ZYNRELEF®: For Optimizing Pain Management and Decreasing Opioid Consumption

Here's a new and effective non-opioid therapy for patients who undergo bunionectomy.

BY RICHARD POLLAK, DPM

Disclaimer: Dr. Pollak has lectured on several occasions for Zynrelef; he has no financial interest in Heron and is not involved in any current clinical trials with Zynrelef.

Surgical bunion correction is one of the most common elective surgical procedures of the foot and ankle, estimated at >200,000 per year.[1,2] Despite use of multimodal analgesia and opioid-sparing protocols, opioids are still frequently prescribed after surgery, including bunionectomy. Use of opioids in the postoperative setting are associated with adverse events (AEs) and the potential for long-term dependence and diversion.[3] The rate of new persistent opioid use among opioid naïve bunionectomy patients who fill a perioperative opioid prescription is approximately 6%.[1] New non-opioid solutions that optimize pain management and decrease opioid consumption are needed.

Under the double-blind study design, neither the patients nor the investigators involved in conducting postsurgical assessments knew which treatment was given.

HTX-011 (ZYNRELEF®) consists of bupivacaine and low-dose meloxicam in an extended-release tri(ethylene glycol) poly(orthoester) based-polymer. This Biochronomer® technology was developed by Heron Therapeutics, Inc. specifically for sustained release drug delivery applications.[4] In HTX-011, the Biochronomer serves to overcome the short half-life of local anesthetics and prolong the duration of bupivacaine exposure to 72 hours. The presence of meloxicam in HTX-011 reduces local inflammation which in turn decreases the local acidic environment and normalizes pH, resulting in enhanced penetration of bupivacaine into the nerve and a potentiated effect.[5] Early Phase 2 studies of HTX-011 in herniorrhaphy and bunionectomy demonstrated the synergy of bupivacaine and meloxicam (formulated in the same polymer)

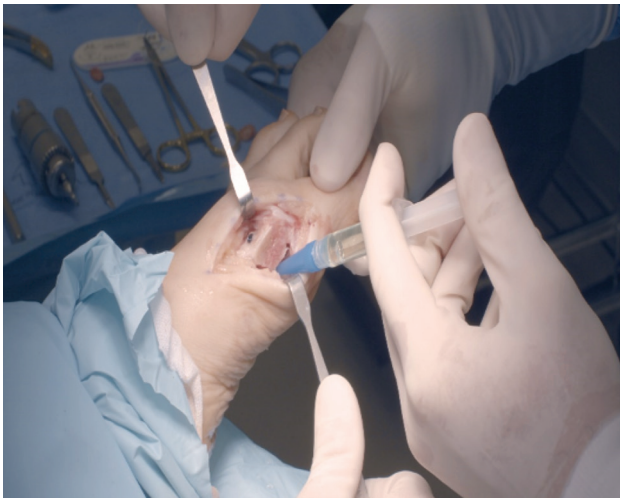

Figure 1: HTX-011 applied below the skin incision, at the level of deeper fascia to directly and adequately coat the pain-generating tissues in bunionectomy. Dose of bupivacaine 60 mg/meloxicam 1.8 mg (2.1 mL) shown.

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Clinical Innovations

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with superior and sustained pain relief through 72 hours after surgery compared to each individual component in the polymer.[6,7]

HTX-011 is a viscous solution and is applied directly into the surgical site, without a needle to coat the affected tissue (Figure 1). After administration, the unique, bioerodible polymer formulation enables controlled, simultaneous release of the active ingredients for approximately 72 hours. After the bupivacaine and meloxicam have been released from the polymer, hydrolysis causes cleavage of the polymer ester bond, creating small water-soluble polymer fragments that are primarily eliminated via the kidneys.[4,5]

The U.S. Food and Drug Administration (FDA) granted the initial approval of HTX-011 in May 2021 for use in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty. The label was expanded by the FDA in December 2021 to include foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.[7] The approval and subsequent label expansion was based on data from three randomized, double-blind, placebo- and active comparator-controlled pivotal trials: a phase 3 bunionectomy study (EPOCH-1), a phase 3 hernia repair study (EPOCH-2), and a phase 2b total knee arthroplasty study.[8-10] In addition, open-label follow-on studies were designed to assess HTX-011 in the same surgical models but as part of a scheduled, non-opioid, multimodal analgesia (MMA) MMA regimen.[11,12] EPOCH-1 and the open-label follow-on study of HTX-011 in bunionectomy (Study 218), are summarized below.

Phase 3 Study in Bunionectomy (EPOCH-1)

EPOCH-1 was a Phase 3, randomized, double-blind, saline placebo- and bupivacaine active-controlled, single-dose multicenter study in patients undergoing a primary unilateral, first metatarsal bunionectomy with osteotomy and internal fixation.[8] Key inclusion criteria were patients ≥18 years of age with an American Society of Anesthesiologists physical status score of I-III. All patients had to provide informed consent and adhere to the study visit schedule. Key exclusion criteria consisted of contralateral foot bunionectomy in the past 3 months, pre-existing acute or chronic painful physical conditions that could confound postoperative assessments, daily opioid use ≥7 consecutive days within past 6 months, and any nonsteroidal anti-inflammatory drugs (NSAIDs) within past 10 days (exception of subjects on low dose daily acetylsalicylic acid for cardioprotection), long-acting opioids within 72 hours, and any opioid within 24 hours.

Under the double-blind study design, neither the patients nor the investigators involved in conducting postsurgical assessments knew which treatment was given. This study was conducted at 13 sites across the US. Patients were randomized in a 3:3:2 ratio to: 1) HTX-011 (bupivacaine 60 mg/meloxicam 1.8 mg; 2.1 mL) administered via application into the surgical site, 2) bupivacaine HCl 0.5%, 50 mg (10 mL) via injection into the surgical site, or 3) saline placebo (2.1 mL) via application into the surgical site. On the day of surgery, patients underwent a unilateral Austin-type bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine (without epinephrine) administered as a Mayo block. Epidural or spinal anesthesia was not permitted. During surgery, the use of opioids other than intravenous fentanyl (up to 4 mcg/kg) or other analgesics was prohibited. Near the end of surgery, after final irrigation and suction were completed, a single dose of HTX-011 was administered without a needle into the surgical site.

Patients were required to remain hospitalized for 72 hours to undergo postoperative efficacy and safety assessments (by blinded assessors) and blood draws for pharmacokinetic (PK) analysis. During the 72-hour postoperative observation period, patients could receive rescue pain medication upon request. Available rescue medication consisted of: intravenous (IV) morphine (up to 10 mg within a 2-hour period), oral oxycodone (up to 10 mg within a 4-hour period), and/or oral acetaminophen (up to 1000 mg in a 6-hour window). Of note, NSAIDs were not permitted in EPOCH-1.

After discharge through Day 28, patients were to complete a daily diary to record whether they took opioids.

After discharge through Day 28, patients were to complete a daily diary to record whether they took opioids. Safety was assessed through Day 28 with an additional visit occurring on Day 42 to perform X-rays to evaluate bone and wound healing.

The primary endpoint was the mean area under the concentration curve (AUC) of the numeric rating scale of pain intensity score (NRS) through 72 hours ($AUC_{0\text{-}72}$) for HTX-011 compared with saline placebo. Key secondary endpoints included mean $AUC_{0\text{-}72}$ of the NRS of pain intensity scores for HTX-011 compared with bupivacaine HCl, mean total postoperative opioid consumption through 72 hours for HTX-011 compared with saline placebo, proportion of opioid-free patients through 72 hours for HTX-011 compared with bupivacaine HCl, and mean total postoperative opioid consumption through 72 hours for HTX-011 compared with bupivacaine. A strict testing hierarchy of the primary and key secondary endpoints was applied to control study-wise alpha level at 0.05.

A total of 412 patients received the study drug in the intention to treat (ITT) population. Baseline characteristics were similar across the three treatment groups, and the majority of patients were female, which was expected given the surgical procedure.

Overall HTX-011 demonstrated a statistically significant benefit based on the primary endpoint and all four

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key secondary endpoints. The patients who received HTX-011 showed a significant reduction in mean area under the curve of pain intensity over 72 hours compared with saline placebo (323.3 vs 445.3; $p < 0.001$; the primary endpoint) and compared with bupivacaine HCl (323.3 vs 393.5; $p < 0.001$; the first key secondary endpoint).

In addition to experiencing significantly less pain, patients treated with HTX-011 consumed significantly less opioids. Total postoperative opioid consumption through 72 hours was reduced by 37% in the HTX-011 group compared to placebo ($p < 0.0001$; second key secondary endpoint) and by 25% compared to bupivacaine HCl ($p = 0.0022$; fourth secondary endpoint). In addition, significantly more patients treated with HTX-011 were able to completely avoid postoperative opioids. Overall, 29% of patients who received HTX-011 were opioid-free through 72 hours, whereas 11% of those who received bupivacaine HCl ($p < 0.001$; third key secondary endpoint) and 2% of those who received placebo ($p < 0.001$) were opioid-free. Of the 45 patients in the HTX-011 group who were opioid-free through 72 hours, 41 patients (91.1%) remained opioid-free through Day 10 and 37 patients (82.2%) remained opioid-free through Day 28 recovery.

In addition to experiencing significantly less pain, patients treated with HTX-011 consumed significantly less opioids.

Overall, HTX-011 was well tolerated with a safety profile similar to that of saline placebo and bupivacaine HCl. The most common adverse events were nausea and dizziness, and the incidence was 37.6%, 45.5%, and 43.6%; and 21.7%, 23.4%, and 17.8% for HTX-011, bupivacaine HCl, and saline placebo, respectively. The incidence of local inflammatory adverse events was higher with HTX-011 compared to bupivacaine HCl and saline placebo. Specifically, the incidences of incision site edema and incision site erythema were 17%, 14%, and 13%; and 13%, 12%, and 8% for HTX-011, bupivacaine HCl, and saline placebo, respectively.[7] Local inflammatory adverse events were likely due to superficial placement of HTX-011 that resulted in erythema from the vasodilatory effect of bupivacaine. However, abnormal wound-healing findings were similar across treatment groups and most resolved by the day 42 follow-up visit. In addition, there was no evidence of impaired bone healing (from X-rays) in any treatment group.

Follow-On study

Having demonstrated the superior analgesic effect of HTX-011 compared to bupivacaine in EPOCH-1, an open-label follow-on study to EPOCH-1 was designed to assess HTX-011 in the same surgical model but as part of a scheduled, non-opioid, MMA regimen of oral acetaminophen and ibuprofen.[11] The study inclusion/exclusion criteria, surgical procedure, and endpoints were identical to EPOCH-1.

In contrast to EPOCH-1 where surgeons were instructed to use the entire HTX-011 dose (60 mg/1.8 mg, 2.1 mL), in the follow-on study they were instructed to utilize only enough HTX-011 to properly coat the tissues in the surgical site, yet avoid excess that could be expressed from the incision upon closure. Syringes were weighed before and after administration to calculate the dose used in each procedure. Permitted rescue medications were oral immediate release oxycodone (≤10 mg within a 4-hour period) or IV morphine (≤10 mg within a 2-hour period).

After surgery, once patients were able to tolerate oral intake, they received oral ibuprofen 600 mg every 6 hours. Three hours after the first dose of ibuprofen, they started oral acetaminophen 1 g every 6 hours, alternating the 2 medications so that an analgesic was administered every 3 hours until the 72-hour inpatient postoperative period was complete. Upon discharge, subjects were instructed to manage pain with the following regimen: oral ibuprofen 600 mg every 6 hours as needed as first-line therapy, and oral APAP 1g every 6 hours as needed as second-line therapy if the patient was still in pain. If a patient requested any opioids in the 12 hours prior to discharge, they were provided with a prescription for 15 tablets of oxycodone (≤5 mg) to be taken every 4 hours, as needed for pain. The planned sample size ($n = 30$) was selected empirically without formal statistical assumption.

Overall, HTX-011 was well tolerated with a safety profile similar to that of saline placebo and bupivacaine HCl.

Thirty-one patients received HTX-011, and patient demographics were similar to EPOCH-1. The mean dose of HTX-011 administered was 58.7 mg/1.8 mg (1.97 mL). Compared with HTX-011 alone (EPOCH-1), the addition of scheduled postoperative acetaminophen and ibuprofen to intraoperative HTX-011 reduced pain and opioid consumption, and increased the proportion of patients who did not require opioid rescue medication during the 72-hour in-patient postoperative period. Mean pain intensity scores were maintained in the mild pain range (NRS < 4) through 72 hours, and the mean NRS score did not exceed 2.5 during the inpatient assessment period (Figure 2). Notably, the lower pain scores were achieved with a substantial reduction in opioids. The mean total opioid consumption over the 72-hour postoperative period was 1.61 mg IV morphine equivalents (MME). Twenty-four patients (77.4%) were opioid free through 72 hours, and they all remained opioid-free through Day 28.

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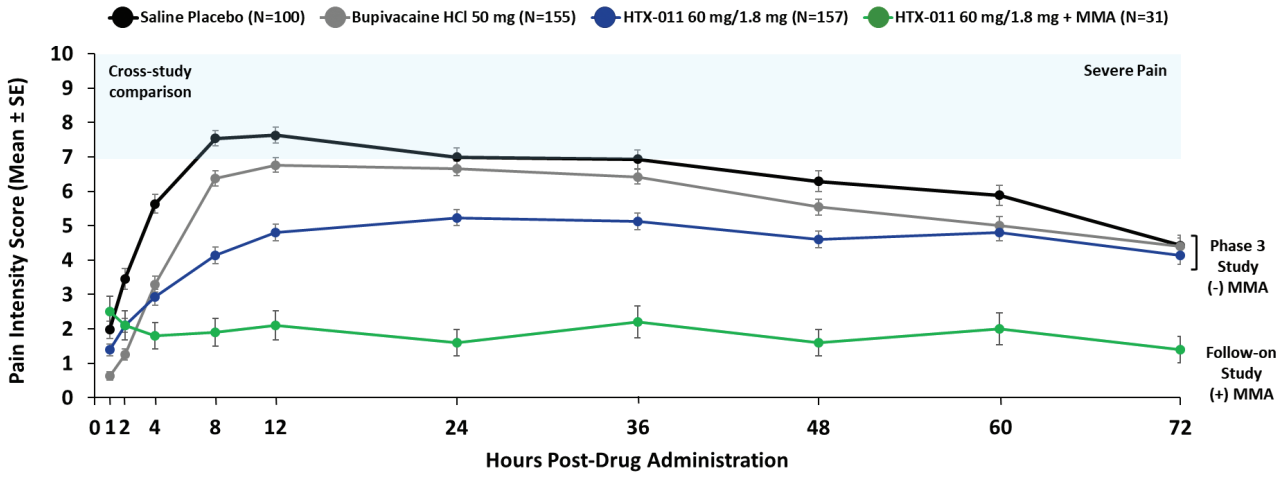

Figure 2: EPOCH-1 and Study 218 Mean Pain Intensity Scores over 72 Hours (ITT Population). MMA=multimodal analgesia; NRS=numeric rating scale; SE=standard error. Mean NRS scores computed with the windowed worst observation carried forward (wWOCF).

This figure was published in JAPMA, *Vol. 111, No. 3, Richard Pollak DPM, Danlin Cai PhD, and Tong J. Gan MD, MBA, MHS, Opioid-Free Recovery from Bunionectomy with HTX-011, a Dual-Acting Local Anesthetic Combining Bupivacaine and Meloxicam, as the Foundation of Non-Opioid Multimodal Analgesia, Copyright American Podiatric Medical Association. Used with permission.*

Similar to EPOCH-1, HTX-011 was well-tolerated. All adverse events were mild to moderate and resolved by the end of the study, and none led to study withdrawal. The most commonly reported adverse events were nausea and vomiting (22.6% and 9.7%, respectively). In contrast to EPOCH-1, no patients in the follow-on study experienced incision site edema or erythema, likely due to the modified administration instructions that resulted in decreased drug expressed from the surgical site. Because HTX-011 includes a low-dose of meloxicam, the incidence of potential NSAID-related adverse events was assessed to explore any possible safety signal from its combined use with scheduled oral ibuprofen. Two patients (6.5%) experienced a potential NSAID-related AE; one patient had hypertension and one patient had pruritis. No patients experienced any cardiac, bleeding, renal/urinary, or hepatobiliary adverse events. In addition, there was no evidence of toxicity from clinical laboratory evaluations including serum creatinine, estimated glomerular filtration rate, and liver function tests.

Discussion

Similar to other surgical procedures, opioids are often overprescribed after bunionectomy. In a nationwide United States insurance claims database of 41,687 opioid naïve adults who underwent surgical hallux valgus correction, 88% filled an opioid prescription. The overall rate of new persistent opioid use was 6.2%, and the greatest modifiable risk factor was a total prescribed opioid dose (OME) of ≥337.5 mg (~45 oxycodone 5 mg tablets).[1] Although the need to shift away from opioids to non-opioids is apparent, to do so requires effective and reliable non-opioid regimens.

HTX-011 is a unique fixed-dose combination of bupivacaine plus low dose of meloxicam in a proprietary polymer, which helps to overcome the barriers due to the inflammatory process at the surgical site and the short duration of currently available local anesthetics. The synergy observed between bupivacaine and meloxicam results in significantly greater pain reduction observed on days 1, 2 and 3 compared to standard bupivacaine HCl.

In EPOCH-1, 29% of HTX-011 treated patients were opioid free through 72 hours. The addition of scheduled non-opioid MMA in the follow-on study increased opioid free patients to 77% while maintaining mean pain scores in the mild range (NRS < 4) through 72 hours. This multimodal approach has the opportunity to provide patients with significantly less pain after surgery and a reduced need for opioids, which in turn can reduce potential opioid-related adverse events and the risk of developing opioid use disorder.

Although the need to shift away from opioids to non-opioids is apparent, to do so requires effective and reliable non-opioid regimens.

Importantly, HTX-011 was well-tolerated and had a similar safety profile compared to saline placebo and bupivacaine HCl. The presence of the low dose of meloxicam in HTX-011 results in minimal systemic exposure, thus the risk of potential NSAID-related adverse events is expected to be low. Use of HTX-011 with scheduled ibuprofen and acetaminophen during the 72-hour postoperative period did not result in any clinically relevant adverse events or changes in laboratory parameters that would indicate potential NSAID-related toxicity.

The use of HTX-011 as the foundation of a non-opioid MMA regimen offers a new and effective therapy for patients who un-

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dergo bunionectomy, which could assist in transforming opioid prescribing habits to stem the current opioid crisis. **PM**

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Dr. Richard Pollak was president of San Antonio Podiatry Associates from 1979 until his retirement in private practice in 2020. Dr. Pollak has been actively involved in clinical research for the past 25 years and enjoys expertise in analgesic clinical trials for novel pain medications.