ORTHOPEDIC 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

RIGHT TOTAL KNEE ARTHROPLASTY

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CASE PRESENTATION

- **Gender**: Male
- **Chronic pain**: No
- **Prior opioid use**: No
- **Age**: 65 years old
- **Weight**: 226 lbs
- **Height**: 6'4"
- **BMI**: 27.6

TEST RESULTS

- **X-ray revealed**: Medial compartment joint space narrowing, medial compartment osteophytes, lateral compartment bone on bone, joint space loss worse on PA view, lateral compartment osteophytes and subchondral sclerosis, right knee. Kellgren and Lawrence Grade 4 findings present.
- **Preoperative labs included**: BMP – normal, CBC – normal

DIAGNOSIS

- **Presenting diagnosis:** Right knee end-stage arthritis
- **Primary diagnosis:** Osteoarthritis

RECOMMENDED PROCEDURE

- **Recommended procedure**: Right total knee arthroplasty (medial pivot)

HISTORY AND PHYSICAL

- **Patient present for:** 65-year-old male undergoing right total knee arthroplasty with same day discharge.
- This 65-year-old male has a several (>10) year history of right knee pain. On a pain scale, the knee is rated an 8/10 and is constant. The pain is particularly bad with standing, standing for long periods, walking, walking long distances, going down stairs, rising from a chair, getting out of bed and at night. The pain is located essentially throughout the knee. The pain is described as sharp, throbbing, dull and achy. He complains of instability. He has used or is currently using acetaminophen, ibuprofen and naproxen for pain. Other conservative treatment to date has included activity modification, physical therapy, knee bracing, intraarticular steroids, weight reduction and NSAIDs. He had a skiing accident in 2007. He had a lateral meniscus tear followed by an arthroscopy in 2007. He relies heavily on his left knee for skiing and activities. He does not trust his right knee for stability. He can't walk the 5-6 miles he used to, he can't ski anymore, and he can't go down hills because of his knee.
- **Existing medications**: Amlodipine, acetaminophen, ibuprofen, naproxen

PATIENT'S PERIOPERATIVE ANALGESIC PROTOCOL

- **Anesthesia**: Spinal (chloroprocaine 1%) and adductor canal block (ropivacaine 0.5%)
- **Tourniquet(s) used during surgery**: Yes, released at 70 minutes

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)		14 ml (400 mg/ 12 mg)					
CELECOXIB	200 mg			200 mg	200 mg bid	200 mg bid	200 mg bid
IV ACETAMINOPHEN		1 g					
IV KETOROLAC				15 mg			
HYDROCODONE/ ACETAMINOPHEN				10 mg prn			10 mg prn
ORAL ACETAMINOPHEN				500 mg	1000 mg q8hr	1000 mg q8hr	1000 mg q8hr
CHLOROPROCAINE 1%		6 ml					
ROPIVACAINE 0.5%		10 ml					

Do not exceed the recommended maximum daily limits of bupivacaine by all routes.
Do not exceed 4 g for APAP by all routes.
bid: two times a day; **NSAIDs**: nonsteroidal anti-inflammatory drugs; **prn**: as needed; **q8hr**: every 8 hours.

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).

OUTCOMES

PAIN ASSESSMENT*	OPIOID CONSUMPTION
PACU: 2/10	**INTRA-OP**: [0] MMEs
POD 0‡: 0/10	**POD 0**: [10] 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: 1/10 at hour 72	**POD 3-7**: rare hydrocodone use

Office call back after discharge for pain management: None

FUNCTIONAL OUTCOMES

- **Weight bearing**: As tolerated
- **Ambulation**: Yes
- **Time of first ambulation**: Within 3 hours of surgery patient walking in hallway
- **Distance of first ambulation**: 25 ft x 2
- **Assistance needed in first ambulation (eg, boot)**: Walker used
- **Range of motion**: 0-100 degrees prior to discharge
- **Physical therapy participation**: Yes

PATIENT SATISFACTION

- **Patient satisfaction**: Very satisfied†

*Based on a 10-point visual analog scale (VAS).
†Based on 5 point Likert scale.
‡POD 0 = day of surgery.
POD: post operative day.

DISCHARGE

- **Time to discharge**: PACU discharge time: 40 minutes
- **Facility length of stay after surgery**: 3.5 hours after surgery
- **"Other" Outcomes**: Reports "No pain at all, period, for the first 3 days!"

FOLLOW-UP

- **Follow-up visit**: Rare opioid use in first week
- **Pain level**: Minimal pain

"Large, young, athletic males can be some of our most challenging knee replacement patients. It is great to have locally applied, non-opioid medication options which can reduce pain and speed up recovery in these types of patients." – Alexander Sah, MD

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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