than half required rescue ≤ 2 times in the hydroxypropyl-β-cyclodextrin diclofenac and ketorolac groups, compared with ≤ 6 times in the placebo group.
surgery. Blood loss in this study was slightly greater with the active treatments than with placebo. In a single-dose crossover trial in healthy volunteers, injectable HPβCD diclofenac 37.5 mg resulted in significantly less platelet function disruption compared with ketorolac and acetylsalicylic acid. The 1 patient on HPβCD diclofenac who developed acute renal failure in the present study had multiple pre-existing risk factors for acute renal failure, but reverted toward baseline upon correction of underlying volume disturbances.

In studies that compared HPβCD diclofenac with other IV formulations of diclofenac available in Europe for over 10 years, a greater opioid-sparing effect versus that of placebo, ketorolac, or other NSAIDs has been consistently demonstrated. Diclofenac has effects not shared by other NSAIDs, which may account for its efficacy after orthopedic surgery. These include relatively equal inhibition of COX-1 and COX-2, and central effects such as increasing plasma β-endorphin levels and inhibiting the N-methyl-D-aspartate pathway. Studies of other IV nonopioid IV analgesic options are not directly comparable with the current trial design. However, in the trial of IV ibuprofen (Caldolor; Cumberland Pharmaceuticals Inc., Nashville, TN) after orthopedic or abdominal surgery, overall morphine consumption during the first 24 hours was reduced by 19% with IV ibuprofen 800 mg versus placebo (P < 0.005), versus the >50% reduction demonstrated in this trial. Furthermore, as opposed to the prolonged infusion required with IV ibuprofen, HPβCD diclofenac can be administered by bolus, allowing for more rapid onset of pain relief and reducing the time that the IV line is restricted.

"Fast-track" surgery, which combines regional anesthesia, minimally invasive techniques, optimal pain control, and aggressive postoperative rehabilitation, significantly enhances recovery and reduces morbidity. Still, even after fast-track hip and knee arthroplasty, most patients have moderate or severe pain for the first 48 hours. Evidence-based guidelines for multimodal postoperative analgesia hold that NSAIDs are useful for moderately severe pain but not directly comparable with the current trial design. However, in the trial of IV ibuprofen (Caldolor; Cumberland Pharmaceuticals Inc., Nashville, TN) after orthopedic or abdominal surgery, overall morphine consumption during the first 24 hours was reduced by 19% with IV ibuprofen 800 mg versus placebo (P < 0.005), versus the >50% reduction demonstrated in this trial. Furthermore, as opposed to the prolonged infusion required with IV ibuprofen, HPβCD diclofenac can be administered by bolus, allowing for more rapid onset of pain relief and reducing the time that the IV line is restricted.

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TABLE 3. Summary of Adverse Events (AEs)

<table>
<thead>
<tr>
<th></th>
<th>HP(\beta)CD</th>
<th>Ketorolac</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total GI-related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse events</td>
<td>(n = 145)</td>
<td>(n = 60)</td>
<td>(n = 72)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36 (24.8%)</td>
<td>18 (30.0%)</td>
<td>26 (36.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (7.6%)</td>
<td>6 (10.0%)</td>
<td>14 (19.4%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>19 (13.1%)</td>
<td>6 (10.0%)</td>
<td>11 (15.3%)</td>
</tr>
<tr>
<td>Total renal-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse events</td>
<td>(n = 5)</td>
<td>1 (1.7%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>(0.7%)*</td>
<td>0</td>
<td>1 (1.4%)†</td>
</tr>
<tr>
<td>Acute tubular</td>
<td>0</td>
<td>0</td>
<td>1 (1.4%)†</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>3 (2.1%)</td>
<td>0</td>
<td>1 (1.4%)†</td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysuria (burning,</td>
<td>1 (0.7%)</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>difficulty urinating)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bleeding-related adverse events</td>
<td>23 (15.9%)</td>
<td>13 (21.7%)</td>
<td>12 (16.7%)</td>
</tr>
<tr>
<td>Most common bleeding-related adverse events</td>
<td>Anemia</td>
<td>Epistaxis</td>
<td>Contusion</td>
</tr>
<tr>
<td></td>
<td>16 (11.0%)</td>
<td>2 (1.4%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>9 (15.0%)</td>
<td>0</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td></td>
<td>11 (15.3%)</td>
<td>0</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Fever/increase body</td>
<td>6 (4.1%)</td>
<td>5 (8.3%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences between groups.

*An 81-year-old obese male undergoing hip replacement. Preoperative history of renal insufficiency, anemia, pulmonary HTN, and CHF. Patient experienced postoperative anemia and hypotension and increase in creatinine (1.5 to 2.6). Received patient hydration with normal saline, 1L packed red blood cells and d/c furosemide, valsartan, and HP\(\beta\)CD diclofenac. Mild renal insufficiency resolved after 1 day.

†A 63-year-old obese female undergoing knee replacement. Preoperative history of kidney stones and urinary incontinence. Patient experienced postoperative hypotension that did not respond to fluid boluses, creatinine increased from normal to 2.5 mg/dL. Patient transferred to intensive care unit and treated with vasoppressors. Patient responded and weaned from vasopressors after 2 days. Creatinine returned to normal 3 days after its initial increase. Acute renal failure, tubular necrosis resolved after 5 days. HP\(\beta\)CD indicates hydroxypropyl-\(\beta\)-cyclodextrin; GI, gastrointestinal.

not severe pain. In this study, HP\(\beta\)CD diclofenac proved efficacious in the immediate postoperative period for the 118 (43%) of the 277 patients who had severe pain at baseline, as well as for those with moderate pain. Our results suggest giving HP\(\beta\)CD diclofenac to patients with a pain severity not previously thought to be controllable with an NSAID alone (plus minimal amounts of rescue medication). This could have particularly important implications for the elderly patient populations that routinely undergo orthopedic procedures.

In conclusion, this study demonstrates that a novel IV formulation of diclofenac, a long-trusted NSAID with a well-characterized safety profile, is safe and efficacious for treatment of acute moderate and severe pain after commonly performed orthopedic surgeries, particularly in the >elderly. Although renal insufficiency and bleeding complications were infrequent, awareness of risk factors associated with their origins should be carefully assessed. Furthermore, the data suggest using HP\(\beta\)CD diclofenac as a default primary postoperative analgesic, with morphine added as necessary, rather than the reverse. Future studies should explore the use of HP\(\beta\)CD diclofenac in dedicated outpatient surgicenters and as part of clinical pathways in protocol-driven approaches to orthopedic surgery.

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REFERENCES


