PODIATRY CLINICAL CONNECTIONS

CASE STUDIES IN POSTOPERATIVE PAIN MANAGEMENT

ZYNRELEF® (bupivacaine and meloxicam) extended-release solution, for instillation use 29.25 mg/mL and 0.88 mg/mL

FIRST TARSOMETATARSAL FUSION WITH A CHEILECTOMY, RIGHT FOOT

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CASE PRESENTATION

- **Gender**: Female
- **Chronic pain**: Yes
- **Opioid use**: Intermittent
- **Age**: 18 years old
- **Weight**: 145 lbs
- **Height**: 70 in
- **BMI**: 20.8

HISTORY AND PHYSICAL

- **Patient presented for**: Chronic stress fracture of the right 2nd metatarsal.
- **History**: Presents with chronic stress fracture of the right second metatarsal after addressing issues related to CRPS and AV malformation. AV malformation, 1st interspace, removal 2018; CRPS developed in deep and superficial peroneal followed by neurectomy 2019; pain relief with development of chronic stress fracture recalcitrant to conservative care.
- **Existing medications**: Intermittent use of hydrocodone and gabapentin during her CRPS diagnosis.

TEST RESULTS

- **Physical exam revealed**: Hypermobility of the 1st TMT with functional hallux rigidus causing overloading of the 2nd metatarsal with chronic stress fracture and periostitis.
- **X-ray revealed**: Intramedullary sclerosis.
- **Preoperative labs included**: HCG negative.

DIAGNOSIS

- **Presenting diagnosis**: Right foot pain near site of previous surgery
- **Primary diagnosis**: Chronic stress fracture right 2nd metatarsal secondary to overloading, right
- **Revision diagnosis**: Metatarsus primus elevatus with functional hallux rigidus, right

RECOMMENDED PROCEDURE

- **Recommended procedure**: 1st TMT fusion with cheilectomy, right

PATIENT'S PERIOPERATIVE ANALGESIC PROTOCOL

- **Anesthesia**: Propofol drip with popliteal/adductor canal block (ropivacaine HCl 0.5%)
- **Tourniquet used during surgery**: Yes

MEDICATION	Pre-Op	Intra-Op	PACU	Post-Op Day 0	Post-Op Day 1	Post-Op Day 2	Post-Op Days 3 to 7
ZYNRELEF (bupivacaine/meloxicam)		3 ml (87.75 mg/ 2.64 mg)					
IV MIDAZOLAM	2 mg						
IV ROPIVACAINE HCl 0.5%*	20 ml						
IV PROPOFOL		200 mg					
PO HYDROCODONE							10 mg qid†
IV FENTANYL	200 mcg						
IV KETOROLAC		30 mg					

*Administered in the popliteal block.
†This is the same dose the patient came in on.
Do not exceed the recommended maximum daily limits of bupivacaine by all routes.
AV: arteriovenous; **CRPS**: complex regional pain syndrome; **HCG**: human chorionic gonadotropin; **qid**: four times a day; **TMT**: tarsometatarsal.

INDICATION

ZYNRELEF is indicated in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic procedures including foot and ankle, and other procedures in which direct exposure to articular cartilage is avoided.

Limitations of Use: Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large 4 or more level spinal, and head and neck procedures.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.**
- **ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.**

Please see additional Important Safety Information on next page and full Prescribing Information, including Boxed Warning and updated Warnings and Precautions for serious skin reactions caused by nonsteroidal anti-inflammatory drugs (NSAIDs).

This case study is intended only to provide healthcare professionals with an example of the use of ZYNRELEF in the treatment of one specific patient. The outcomes described may not be representative of, and may differ significantly from, outcomes that may be obtained in treating other patients. This case study is not intended to provide specific treatment advice, recommendations, or opinions, and should not replace a clinician's judgment with respect to the treatment of any particular patient.

OUTCOMES

PAIN ASSESSMENT*	OPIOID CONSUMPTION
PRE-OP: 3-4/10	**PRE-OP**: [20] MMEs
PACU: 0/10	**INTRA-OP**: [32] MMEs
POD 0[¶]: 0/10	**POD 0**: [0] MMEs
POD 1: 0/10 at hour 8 and 24	**POD 1**: [0] MMEs
POD 2: 0/10 at hour 48	**POD 2**: [0] MMEs
POD 3: 5/10 at hour 72	**POD 3-7**: [40] MMEs[†]

Office call back after discharge for pain management: 0

FUNCTIONAL OUTCOMES

- **Weight bearing**: Yes
- **Ambulation**: Active ROM postop
- **Time of first ambulation**: Day one
- **Distance of first ambulation**: Transfer weight from foot to Cam Walker while standing
- **Assistance needed in first ambulation (eg, boot)**: Cam Walker
- **Range of motion**: Active ankle ROM
- **Physical therapy participation**: N/A

PATIENT SATISFACTION

- **Patient satisfaction**: Satisfied[‡]

"Pain phone-calls postoperatively are a thing of the past!" – Bryce Karulak, DPM

DISCHARGE

- **Time to discharge**: 1.5 hours
- **Facility length of stay after surgery**: 1.5 hours
- **Notes**: Reduced post-op phone calls relating to pain

FOLLOW-UP

- **Follow-up visit**: 1 week
- **Pain level**: 3/10[§]

*Based on a 10-point visual analog scale (VAS).
[†]This is the same dose the patient came in on.
[‡]Verbally confirmed with patient on a scale of 1-10.
[§]Patient confirmed that the pain was manageable.
[¶]POD 0 = day of surgery.

POD: post operative day; **ROM:** range of motion.

IMPORTANT SAFETY INFORMATION (CONT)

Contraindications

ZYNRELEF is contraindicated in patients with a known hypersensitivity (eg, anaphylactic reactions and serious skin reactions) to any amide local anesthetic, NSAIDs, or other components of ZYNRELEF; with history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients); undergoing obstetrical paracervical block anesthesia; or undergoing CABG.

Warnings and Precautions

Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after application of ZYNRELEF. When using ZYNRELEF with other local anesthetics, overall local anesthetic exposure must be considered through 72 hours.

Hepatotoxicity: If abnormal liver tests persist or worsen, perform a clinical evaluation of the patient.

Hypertension: Patients taking some antihypertensive medication may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Heart Failure and Edema: Avoid use of ZYNRELEF in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure.

Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ZYNRELEF in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal failure.

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.

Risk of Joint Cartilage Necrosis and Degeneration with Unapproved Intra-articular Use: Animal studies evaluating the effects of ZYNRELEF following intra-articular administration in the knee joint demonstrated cartilage necrosis and degeneration.

Chondrolysis: Limit exposure to articular cartilage due to the potential risk of chondrolysis.

Methemoglobinemia: Cases have been reported with local anesthetic use.

Serious Skin Reactions: NSAIDs, including meloxicam, can cause serious skin adverse reactions. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. If symptoms present, evaluate clinically.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): If symptoms are present, evaluate clinically.

Fetal Toxicity: Due to the risk of oligohydramnios/fetal renal dysfunction and premature closure of the ductus arteriosus with NSAIDs, limit use of ZYNRELEF between about 20 to 30 weeks gestation, and avoid use after about 30 weeks.

Hematologic Toxicity: Monitor hemoglobin and hematocrit in patients with any signs or symptoms of anemia.

Drug Interactions

Drugs That Interfere with Hemostasis: Monitor patients for bleeding who are using ZYNRELEF with drugs that interfere with hemostasis (eg, warfarin, aspirin, SSRIs/SNRIs).

ACE Inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers: Use with ZYNRELEF may diminish the antihypertensive effect of these drugs. Monitor blood pressure.

ACE Inhibitors and ARBs: Use with ZYNRELEF in elderly, volume-depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function.

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects.

Use in Specific Populations

Infertility: NSAIDs are associated with reversible infertility. Consider avoidance of ZYNRELEF in women who have difficulties conceiving.

Severe Hepatic Impairment: Only use if benefits are expected to outweigh risks; monitor for signs of worsening liver function.

Severe Renal Impairment: Not recommended.

Adverse Reactions

Most common adverse reactions (incidence ≥5%) in controlled clinical trials with ZYNRELEF are soft tissue procedures: vomiting and orthopedic procedures: constipation and headache.

Report side effects to Heron at 1-844-437-6611 or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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