The Clinical and Economic Benefits of Multimodal Pain Management

- Local anesthetics
- Anti-inflammatory drugs
- General anesthetics
- Alpha₂ agonists

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What Is Multimodal Analgesia?

Multimodal analgesia is the utilization of multiple pain management modalities for more effective pain control that can lead to enhanced clinical and economic benefits.

Decreases in...

- Opioid use\(^1\)
- Length of hospital stay\(^1,2\)
- Acute postsurgical pain\(^3\)
- Risk of developing chronic pain\(^4\)
- Postsurgical complications\(^5\)
- Costs per patient\(^1,2\)

Improvement in...

- Efficiency of hospital resources\(^1,2\)
- Patient satisfaction\(^3,5,6\)

**EXPAREL**® (bupivacaine liposome injectable suspension) Can Be Part of Multimodal Analgesia

**EXPAREL** is a non-opioid injectable analgesic indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks. It can function on its own or in combination with conventional analgesic options as part of multimodal therapy. The studies presented on the following pages highlight the efficacy of **EXPAREL** as part of multimodal therapy in outcomes such as pain control, lower opioid utilization, and decreased length of stay (LOS).

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Total Knee Arthroplasty

Study Design
- Phase 4, multicenter, randomized, double-blind, controlled, parallel-group study comparing the safety and efficacy of infiltration of EXPAREL (n=70) versus standard bupivacaine (n=69) in adults undergoing primary unilateral total knee arthroplasty (TKA).

Multimodal Protocol

PREOPERATIVE
- Celecoxib 200 mg orally
- Acetaminophen 1000 mg orally
- Pregabalin 300 mg orally
- Tranexamic acid 1 g intravenously
- Spinal anesthesia

INTRAOPERATIVE
- Both groups:
  - Fentanyl (or fentanyl analogs)
- EXPAREL group:
  - EXPAREL 20 mL + 0.5% bupivacaine HCl 20 mL + saline 80 mL
- Bupivacaine HCl group:
  - 0.5% bupivacaine HCl 20 mL + saline 100 mL

POSTSURGICAL
- Celecoxib 200 mg orally every 12 hours until discharge
- Acetaminophen 1000 mg orally every 8 hours (maximum of 3000 mg/day)
- Immediate-release oxycodone 10 mg orally every 4 hours (maximum) or as needed; if oral therapy was not tolerated, morphine 2.5 to 5 mg intravenously or hydromorphone 0.5 to 1 mg every 4 hours or as needed
- Celecoxib 200 mg orally
- Acetaminophen 1000 mg orally
- Pregabalin 300 mg orally
- Tranexamic acid 1 g intravenously
- Spinal anesthesia

Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

Less Pain
- 180.8 vs 209.3 cumulative AUC of VAS 12 to 48 hours after surgery (P=0.0381)

Fewer Opioids
- 18.7 mg vs 84.9 mg 0 to 48 hours (P=0.0048)

More Patients Opioid Free
- 10% vs 0% in the first 72 hours (P=0.01)

AUC=area under the curve; VAS=visual analog scale.
Study Design

- Retrospective study comparing the efficacy of EXPAREL and dexamethasone intraoperatively as part of multimodal pain management (n=31) versus standard multimodal pain management (n=24) in patients undergoing elective shoulder arthroplasty.

Multimodal Protocol

PREOPERATIVE

• Single-injection interscalene block
  – Acetaminophen 1000 mg intravenously
  – Gabapentin 600 mg orally
  – Oxycodeone 10 mg orally
  – Celecoxib 200 mg orally

INTRAOPERATIVE

• Standard multimodal group: none
• EXPAREL group:
  – EXPAREL 20 mL + saline 20 mL + 0.25% bupivacaine HCl with epinephrine 10 mL
  – Dexamethasone 8 to 10 mg intravenously

POSTSURGICAL

• Ketorolac intravenously
• Acetaminophen intravenously
• Gabapentin orally
• Oxycodeone 5 mg and 10 mg orally for mild to moderate pain
• Hydromorphone 0.5 mg, 1 mg, and 2 mg intravenously for moderate to severe pain

Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

*In patients who utilized preoperative opioids*

Lower Pain Level

- 3.5 vs 7.5 VAS pain score on POD 1 (P<0.001)

Fewer Opioids Used

- 20 mg vs 40.5 mg in cumulative utilization (P<0.001)

Shorter LOS

- 1 vs 2 days (P<0.001)

POD=postoperative day.

*The use of EXPAREL in combination with epinephrine is not part of the approved label.

*Opioid intake measured in morphine equivalent dosing (MED) (mg).
Study Design

- Retrospective study comparing the efficacy of standard total hip arthroplasty (THA) pain management with adjunct EXPAREL (n=586) versus standard THA pain management alone (n=686) in patients undergoing THA.

  - 8 hours after surgery ($P=0.031$)
  - POD 1 ($P=0.001$)
  - POD 2 ($P=0.016$)
  - Gait: 82% vs 64% ($P<0.001$)
  - Stairs: 93% vs 76% ($P<0.001$)

Multimodal Protocol

<table>
<thead>
<tr>
<th>PREOPERATIVE</th>
<th>INTRAOPERATIVE</th>
<th>POSTSURGICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 200 mg orally</td>
<td>Both groups: - Spinal (preferred) or general (alternate) anesthesia - Injection of bupivacaine HCl + epinephrine 0.25% 40 mL, morphine sulfate 1 mg/mL 5 mL, and ketorolac 30 mg/mL 1 mL$^a$</td>
<td>Patient-controlled analgesia for up to 24 hours after surgery</td>
</tr>
<tr>
<td>Acetaminophen 1000 mg orally</td>
<td>THA + EXPAREL group: - Periarticular EXPAREL 20 mL in 40 mL 0.9% saline</td>
<td>Oral opioids as needed</td>
</tr>
<tr>
<td>Pregabalin 50 mg orally</td>
<td>THA group: - No EXPAREL administered</td>
<td>Morphine/Hydromorphone HCl intravenously as needed for breakthrough pain</td>
</tr>
<tr>
<td>Celecoxib 200 mg orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen 1000 mg orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin 50 mg orally</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

- Significant Pain Reduction: 8 hours after surgery ($P=0.031$)
- Fewer Opioids Used: POD 1 ($P=0.001$), POD 2 ($P=0.016$)
- More Patients Achieved Physical Therapy Milestones: Gait: 82% vs 64% ($P<0.001$), Stairs: 93% vs 76% ($P<0.001$)
## Study Design

- Overview of a “fast track” surgical approach for lumbar fusion through the incorporation of an ERAS protocol

## Spinal ERAS Recommendations

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preadmission Counseling</td>
<td>Expectation of patient’s role in recovery</td>
</tr>
<tr>
<td>Preoperative Enteral Nutrition</td>
<td>Optimized enteral nutrition, including increased protein intake and preoperative constipation treatment for at-risk patients</td>
</tr>
<tr>
<td>Preoperative Fasting and Carbohydrate Loading</td>
<td>Fasting windows of 12 hours for food and 8 hours for liquids, with routine carbohydrate loading</td>
</tr>
<tr>
<td>Antithrombotic Prophylaxis</td>
<td>Compression stockings and intermittent pneumatic compression</td>
</tr>
<tr>
<td>Antimicrobial Prophylaxis and Skin Preparation</td>
<td>First-generation cephalosporin 1 hour before incision and suggestion for MRSA vaccination</td>
</tr>
<tr>
<td>Anesthesia Protocol</td>
<td>Recommendation for no general anesthesia and avoidance of long-acting opioids and anesthetic agents with a preference for short-acting sedation as necessary</td>
</tr>
<tr>
<td>Local Analgesia</td>
<td>Skin blocks by local anesthesia for every skin incision, with EXPORTEL used for screw entry sites</td>
</tr>
<tr>
<td>Minimally Invasive Spinal Surgery</td>
<td>Endoscopic decompression and deployment of expandable cages for interbody fusion; percutaneous instrumentation of pedicle screws is required</td>
</tr>
<tr>
<td>Osteobiologics</td>
<td>Routine application of osteobiologic adjuvants to promote fusion, removing the need for bone graft harvesting and promoting likelihood of successful arthrodesis</td>
</tr>
<tr>
<td>Surgical Drainage</td>
<td>Routine use of surgical drains is not recommended</td>
</tr>
<tr>
<td>Hypothermia and Hypotension Avoidance</td>
<td>Intraoperative maintenance of normothermia and blood pressure</td>
</tr>
<tr>
<td>Fluid Balance</td>
<td>Noninvasive cardiac output monitoring is used for minimally invasive monitoring of fluid status during surgery. Hypovolemia should be avoided</td>
</tr>
<tr>
<td>Urinary Drainage</td>
<td>Avoidance of urinary catheterization to reduce likelihood of postsurgical urinary retention</td>
</tr>
<tr>
<td>Postsurgical Analgesia Protocol</td>
<td>Gabapentin, tramadol, and acetaminophen favored to decrease potential risk of bone fusion; early and effective pain control reduced patient anxiety and fear, resulting in rapid mobilization</td>
</tr>
<tr>
<td>Postsurgical Nutrition</td>
<td>Patients are encouraged to have oral intake at will after recovery from surgery</td>
</tr>
<tr>
<td>Early Mobilization</td>
<td>Early mobilization using a brace is recommended; no bending or weight lifting for patients who undergo fusion surgery</td>
</tr>
<tr>
<td>Audit</td>
<td>Systemic audit is recommended; no bending or weight lifting for patients who have had fusion surgery</td>
</tr>
</tbody>
</table>
Microsurgical Breast Reconstruction

**Study Design**

- Retrospective analysis comparing an enhanced recovery pathway (ERP) with patient-controlled analgesia (PCA) of ketorolac and an **EXPAREL** transversus abdominis plane (TAP) block (n=42) with historical controls (n=49) in patients undergoing deep inferior epigastric perforator or free transverse rectus abdominis myocutaneous flap breast reconstruction.

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**Multimodal Protocol**

**INTRAOPERATIVE**
- Bilateral TAP block with **EXPAREL** 266 mg/20 mL expanded with 180 mL of saline
- Acetaminophen intravenously
- Ketenolac intravenously

**POSTSURGICAL**
- Postanesthesia care unit (PACU)
  - Ketenolac 15 mg intravenously every 6 hours for 3 days
  - No intravenous PCA
  - Provision of oral or intravenous opioids for breakthrough pain
- POD 1
  - Ketenolac 15 mg orally as needed after intravenous regimen

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**Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia**

**Less Postsurgical Morphine**
- 46.0 mg vs 70.5 mg ($P=0.003$)

**Shorter LOS**
- 4.0 vs 5.0 days ($P=0.0001$)
Microvascular Breast Reconstruction

Study Design

- Retrospective study comparing the efficacy of EXPAREL as a TAP block and local infiltration as part of an enhanced recovery after surgery (ERAS) pathway (n=49) with a historical cohort of patients who received traditional care after surgery (n=51)

Multimodal Protocol

**PREOPERATIVE**
- Celecoxib orally
- Acetaminophen orally
- Gabapentin orally
- Antibiotic prophylaxis

**INTRAOPERATIVE**
- Bilateral TAP block and local infiltration with EXPAREL 266 mg/20 mL expanded with normal saline
- Antiemetic protocol

**POSTSURGICAL**
- Celecoxib and acetaminophen as needed; oral opioids as needed for rescue

Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

- Less Postsurgical Morphine
  - 167.3 mg vs 574.3 mg ($P<0.001$)
- Shorter LOS
  - 3.9 vs 5.5 days ($P<0.001$)
Abdominal Wall Reconstruction

Study Design

• Single-center, parallel-group study comparing the efficacy of an ERAS protocol that included a TAP block with EXPAREL (n=42) compared with previously used standard of care

Multimodal Protocol

MULTIMODAL PAIN CONTROL

• Intraoperative TAP block with EXPAREL 266 mg/20 mL expanded to 120 mL with normal saline
• Hydromorphone PCA of 0.2 mg every 6 minutes until able to administer orally
• Acetaminophen 1 g intravenously every 6 hours for 48 hours; transition to 650 mg orally every 6 hours with scheduled oxycodone 5 to 10 mg orally every 4 hours as needed
• Gabapentin 300 mg orally 3 times daily until discharge
• Diazepam 5 mg intravenously every 6 hours for 48 hours; hold for obstructive sleep apnea and one-half dose for patients aged >65 years
• Nonsteroidal anti-inflammatory drugs (NSAIDs) as needed, starting 48 hours postsurgically, with a hold for any renal dysfunction

ACCELERATION OF INTESTINAL RECOVERY

• Minimization of opioids through multimodal pain control
• Alvimopan 12 mg orally preoperatively in the holding area and every 12 hours postsurgically until discharge or POD 7

Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

Faster Return to Bowel Function

• 3.6 vs 5.0 days (P<0.0001)

Shorter LOS

• 4.4 vs 5.8 days (P<0.0001)
# Laparoscopic Colorectal Surgery

**Study Design**
- Retrospective trial comparing patients receiving local infiltration of EXPAREL (n=70) as part of an ERP with those being placed in an ERP (n=70)

## Multimodal Protocol

### PREOPERATIVE
- Gabapentin 300 mg orally the night before surgery and 2 hours before surgery
- Celecoxib 400 mg orally 2 hours before surgery
- Alvimopan 12 mg orally 2 hours before surgery

### INTRAOPERATIVE
- Dexamethasone 8 mg and acetaminophen 1 g intravenously at induction
- Ketorolac 30 mg intravenously 30 minutes before emergence
- Acetaminophen 1 g intravenously 30 minutes before emergence
- Ondansetron 4 mg intravenously 30 minutes before emergence
- **EXPAREL group:** local infiltration at port sites with EXPAREL 266 mg/20 mL expanded with 20 mL normal saline and 0.25% regular bupivacaine to a total volume of 60 mL
- Acetaminophen 1 g scheduled every 6 hours intravenously until oral form is tolerated, at which point transitioned to 650 mg orally every 6 hours
- Ketorolac scheduled 30 mg intravenously every 6 hours for 48 hours, followed by celecoxib 400 mg orally twice daily
- Gabapentin scheduled 300 mg orally every 8 hours
- Alvimopan scheduled 12 mg orally twice daily until discharge or a maximum of 7 days
- Oxycodone 5 to 10 mg orally every 6 hours as needed for breakthrough pain intensity of 4 to 8 on a scale of 10
- Hydromorphone HCl 0.4 to 0.6 mg intravenously every 2 hours as needed for breakthrough pain intensity of 8 to 10 on a scale of 10
- Enoxaparin sodium 40 mg subcutaneously daily and pneumatic antiembolism stockings
- Gabapentin 300 mg orally the night before surgery and 2 hours before surgery
- Celecoxib 400 mg orally 2 hours before surgery
- Alvimopan 12 mg orally 2 hours before surgery

### POSTSURGICAL
- **EXPAREL group:** local infiltration at port sites with EXPAREL 266 mg/20 mL expanded with 20 mL normal saline and 0.25% regular bupivacaine to a total volume of 60 mL
- Oxycodone 5 to 10 mg orally every 6 hours as needed for breakthrough pain intensity of 4 to 8 on a scale of 10
- Hydromorphone HCl 0.4 to 0.6 mg intravenously every 2 hours as needed for breakthrough pain intensity of 8 to 10 on a scale of 10
- Enoxaparin sodium 40 mg subcutaneously daily and pneumatic antiembolism stockings
- Gabapentin 300 mg orally the night before surgery and 2 hours before surgery
- Celecoxib 400 mg orally 2 hours before surgery
- Alvimopan 12 mg orally 2 hours before surgery

## Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

- **Lower Mean Pain Scores in PACU**
  - 1.92 vs 4.71 (P=0.001)

- **Fewer Opioids Used in PACU**
  - 1.16 vs 3.56 (P<0.01)

- **Shorter LOS**
  - 2.96 vs 3.93 days (P=0.003)

*Drug utilization was measured with the World Health Organization’s defined daily dose (DDD), with the following conversion formulas for drugs administered: fentanyl intravenously (1 DDD = 100 mcg), hydromorphone HCl intravenously (1 DDD = 2 mg), hydromorphone HCl orally (1 DDD = 4 mg), oxycodone orally (1 DDD = 20 mg), and hydrocodone orally (1 DDD = 10 mg).*
Study Design

- Retrospective analysis to identify amount of opioids required and LOS for patients undergoing lung resection (n=52) or foregut surgery (n=54). All patients were placed on an ERP, with local infiltration of EXPAREL for lung resections and a rib block with EXPAREL for foregut surgeries.

Multimodal Protocol

<table>
<thead>
<tr>
<th>INTRAOPERATIVE</th>
<th>EMERGENCE FROM ANESTHESIA</th>
<th>POSTSURGICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to anesthesia</td>
<td>- Tramadol 100 mg orally</td>
<td>- Acetaminophen 1000 mg intravenously every 8 hours for 24 hours, then orally every 8 hours</td>
</tr>
<tr>
<td>- Gabapentin 300 mg orally</td>
<td>- Ketorolac 15 mg intravenously every 6 hours for 48 hours, then ibuprofen 400 mg orally every 12 hours</td>
<td></td>
</tr>
<tr>
<td>- Famotidine 20 mg intravenously</td>
<td>- Acetaminophen 1000 mg intravenously</td>
<td></td>
</tr>
<tr>
<td>- Ondansetron 4 mg intravenously</td>
<td>- Gabapentin 300 mg orally every 8 hours</td>
<td></td>
</tr>
<tr>
<td>- Midazolam up to 1 mg intravenously</td>
<td>- Tramadol 10 mg orally every 6 hours as needed for pain</td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>- After induction of general anesthesia</td>
<td>- Prior to extubation</td>
</tr>
<tr>
<td>- Propofol up to 2 mg/kg intravenously</td>
<td>- Ketorolac 15 mg intravenously</td>
<td>- Stop remifentanil infusion</td>
</tr>
<tr>
<td>- Lidocaine 1 mg/kg intravenously</td>
<td>- Acetaminophen 1000 mg intravenously</td>
<td>- Ondansetron 4 mg intravenously</td>
</tr>
<tr>
<td>- Muscle relaxant</td>
<td>- EXPAREL local infiltration; in lung procedures, EXPAREL rib block from 2 to 11 was done</td>
<td></td>
</tr>
<tr>
<td>- Fentanyl up to 100 mcg intravenously as needed</td>
<td>- Dexamethasone 4 to 8 mg intravenously</td>
<td></td>
</tr>
<tr>
<td>- Total intravenous anesthesia infusion</td>
<td>- Stop dexmedetomidine</td>
<td></td>
</tr>
<tr>
<td>- Remifentanil 0.05-0.1 mcg/kg/min or ketamine 0.05-0.1 mcg/kg/hr</td>
<td>- Decrease propofol infusion by 50%</td>
<td></td>
</tr>
<tr>
<td>- Propofol 60-100 mcg/kg/min</td>
<td>- Decrease remifentanil or ketamine by 50%</td>
<td></td>
</tr>
<tr>
<td>- Dexmedetomidine 0.3 mcg/kg/hr</td>
<td>- 20 minutes prior to completion</td>
<td></td>
</tr>
<tr>
<td>- After induction of general anesthesia</td>
<td>- Stop propofol</td>
<td></td>
</tr>
<tr>
<td>- Ketorolac 15 mg intravenously</td>
<td>- Prior to extubation</td>
<td></td>
</tr>
<tr>
<td>- Acetaminophen 1000 mg intravenously</td>
<td>- Stop remifentanil infusion</td>
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<td>- Ondansetron 4 mg intravenously</td>
<td></td>
</tr>
<tr>
<td>- Dexamethasone 4 to 8 mg intravenously</td>
<td>- Midazolam up to 1 mg intravenously as needed</td>
<td></td>
</tr>
<tr>
<td>- Ondansetron 4 mg intravenously</td>
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</tr>
</tbody>
</table>

Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia

- Percentage of Patients Transferring From Recovery to Inpatient With Schedule 2 Opioids
  - 10% of lung resections
  - 2% of foregut surgeries

- Median LOS
  - 2 days for lung resections
  - 1 day for foregut surgeries
Open Ventral Hernia Repair

Study Design

- Retrospective, observational study comparing patients who received an ERAS protocol with EXPAREL (n=100) with a historical group prior to the introduction of the protocol (n=100)

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>With ERAS</th>
<th>Without ERAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter Time to Liquids</td>
<td>1.1 vs 2.7 days (P&lt;0.001)</td>
<td>2.7 vs 4.8 days (P&lt;0.001)</td>
</tr>
<tr>
<td>Shorter Time to Regular Diet</td>
<td>3.0 vs 4.8 days (P&lt;0.001)</td>
<td>4.8 vs 7.2 days (P&lt;0.001)</td>
</tr>
<tr>
<td>Shorter Time to Flatus</td>
<td>3.1 vs 3.9 days (P&lt;0.001)</td>
<td>3.9 vs 6.1 days (P&lt;0.001)</td>
</tr>
<tr>
<td>Bowel Movement</td>
<td>3.6 vs 5.2 days (P&lt;0.001)</td>
<td>5.2 vs 7.8 days (P&lt;0.001)</td>
</tr>
<tr>
<td>Fewer 90-Day Readmissions</td>
<td>4% vs 16% (P=0.008)</td>
<td>16% vs 32% (P=0.008)</td>
</tr>
</tbody>
</table>

Multimodal Protocol

**PERIOPERATIVE**
- Heparin 5000 units subcutaneously
- Alvimopan 12 mg orally
- Gabapentin 100 to 300 mg orally
- First-generation cephalosporin and vancomycin for positive MRSA screen

**INTRAOPERATIVE**
- Minimization of opioids and/or paralytics
- Intraoperative TAP block with EXPAREL 266 mg/20 mL expanded to 200 mL (100 mL per side)
- Hydromorphone intravenously in PCA: 0.2 mg every 6 to 10 minutes with no breakthrough dose or basal rate; stopped on POD 2 once on clear liquids
- Oxycodone 5 to 10 mg orally every 4 hours as needed once off intravenous PCA
- Acetaminophen 650 mg orally every 6 hours immediately after surgery
- Gabapentin 100 to 300 mg orally every 6 hours 3 times daily starting on POD 1
- Diazepam 5 mg intravenously every 6 hours as needed; 2.5 mg for patients >65 years old. Not used for patients with OSA, sedation, or any respiratory compromise
- NSAID 600 to 800 mg orally every 6 to 8 hours as needed; held for renal dysfunction and substituted with ketorolac 15 to 30 mg intravenously every 6 hours

**POSTSURGICAL**
- Heparin 5000 units subcutaneously
- Alvimopan 12 mg orally
- Gabapentin 100 to 300 mg orally
- First-generation cephalosporin and vancomycin for positive MRSA screen

**PACIRA PHARMACEUTICALS, INC.**

MRSA=methicillin-resistant Staphylococcus aureus, OSA=obstructive sleep apnea.
**Study Design**
- Retrospective analysis comparing live kidney donors undergoing a laparoscopic nephrectomy under an ERAS protocol with EXPAREL (n=39) with live kidney donors under standard of care (n=40)

**Multimodal Protocol**

**PREOPERATIVE**
- Acetaminophen 975 mg orally
- Gabapentin 600 mg orally
- Scopolamine patch
- Heparin 5000 units subcutaneously
- Cefazolin 1 to 2 g intravenously or clindamycin 600 mg intravenously (if allergic to cefazolin)

**INTRAOPERATIVE**
- Fentanyl boluses
- Subfascial EXPAREL
- Dexamethasone 4 mg intravenously
- Acetaminophen 1 g intravenously at start of case
- Ketorolac 15 mg intravenously toward end of case
- Ondansetron 4 mg intravenously when closing wound
- Repeat antibiotic prophylaxis if procedure lasts longer than 4 hours

**POSTSURGICAL**
- Acetaminophen orally
- Ketorolac intravenously within first 24 hours
- Gabapentin orally
- Tramadol orally as needed
- Scopolamine patch
- Ondansetron
- Promethazine as needed

**Patients Receiving Multimodal Pain Management With EXPAREL for Analgesia**

- Decreased Pain Scores Morning After Surgery
  - 3 vs 7 ($P<0.001$)

- Shorter LOS
  - 1 vs 2 days ($P<0.001$)
## Study Design

- Analysis of hepatectomy patients, rated symptom severity and life interference using the validated MD Anderson Symptom Inventory (MDASI) preoperatively and postsurgically at every outpatient visit until 31 days after surgery, to compare those on an ERP with EXPAREL (n=75) with patients treated on a traditional pathway (n=43).

## Multimodal Protocol

<table>
<thead>
<tr>
<th>PREOPERATIVE</th>
<th>INTRAOPERATIVE</th>
<th>POSTSURGICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Celecoxib 400 mg orally</td>
<td>- Perioperative steroids: dexamethasone 10 mg intravenously on induction of anesthesia</td>
<td>- Baseline analgesia: pregabalin 75 mg orally twice daily, start in PM of POD 0 for 48 hours; acetaminophen 500 mg orally, start in PM of POD 0; celecoxib 200 mg orally twice daily, start in POD 1; tramadol 50 mg orally every 6 hours, start in POD 1 for 48 hours; epidural basal rate if placed in operating room</td>
</tr>
<tr>
<td>- Pregabalin 75 mg orally (unless &gt;65 years)</td>
<td>- Opioid-sparing anesthesia</td>
<td>- As-needed analgesia: analgesia titrated per pain service for epidural patients</td>
</tr>
<tr>
<td>- Tramadol extended release 300 mg orally morning of surgery</td>
<td>- Intravenous and inhalational anesthetics: propofol as main anesthetic agent; dexmedetomidine intravenously, ketamine intravenously, lidocaine infusion titrated</td>
<td>- As-needed analgesia in non-epidural patients: acetaminophen 500 mg orally every 6 hours with a limit of 2 g/day for mild pain, tramadol 50 mg orally every 6 hours for moderate pain, and hydromorphone 0.5 mg every 15 minutes for 2 doses for severe pain</td>
</tr>
<tr>
<td>- Anxiolytics and anti-nausea as needed</td>
<td>- Regional analgesia for minimally invasive surgery: local infiltration with EXPAREL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Without ERP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Anxiolytics and anti-nausea as needed</td>
<td>- Combined protocol with opioid and inhalational agents</td>
<td>- Baseline analgesia: epidural, PCA hydromorphone, hydrocodone orally</td>
</tr>
<tr>
<td></td>
<td>- Local wound infiltration with bupivacaine in minimally invasive surgery</td>
<td>- Hydromorphone intravenously, tramadol orally, hydrocodone orally, acetaminophen orally or intravenously, ketorolac intravenously</td>
</tr>
</tbody>
</table>

## Patients Receiving Multimodal Pain Management With EXPAREL as a Part of ERAS for Analgesia

- **Higher Percentage of Patients With Lower PACU Pain Scores**
  - 76% vs 56% (P=0.023)

- **Shorter LOS**
  - 4.8 vs 6.1 days (P=0.027)
Multimodal Analgesia Is Key for Improved Outcomes

Data from multiple studies prove that multimodal analgesia is key to optimal pain management and improved clinical outcomes. EXPAREL, as part of multimodal therapy, has a demonstrated benefit, whether through shorter LOS, improved pain management, or less opioid utilization. Multiple important organizations echo the need for improved multimodal pain management strategies.

“Effective pain management demands a multimodal assessment and treatment plan that identifies and addresses all components of the individual’s pain experience.”

“Whenever possible, anesthesiologists should use multimodal pain management therapy.”

“…committed to the implementation of a multimodal plan focused on policy, physician education, and patient/caregiver education to address opioid abuse.”

The inclusion of EXPAREL on formulary as part of multimodal therapy may promote progress in achieving these improved clinical outcomes.

Visit www.EXPAREL.com to find out more.
EXPAREL® (bupivacaine liposome injectable suspension) is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

Important Safety Information

EXPAREL is contraindicated in obstetrical paracervical block anesthesia.

Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation.

If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine.

EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.

Warnings and Precautions Specific to EXPAREL

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks other than interscalene brachial plexus nerve block, or intravascular or intra-articular use.

The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.

Warnings and Precautions for Bupivacaine-Containing Products

Central Nervous System (CNS) Reactions: There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression.

Cardiovascular System Reactions: Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death.

Allergic Reactions: Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients.

Chondrolysis: There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use.

Methemoglobinemia: Cases of methemoglobinemia have been reported with local anesthetic use.