Original Research Article

SoluMatrix® Diclofenac: Sustained Opioid-Sparing Effects in a Phase 3 Study in Patients with Postoperative Pain

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Abstract

Objectives. To evaluate opioid rescue medication usage and the opioid-sparing effect of low-dose SoluMatrix® diclofenac developed using SoluMatrix Fine Particle Technology™ in a phase 3 study in patients experiencing pain following bunionectomy surgery.


Setting. Four clinical research centers in the United States.

Subjects. Four hundred twenty-eight patients aged 18 to 65 years who experienced moderate-to-severe pain following bunionectomy surgery.

Methods. Patients were randomized to receive low-dose SoluMatrix diclofenac 35 mg or 18 mg capsules three times daily (35-mg group or 18-mg group), celecoxib 400 mg loading dose followed by 200-mg capsules twice daily (celecoxib 200-mg group), or placebo capsules postsurgery. Patients were permitted to receive opioid-containing rescue medication as needed.

Results. Significantly fewer patients who received SoluMatrix diclofenac 35 mg or 18 mg or celecoxib required rescue medication during 0–24 h and >24–48 h postsurgery compared with placebo. Patients in the SoluMatrix diclofenac 35 mg or 18 mg groups or in the celecoxib group used fewer mean rescue medication tablets over 0–24 h and >24–48 h compared with placebo-treated patients. Patients in the SoluMatrix diclofenac 35 mg and 18 mg groups and in the celecoxib group also required rescue medication.
at later times and at slower rates compared with placebo-treated patients. No serious adverse effects occurred in patients receiving SoluMatrix diclofenac.

Conclusions. SoluMatrix diclofenac at two dosage strengths demonstrated an opioid-sparing effect postoperatively in this phase 3 study.

Summary. The opioid-sparing effect following low-dose SoluMatrix diclofenac (35 mg or 18 mg three times daily) administration was evaluated in patients experiencing pain following bunionectomy. Significantly fewer patients receiving SoluMatrix diclofenac or celecoxib (400 mg loading, 200 mg twice daily) required rescue medication during 0–24 h and >24–48 h following bunionectomy compared with placebo. No serious adverse events were reported among patients who received SoluMatrix diclofenac. SoluMatrix diclofenac may reduce opioid usage in the postoperative setting in patients with acute pain.

Key Words. Non-Steroidal Anti-Inflammatory Drugs; SoluMatrix®; Diclofenac; Opioid; Acute Pain; Multimodal; ZORVOLEX®

Introduction

Pain affects tens of millions of Americans each year and is among the most frequent reasons that patients seek medical attention [1–3]. Despite the availability of numerous analgesic medications, the general quality of pain management for many patients with acute or chronic pain remains suboptimal [1,4,5].

Increases in opioid use for acute and chronic pain over the past 20 years have been accompanied by an increased incidence of opioid-associated complications including opioid abuse and misuse [6,7]. Opioid use is associated with systemic side effects including constipation, impaired cognitive function, sedation, and respiratory depression [2,8–10], as well as increased risk of hospitalization and mortality in older patients [2,8,11]. Preoperative and immediate postoperative opioid use has been shown to increase the risk of chronic opioid use following a surgical procedure [12–14]. Efforts to reduce perioperative opioid use could affect the number of individuals at risk for complications associated with long-term use.

Multimodal pain management strategies including combining administration of oral and parenteral pharmacologic agents with regional anesthesia have been shown to improve clinical outcomes while reducing opioid consumption and postoperative pain [15]. There is evidence to support the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal treatment regimens [16,17]. However, NSAIDs can be associated with serious dose-related gastrointestinal (GI), cardiovascular (CV), and renal complications [18–20]. The US Food and Drug Administration (FDA) and various medical and scientific organizations recommend that NSAIDs be used at the lowest effective dose for the shortest duration consistent with individual treatment goals [21–24]. Low-dose NSAIDs, including diclofenac, are manufactured using SoluMatrix Fine Particle Technology™ (SoluMatrix Fine Particle Technology is a trademark of iCeutica Inc., and the technology is licensed to Iroko for exclusive use in NSAIDs) and were designed to provide effective pain relief at low doses.

SoluMatrix® (SoluMatrix is a registered trademark of iCeutica Pty Ltd and is licensed to Iroko) diclofenac (ZORVOLEX® (diclofenac) capsules, a registered trademark of Iroko Properties Inc.) is approved by the FDA for the management of mild-to-moderate acute pain and osteoarthritis pain [25–28]. SoluMatrix diclofenac 18- and 35-mg capsules are rapidly absorbed with approximately 62% and 23% lower systemic exposure, respectively, compared with diclofenac potassium 50 mg immediate-release tablets [28]. SoluMatrix diclofenac effectively reduced pain intensity in a placebo-controlled phase 3 study in patients with moderate-to-severe acute pain following bunionectomy [25]. In this study, the primary endpoint was the overall (summed) pain intensity difference over 0 to 48 hours (SPID-48) following the initial dose of study drug, measured using a Visual Analog Scale (VAS; 0–100 mm). Significantly greater differences in mean (± standard error) SPID-48 values were reported for patients in the SoluMatrix diclofenac 35 mg (524.05 ± 86.23; P < 0.001) or 18 mg three times daily (393.25 ± 85.45; P = 0.010) and celecoxib 200 mg twice daily (390.22 ± 86.63; P = 0.011) groups compared with placebo (77.10 ± 86.62) [25]. Here, we evaluate opioid-containing rescue medication use in a post hoc analysis of this phase 3 study.

Methods

Participants

Four hundred and twenty-eight male and female patients, aged 18 to 65 years old with a body mass index (BMI) <40 kg/m² and a body weight ≥45 kg, and who experienced moderate-to-severe pain (≥40 mm/100 mm by VAS) following bunionectomy surgery, were enrolled in the study. All patients provided written informed consent, and an institutional review board approved this study, which was conducted based on the principles described in the Declaration of Helsinki [29]. Participants in previous SoluMatrix diclofenac clinical trials or in any studies of investigational drugs or devices within 30 days prior to the present study were excluded. Other exclusions included: clinically significant intolerance or allergy to any study drug; a history of alcoholism or drug abuse within 2 years prior to enrollment; a clinically significant GI event within 6 months prior to enrollment such as a history of peptic or gastric ulcers, GI bleeding, or perforation; and surgical or medical conditions of the GI or renal systems that might alter the absorption, distribution, or excretion of drug substances. Women of
childbearing age were included if they were not lactating or pregnant and were using medically acceptable forms of birth control.

Study Design

This was a multicenter, phase 3, multiple-dose, randomized, double-blind, parallel-group, active- and placebo-controlled study (ClinicalTrials.gov registered study number NCT01462435). Patients were admitted to 1 of 4 investigational sites, underwent surgery on study day 0, remained on site until day 3, and returned for follow-up 5 to 9 days following surgery. Surgery (study day 0) consisted of primary, unilateral, first-metatarsal bunionectomy with osteotomy and internal fixation. Prior to surgery, regional anesthesia was established via popliteal sciatic nerve block using ropivacaine 0.5% (40 mL). For management of pain on the day of surgery, a short-acting anesthetic, mepivacaine 0.5%, was administered by continuous infusion (8–14 mL per hour) via a popliteal catheter. Up to three additional 10-mL boluses could be injected into the catheter if required for breakthrough pain. The continuous mepivacaine infusion was discontinued at approximately 3:00 AM on the day following surgery. During the 9-hour period following discontinuation of infusion, pain intensity was measured using a Visual Analog Scale (0–100 mm, with 0 mm representing “no pain” and 100 mm representing “worst possible pain”) [25]. Patients who reported pain intensities ≥40 mm were randomized to receive either low-dose SoluMatrix diclofenac 18 mg or 35 mg capsules three times daily, celecoxib 400 mg loading dose followed by 200-mg capsules twice daily, or placebo capsules [25]. All patients were blinded to study drug assignment, as were investigators and study staff who performed efficacy and safety assessments. Patients were permitted to receive opioid-containing rescue medication (hydrocodone/acetaminophen tablet 10 mg/325 mg every 4–6 h or oxycodone/acetaminophen tablet 7.5 mg/325 mg every 6 h) up to six tablets per day as needed prior to randomization for breakthrough pain or as rescue medication throughout the study (Figure 1). Patients were encouraged to wait at least 60 minutes after the first dose of study medication before receiving the first dose of rescue medication.

Efficacy and Safety Assessments

The previously reported primary efficacy endpoint was the overall (summed) pain intensity difference over 0 to 48 hours (SPID-48) following the initial dose of study drug [25]. Protocol-defined assessments included use of opioid-containing rescue medication, analyses of the proportion of patients who required rescue medication, and the elapsed time from the start of study medication to first rescue medication administration. Post hoc analyses included opioid-containing rescue medication use during the period 0-to-24 hours and >24-to-48 hours, following randomization in all patients and in the subgroup of patients that required at least one dose of rescue medication. The proportion of patients who received opioids following surgery and before the first dose of study medication is also summarized here. Safety was evaluated by adverse events (AEs) and changes in vital signs [25]. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0.

Statistical Analyses

All patients in the intent-to-treat (ITT) population used in the analyses also received at least one tablet of study drug.
drug. Odds ratios, corresponding 95% confidence intervals (CIs), and nominal P values were generated from a logistic regression model with treatment group as a factor and baseline pain intensity as a covariate to determine whether the proportion of patients using rescue medication during 0 to 24 hours and >24 to 48 hours following the initial receipt of study medication was significantly different between the active treatment groups and the placebo group. No adjustment for multiple comparisons was performed. The significance of the difference in the mean number of rescue medication tablets administered during 0 to 24 hours and >24 to 48 hours for the active treatment groups compared with placebo was determined using two-sided, unadjusted, two-sample t-tests. The Kaplan-Meier method was used to evaluate time to first receipt of rescue medication; each active treatment group and the placebo group were compared using a Cox proportional hazard regression model, which included treatment and gender as factors and baseline pain intensity as a covariate. Times to rescue medication receipt for each of the treatment groups were compared with placebo by log-rank tests.

Results

Patient Demographics

Overall, a majority of patients were female (371/428, 87%). The study population was 77% white (329/428), 19% black or African-American (82/428), 2% Asian (10/428), 2% American Indian (10/428), and 2% Native Hawaiian (8/428). Detailed patient disposition and demographics have been described previously; demographics were similar across all treatment groups [25]. For the overall patient population, mean age ± standard deviation (SD) was 55.7 ± 12.0 years, weight 74.2 ± 16.4 kg, height 166.3 ± 8.3 cm, and BMI 26.6 ± 5.1 kg/m². The mean ± SD baseline pain intensity was 75.4 ± 16.3 mm measured by VAS. The mean ± SD duration of surgical procedures was 29.2 ± 8.7 minutes (minimum: 15 minutes, maximum: 115 minutes), and the length of surgical procedures was consistent across treatment groups.

Proportion of Opioid-Containing Rescue Medication Use

The number of patients who received opioid-containing medication to supplement continuous infusion of regional anesthetic prior to randomization was similar for all treatment groups, and no group differed significantly from placebo; 70/107 patients (65.4%, P = 0.13) in the SoluMatrix diclofenac 35-mg group, 68/109 patients (62.4%, P = 0.32) in the 18-mg group, 61/106 patients (57.5%, P = 0.74) in the celecoxib 200-mg group, and 59/106 patients (55.7%) in the placebo group received rescue medication postsurgery and prior to randomization.

Postrandomization, significantly fewer patients in the SoluMatrix diclofenac 35 mg (88/107, 82.2%, P = 0.003), 18 mg (92/109, 84.4%, P = 0.006), or celecoxib 200 mg (90/106, 84.9%, P = 0.010) groups received rescue medication during the first 24 hours following randomization compared with placebo (102/106, 96.2%) (Figure 2).

Fewer patients in the SoluMatrix diclofenac 35 mg group (30/107, 28.0%, P < 0.001) and the 18 mg group (40/109, 36.7%, P < 0.001) received opioid-containing rescue medication during the subsequent 24 to 48-hour period following randomization compared with patients in the placebo (64/106, 60.4%) group. Fewer patients in the celecoxib 200 mg group received rescue medication (45/106, 42.5%, P = 0.011) compared with placebo (Figure 2).

Amount of Opioid-Containing Rescue Medication Use

The mean (± SD) numbers of tablets of opioid-containing rescue medication used per patient during the first 12 hours following the first administration of study drug by treatment group were as follows: SoluMatrix diclofenac 35 mg, 1.5 ± 1.13 tablets; SoluMatrix diclofenac 18 mg, 1.7 ± 1.10 tablets; celecoxib 200 mg, 1.9 ± 1.21 tablets; placebo: 2.4 ± 1.05 tablets (Figure 3).

Significantly fewer opioid-containing rescue medication tablets were administered to patients in the SoluMatrix diclofenac 35 mg (mean ± SD: 2.0 ± 1.57 tablets, P < 0.001; median: 2.0 tablets), SoluMatrix diclofenac 18 mg (mean ± SD: 2.3 ± 1.67 tablets, P < 0.001; median: 2.0 tablets), or celecoxib 200 mg (mean ± SD: 2.6 ± 1.81 tablets, P < 0.001; median: 2.0 tablets) group compared with the mean number of opioid-containing rescue medication tablets administered to patients in the placebo group (mean ± SD: 3.7 ± 1.57 tablets; median: 4.0 tablets) during the 0-to-24-hour time period.
following randomization (Figure 4A). Patients in the placebo group used twice the median amount of rescue medication on the first post-operative day compared with patients in the SoluMatrix diclofenac treatment groups and the celecoxib treatment group.

Patients in the SoluMatrix diclofenac 35 mg (mean \( \pm SD \): 0.5 \( \pm 0.95 \) tablets, \( P < 0.001 \); median: 0.0 tablets), 18 mg (mean \( \pm SD \): 0.7 \( \pm 1.20 \) tablets, \( P < 0.001 \); median: 0.0 tablets), or celecoxib 200 mg (mean \( \pm SD \): 0.8 \( \pm 1.21 \) tablets, \( P = 0.003 \); median: 0.0 tablets) group continued to require less opioid-containing analgesia during the second day (>24–48 h) postrandomization compared with placebo (mean \( \pm SD \): 1.4 \( \pm 1.42 \) tablets; median: 1.0 tablets; Figure 4A). During the 24-to-48-hour period postrandomization, patients in the placebo group on average received more than twice as much rescue medication compared with the SoluMatrix diclofenac and the celecoxib treatment groups.

In the subgroup analysis that included only patients who were administered rescue medication, patients in the SoluMatrix diclofenac 35 mg (mean \( \pm SD \): 2.5 \( \pm 1.39 \) tablets, \( P < 0.001 \), 18 mg (mean \( \pm SD \): 2.7 \( \pm 1.47 \) tablets, \( P < 0.001 \)), or celecoxib 200 mg (mean \( \pm SD \): 3.1 \( \pm 1.56 \) tablets, \( P < 0.001 \)) groups required fewer tablets of opioid-containing rescue medication 0 to 24 hours following randomization compared with placebo (mean \( \pm SD \): 3.8 \( \pm 1.42 \); Figure 4B).

During the second postoperative day in the subgroup of patients who were administered rescue medication, opioid rescue medication use was significantly lower among patients in the SoluMatrix 35 mg group compared with placebo. Patients in the SoluMatrix diclofenacin diclofenac 35 mg group received a mean (\( \pm SD \)) of 1.8 \( \pm 0.97 \) tablets (\( P = 0.027 \)), patients in the SoluMatrix diclofenacin 18 mg group received 1.9 \( \pm 1.29 \) tablets (\( P = 0.120 \)), and patients in the celecoxib group received 1.9 \( \pm 1.14 \) tablets (\( P = 0.096 \)), while patients in the placebo group received an average of 2.3 \( \pm 1.12 \) tablets (Figure 4B).

**Time to First Use of Rescue Medication**

Following the initial administration of study medication, the median time to first use of opioid-containing rescue medication was significantly earlier in the placebo group compared with the SoluMatrix diclofenacin 35 mg and 18 mg groups and the celecoxib 200 mg group (Table 1). Hazard ratios were consistent with significantly slower rates of rescue medication use in the SoluMatrix diclofenacin 35 mg and 18 mg groups and the celecoxib 200 mg group compared with the placebo group (Table 1).

**Safety**

SoluMatrix diclofenacin 35 mg and 18 mg were generally well tolerated. The most frequently reported treatment-emergent AEs (TEAEs; >5% of patients in any treatment group) among patients in active treatment groups included postprocedural edema, nausea, headache, vomiting, dizziness, constipation, postprocedural hema-
toma, pruritus, and paresthesia (Table 2). One serious
AE (SAE) was reported: deep vein thrombosis in a patient in the celecoxib 200 mg group.

**Discussion**

Clinical trials of analgesic agents studied in patients experiencing pain following bunionectomy surgery provide a validated model for investigation of analgesic agents in patients with moderate-to-severe acute pain [30–35]. These placebo-controlled studies typically require provision of protocol-defined rescue medication, generally containing opioids, due to the severity of pain following bunionectomy surgery [30–33], but this model can be used to estimate the contribution of investigational oral analgesic agents administered as monotherapy [34]. As opioids lack the anti-inflammatory properties of NSAIDs, they may be less effective in relieving pain in conditions associated with inflammation, such as bunionectomy surgery, which produces a robust inflammatory response [4,34].

This study, which confirmed the efficacy of different doses of SoluMatrix diclofenac for the treatment of
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acute pain, provided an opportunity to assess the impact of these novel formulations of diclofenac on limiting postoperative opioid-containing rescue medication use. As expected, a substantial percentage of patients who enrolled in the study received at least one tablet of opioid-containing rescue medication. Despite the high rates of use, there were clear differences in the amount of rescue medication used in the SoluMatrix diclofenac and celecoxib treatment groups compared with placebo. Fewer patients in the SoluMatrix diclofenac 18 mg and 35 mg groups, along with patients in the celecoxib 200 mg treatment group, elected to receive any opioid-containing rescue medication, and among those who received rescue medication, patients in the active treatment groups required less opioid-containing rescue medication compared with patients in the placebo group. Generally, this opioid-sparing effect was most pronounced in the SoluMatrix diclofenac 35 mg group.

The study design also enabled an assessment of the time course of pain relief and patterns of rescue medication use. We observed a significant decrease in the proportion of patients requiring rescue medication during the second 24-hour period following bunionectomy compared with the initial 0-to-24-hour period following randomization, generally with a larger reduction across these periods occurring in the active treatment groups. Furthermore, in the 24-to-48-hour period, placebo-treated patients were significantly more likely to require opioid-containing rescue medication compared with the active treatment groups. Patients receiving SoluMatrix diclofenac also received the initial dose of opioid rescue medication at later median times and at slower rates compared with patients receiving placebo. Low-dose SoluMatrix diclofenac was generally well tolerated and no SAEs were reported in patients who received SoluMatrix diclofenac. The potential impact of NSAID treatment in this study may be reflected in the AEs observed by treatment group—with higher rates of dizziness, nausea, and vomiting occurring in the placebo group, likely due to the higher rates of opioid rescue medication use, as these AEs have been associated with opioids [8] (Table 2).

Earlier studies have reported opioid-sparing effects of 25 mg diclofenac potassium liquid gel-filled capsules used for pain relief postsurgery in a bunionectomy model [16,35,36]. A pooled analysis of data from two potassium liquid gel-filled capsule studies [16] used a similar design to the present study; however, there were a number of key differences that preclude a direct comparison between the observed opioid-sparing effects in the gel-filled capsule study and this SoluMatrix diclofenac study. In the SoluMatrix diclofenac study, 56.5% of patients received oral opioid-containing medications during the postoperative period prior to randomization; in contrast, 56.5% of patients in the study of liquid gel-filled capsules received oral opioid-containing medication during the period prior to randomization [16]. The SoluMatrix diclofenac study did not allow ice packs during the prerandomization period, whereas 77.1% of patients in the liquid gel-filled capsule study used ice packs during this period. Together, these differences in practices during the perioperative period may have accounted for the differences in pain experiences between patients in these two studies at the time of randomization. Other key differences include the differing methodology in the collection of pain scores in the two studies. In the morning following surgery, patients in the liquid gel-filled capsule study underwent regular assessments of pain intensity until threshold pain intensity criteria for study entry were met [16]. In contrast, in the SoluMatrix diclofenac study, patients were required to spontaneously complain of pain, unprompted by the study personnel, prior to pain intensity assessments. Finally, patients in the liquid gel-filled capsule study received a second dose of study medication before administration of opioid-containing rescue medication was considered [16,35,36], potentially affecting opioid rescue medication usage. The additional 25 mg diclofenac liquid gel-filled capsule dose—corresponding to up to 50 mg of diclofenac in the first 6 hours and up to 75 mg in the first 8 hours following randomization—in patients in the active treatment group may have contributed to the observed patterns of opioid-containing rescue medication usage. Taken together, differences in surgical and postoperative management and overall differences in the investigational plans between these trials prevent meaningful comparisons of relative opioid-sparing effects of the SoluMatrix diclofenac product vs the diclofenac potassium liquid gel-filled capsule drug product.

Efforts to diminish the prevalence of perioperative opioid-containing rescue medication use have practical value. The severity of AEs, as well as the potential to reduce risk of unintentional opioid overdose and opioid dependence, may also be lessened by employing NSAIDs acutely as part of multimodal analgesia in patients presenting with acute postoperative pain. The use of NSAIDs as part of multimodal analgesia regimens in the perioperative setting suggests that similar approaches in settings of acute pain merit further study.

Conclusions

SoluMatrix diclofenac administered to patients with acute pain following surgery was associated with significantly less opioid-containing rescue medication use compared with placebo. Patients treated with SoluMatrix diclofenac 35 mg and 18 mg required less opioid-containing rescue medication on average on the first and second postoperative days compared with placebo-treated patients. Additionally, patients receiving SoluMatrix diclofenac 35 mg and 18 mg required initial opioid rescue medication at later median times and at slower rates compared with patients receiving placebo. Low-dose SoluMatrix diclofenac was generally well tolerated. These results suggest that treatment with low-dose SoluMatrix diclofenac may reduce the need for opioid rescue medication in the days following surgery in patients with acute pain.
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