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# Advancing Orthopedic Postsurgical Pain Management & Multimodal Care Pathways: Improving Clinical & Economic Outcomes

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# Recent Advances in Incorporation of Local Analgesics in Postsurgical Pain Pathways

Adolph V. Lombardi Jr, MD, FACS

## Abstract

Total knee and hip replacement surgeries are highly invasive, and a significant level of postoperative pain is commonplace in patients undergoing these procedures. It is now known that postoperative pain can affect hospital stay, patient satisfaction, postsurgical rehabilitation, and a range of other clinical and administrative outcomes. The need for a multimodal approach to the control of postoperative pain, using combinations of agents that have synergistic effects, is now widely accepted.

There has been increasing interest in local periarticular and intra-articular injections, which can result in significantly less pain in the postanesthesiology care unit (PACU), significantly less use of rescue opioids in the PACU, significantly less confusion, significantly less blood loss, and a significantly lower bleeding index. EXPAREL® (bupivacaine liposome injectable suspension) is an extended-release anesthetic that is approved by the US Food and Drug Administration for single-dose injection into the surgical site to produce postsurgical analgesia. Several phase 2 and phase 3 studies across a range of surgical procedures have demonstrated that the inclusion of EXPAREL® in the multimodal regimen can significantly reduce both pain scores (including cumulative pain scores at 24 hours) and opioid consumption, as well as resulting in delayed time to the first use of opioids and more opioid-free patients at 72 hours. Multimodal regimens that include EXPAREL® may have important benefits in total joint arthroplasty.

Orthopedic procedures are reported to be among the most painful surgical procedures, and more than half of all patients experience suboptimal postoperative pain control.[1] Total knee and hip replacement surgeries, in particular, are invasive, and a significant level of postoperative pain is commonplace in patients undergoing these procedures.

The volume of orthopedic surgical procedures makes postoperative pain an issue that not only affects a vast number of patients but also has a major impact on health care costs. More than 90 million orthopedic surgical procedures are performed in the United States each year, of which approximately 56 million are conducted on an inpatient basis and 35 million are ambulatory.[2,3] Around 719,000 total knee replacement procedures and around 332,000 hip replacements were performed in 2010.[4]

## The Need for Improved Management of Postoperative Pain

For more than a decade now, there has been growing interest in improving ways to assess, monitor, and control postoperative pain, which continues to be a considerable unmet health care issue.[5] Pain is a chief reason for both prolongation of hospital stay and patient dissatisfaction,[6] and poor pain management has been shown to have major personal, organizational, and financial costs.[7] Rehabilitation after total knee arthroplasty (TKA) and total hip arthroplasty (THA) is tied directly to pain and comfort levels—how patients feel following surgery influences how well they participate in rehabilitation therapy and, ultimately, affects outcomes.[1] Furthermore, untreated acute pain is a predictor of chronic pain and disability, which has considerable impact on quality of life and represents a major societal burden.[6]

The incidence of severe, debilitating pain has been reported to range from approximately 2% to 10% of cases.[8] In one survey of 1490 surgical inpatients, which measured postoperative pain using a visual analog scale from 0 to 100, moderate or severe pain was reported by 41% of subjects.[9] So today, pain remains a prevalent problem following orthopedic surgery.

There are several factors that can predispose patients to pain following surgery, and these factors can be either patient- or procedure-specific. For example, men tend to experience a higher level of postoperative pain than women, and younger

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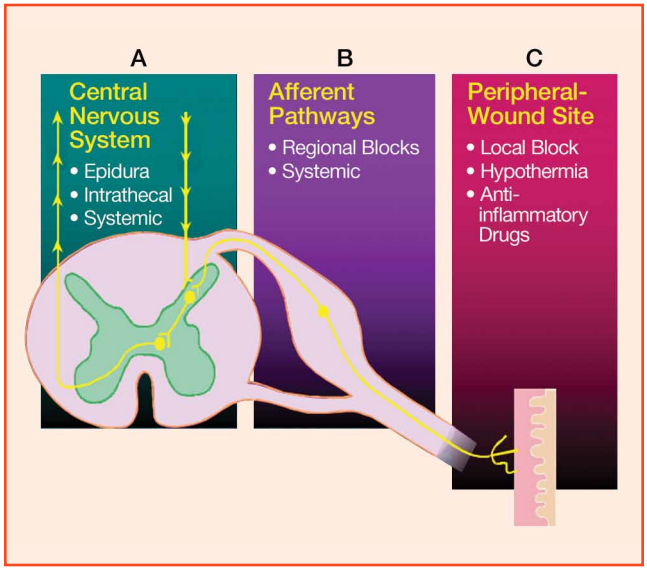


Figure 1. Effective control of postoperative pain requires a multimodal approach. Data source: Mallory[17]; Mallory.[18] Reproduced courtesy of Joint Implant Surgeons, Inc.

patients may have more pain than older patients.[8,10] Some individuals may have a genetic predisposition to increased pain susceptibility. There are differences according to race and among different ethnic groups. Also, individuals who have been abusing opioids for some time prior to surgery require more vigilance with respect to their postoperative pain.

## Reliance on Opioids Is a Barrier to Effective Pain Management

One major contributor to the high rate of postoperative pain is the continued reliance on opioid agents as the treatment of choice for postoperative pain.[11]

It is now well established that opioid-related adverse events (ORAEs) are pervasive following surgery. These ORAEs include:

- Central nervous system effects, such as sedation and respiratory depression;
- Nausea, vomiting, ileus, which are less serious medically, but still troublesome to patients[12,13]; and
- Constipation due to decreased gastrointestinal motility.[12,14]

An exacerbating factor that further inhibits effective control of postoperative pain using opioids is the multitude of steps that are typically required between the patient's perception of returning pain and the administration of analgesic medication.[15] These steps delay pain relief and leave the care team constantly "chasing the pain." At one time, it was felt that the introduction of patient-controlled analgesia represented a solution to this problem. Unfortunately, this approach not only failed to provide adequate pain relief in many instances, but also led to increased use of opioid medication, together with the associated side effects.

## Multimodal Analgesia in Joint Replacement Surgery

The trauma of surgery activates the nociceptor system, including nociceptors in both peripheral nerves and the central nervous system.[16] The need for a multimodal approach to the control of postoperative pain, using combinations of agents that have synergistic effects,[17,18] is now widely accepted (**Figure 1**). Typical multimodal regimens may include:

- Preemptive analgesia with agents such as celecoxib, oxycodone, pregabalin, or gabapentin;
- Short-acting spinal anesthesia (hip arthroplasty);
- Adductor canal block (knee arthroplasty);
- General anesthesia;
- Tranexamic acid;
- Pericapsular injectable cocktail;
- Intravenous (IV) acetaminophen;
- IV steroid dexamethasone; and
- Additional postoperative anti-inflammatory medication.

There has been increasing interest in local periarticular and intra-articular injections. As long as 10 years ago, data showed that periarticular and intra-articular injections can result in significantly less pain in the postanesthesiology care unit (PACU), significantly less use of rescue opioids in the PACU, significantly less confusion, significantly less blood loss, and a significantly lower bleeding index.[19] In patients receiving periarticular and intra-articular injections, a trend towards increased range of motion at discharge and reduced need for manipulation has been observed.[19]

A new option for managing postoperative pain is EXPAREL® (bupivacaine liposome injectable suspension; Pacira Pharma-

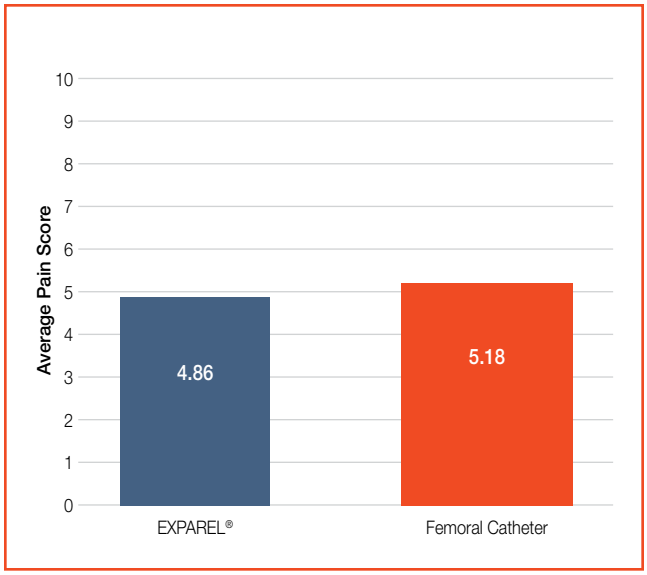


Figure 2. Average resting pain scores, liposomal bupivacaine vs femoral nerve catheter with ropivacaine infiltration. Pain rating scale: 0 = no pain, 10 = worst possible pain. Reproduced with permission from Hawkins.[24]

ceuticals, Inc., San Diego, California), an extended-release anesthetic that is approved by the US Food and Drug Administration (FDA) for single-dose injection into the surgical site to produce postsurgical analgesia.

## EXPAREL® as a Component of Multimodal Analgesia Regimens

A high degree of collaboration between the surgeon and anesthesiologist is essential for optimal outcomes. EXPAREL® can be infiltrated by the surgeon to block nociceptive pain at the site of initiation of surgical trauma, while the anesthesiologist uses other anesthetics and complimentary analgesic modalities to achieve more comprehensive management of perioperative pain.[20] By considering the time to onset of action and the duration of effect for each agent in the multimodal regimen, the surgeon and anesthesiologist can coordinate the administration of each medication to achieve the desired synergies.

The recommended dose of EXPAREL® is based on the surgical site and the volume required to cover the area. Pivotal studies in bunionectomy and hemorrhoidectomy used doses of 106 mg (8 mL volume) and 266 mg (20 mL volume), respectively.[21]

The technique used when administering EXPAREL® has a major influence on the effectiveness of this medication. It must be injected meticulously into the soft tissues, using a small needle (25-gauge or larger) and proceeding very slowly, taking care to aspirate frequently, in order to check for blood and minimize the risk of intravascular injection.

Several phase 2 and phase 3 studies were performed to assess the efficacy of EXPAREL® across a range of surgical procedures, including hemorrhoidectomy, inguinal hernia repair, breast augmentation, and TKA.[21] Inclusion of this medication in the multimodal regimen was shown to significantly reduce both pain scores (including cumulative pain scores at 24 hours) and opioid consumption, as well as resulting in delayed time to the first use of opioids and more opioid-free patients at 72 hours.[22,23]

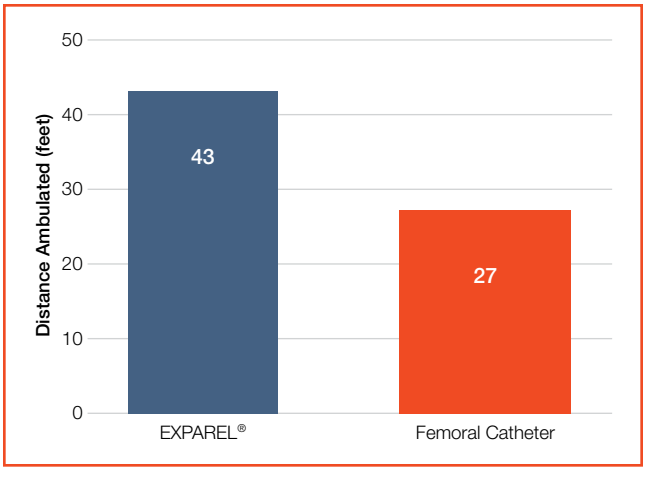


Figure 3. Assisted ambulation, day 0 postoperation, liposomal bupivacaine vs femoral nerve catheter with ropivacaine infiltration. Reproduced with permission from Hawkins.[24]

To determine the benefits of EXPAREL® in total joint replacement, a recent study compared the use of femoral nerve catheter with EXPAREL® in 200 patients undergoing TKA.[24,25] The average resting pain score at 72 hours was lower in the EXPAREL® group than in the femoral nerve catheter with ropivacaine infiltration group (**Figure 2**). Patients who received EXPAREL® also were able to walk farther following surgery (**Figure 3**) and required less assisted ambulation compared with the femoral catheter group. Whereas all patients receiving femoral block required the assistance of 2 persons, those who received EXPAREL® only required moderate assistance from 1 person. In addition, the length of hospital stay was reduced by half a day with EXPAREL®.

## Same-Day Discharge After Total Joint Replacement

Over recent years, there has been a trend towards reducing the length of hospital stay for patients undergoing arthroplasty, and many patients are now sent home the same day if possible.

In June 2013 a new facility was opened with the specific goal of minimizing the need for overnight hospitalization after knee and hip arthroplasty (White Fence Surgical Suites, New Albany, Ohio). Because reducing pain and improving ambulation by including EXPAREL® in the multimodal analgesia regimen can enhance the possibility of sending patients home on the same day as their surgery, this agent is a standard component of analgesic regimens at that facility. To date, 1152 arthroplasty procedures have been performed in the first year by 4 surgeons—387 THAs, 355 TKAs, 379 partial knee replacements, 15 total shoulder replacements, and 16 hip and knee revisions.

The vast majority of patients treated at that facility (89.8%) were able to be discharged on the same day as their surgery. Of the 10.2% who stayed overnight, most remained at the facility either for travel-related convenience or because they underwent surgery late in the day. In addition, 97% of patient satisfaction scores at the facility have been positive.

## Summary

New approaches to multimodal analgesia that offer improved pain control can reduce the use of opioid medications and allow earlier weight-bearing and ambulation. Effective new options, such as EXPAREL®, also have the potential to reduce or eliminate the use of nerve blocks. Safe same-day discharge of patients has become a reality, and with it significant cost savings for the surgeon, facility, patient, and health care system.

Dr. Lombardi is an orthopedic surgeon and president of Joint Implant Surgeons, Inc., Mount Carmel Health System, The Ohio State University, New Albany, Ohio.

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# Transition From Nerve Blocks to Periarticular Injections and Emerging Techniques in Total Joint Arthroplasty

Bryan D. Springer, MD

## Abstract

The emergence of procedure-specific multimodal pain management regimens that provide effective control of postoperative pain, while markedly reducing the amount of opioid medication required, has been one of the most important advances in hip and knee replacement in recent years. When peripheral nerve blockade first became widely available for inclusion in multimodal regimens, it was viewed as a revolution in the management of postoperative pain. This approach, however, is costly and has some important limitations, including an increased incidence of falls.

For many patients, peripheral nerve blocks can now be replaced by a periarticular injection with EXPAREL® (bupivacaine liposome injectable suspension), an extended-release anesthetic infiltrated by the surgeon as part of a multimodal pain regimen. EXPAREL® offers some important clinical and administrative benefits over nerve blocks. Preliminary data from a pilot study comparing the relative effectiveness of EXPAREL® versus sciatic nerve blockade has shown a noticeable reduction in average pain scores at rest with EXPAREL® following both hip and knee arthroplasty, as well as a reduction in the 6- to 12-hour pain score following hip arthroplasty. There was also a significant reduction in opioid use with EXPAREL®, as well as a $411 reduction in the cost of total knee arthroplasty and a $348 reduction in the cost of total hip arthroplasty.

The last decade has brought several remarkable advances in joint replacement surgery. Highly cross-linked polyethylene, for example, has significantly reduced the amount of wear and osteolysis that occurs over time following total joint arthroplasty.[1,2] A multitude of studies have demonstrated the ability of tranexamic acid to reduce perioperative blood loss and transfusion requirements following total hip arthroplasty (THA) and total knee arthroplasty (TKA).[3,4] Rapid rehabilitation protocols have produced a dramatic reduction in recovery and the time required for patients to achieve goals for discharge following THA and TKA.[5,6] And the emergence of procedure-specific multimodal pain management regimens has made it possible to provide effective control of postoperative pain, while markedly reducing the amount of opioid medications.[7,8]

## The Evolution of Perioperative Multimodal Analgesia

There are now ample data demonstrating that patient outcomes following total joint arthroplasty are heavily influenced by how well the patient's postoperative pain is controlled.[9] Effective pain control can enable patients to get out of bed and move about sooner, which reduces their risk of venous thromboembolism following surgery. Earlier ambulation also facilitates more rapid discharge, and there are data showing that shortening the length of time patients spend in the hospital not only has economic benefits but also reduces the likelihood that they will develop an infection.[10]

The initiation, development, and transmission of perioperative pain, as well as potential wind-up that can lead to chronic pain, are known to involve multiple distinct pathways. Therefore, effective control of postoperative pain requires a combination of agents and techniques that work independently and synergistically in both the peripheral and central nervous systems. Many analgesic and anesthetic agents are now available for inclusion in such multimodal regimens (**Figure 1**), and they are combined in various ways. Experts believe that multimodal regimens should be tailored according to the surgical procedure.[7]

## Peripheral Nerve Blockade in Multimodal Analgesia

When peripheral nerve blockade first became widely available for inclusion in multimodal regimens, it was viewed as a

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revolution in the management of postoperative pain. Patient-controlled analgesia could be eliminated in many cases and, with a femoral nerve block, a catheter, and a single-shot sciatic block, patients who would previously have been in a significant amount of pain were experiencing no pain at all during the immediate postoperative period.

The absence of postoperative pain with nerve blocks, however, is also associated with significant motor blockade leading to weakness in the leg. This has been shown to increase the risk of falls following surgery. Two recent studies found that, despite the implementation of multiple fall prevention protocols, use of femoral nerve catheters for TKA was associated with a significant risk of falls and associated morbidity.[11,12] In addition, the goals of rapid rehabilitation protocols involve early mobilization. The resulting weakness from nerve blocks, however, often prevents or limits patient mobility following surgery.

Another important limitation of peripheral nerve blockade is the occurrence of rebound pain when the block wears off. Patients often feel sufficiently pain-free during the immediate postoperative period that they neither need nor request pain medication. Once the effects of the block subside, the patient often has a sudden increase in pain, and the care team is suddenly playing "catch-up" with opioid pain medications to get the problem under control. Patients who have received

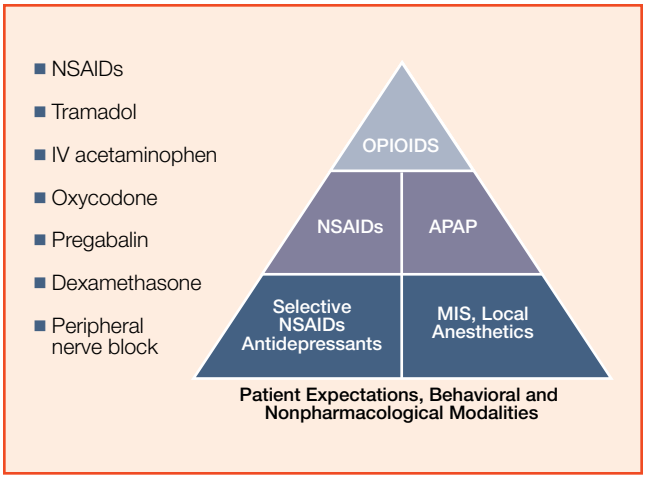


Figure 1. Rationale for a multimodal approach to the management of postoperative pain. Abbreviations: APAP, acetaminophen; IV, intravenous; MIS, minimally invasive surgery; NSAID, nonsteroidal anti-inflammatory drug.

**Table 1. Comparison of Femoral and Sciatic Nerve Blocks (Control) With EXPAREL® as Components of Multimodal Perioperative Pain Regimens for Total Hip or Total Knee Arthroplasty**

| | Total Hip Arthroplasty | | | Total Knee Arthroplasty | | |
|---|---|---|---|---|---|---|
| | Control (n = 16) | EXPAREL® (n = 14) | *P* | Control (n = 32) | EXPAREL® (n = 26) | *P* |
| Mean (SD) Age, y | 61.63 (11.25) | 62.64 (9.52) | 0.7926 | 64.94 (11.38) | 63.04 (13.33) | 0.5607 |
| Sex, female, n (%) | 10 (63%) | 8 (57%) | 0.7651 | 22 (69%) | 21 (81%) | 0.2287 |
| Mean (SD) BMI | 29.99 (4.85) | 31.44 (9.57) | 0.6074 | 32.57 (6.44) | 35.14 (6.08) | 0.1325 |
| Mean (SD) LOS, d | 2.44 (0.51) | 2.71 (0.91) | 0.3070 | 3.31 (1.64) | 3.19 (1.13) | 0.7518 |
| Mean (SD) 6-12 h PO pain score | 5.25 (2.34) | 1.8 (2.10) | 0.0018 | 4.29 (2.23) | 3.5 (2.04) | 0.2657 |
| Mean (SD) pain score at rest | 5.01 (1.66) | 3.11 (2.31) | 0.0140 | 4.70 (2.05) | 3.57 (1.99) | 0.0386 |
| Mean (SD) opioids, mg/d MEDD, DOS | 87.94 (44.69) | 77.5 (55.45) | 0.7308 | 83.44 (97.92) | 72.50 (33.06) | 0.7144 |
| Mean (SD) opioids, mg/d MEDD, POD 1 | 82.97 (68.30) | 74.96 (43.08) | 0.7088 | 78.28 (79.99) | 67.12 (43.85) | 0.5264 |
| Mean (SD) opioids, mg/d MEDD, POD 2 | 68.59 (91.28) | 51.79 (39.99) | 0.5296 | 51.31 (49.79) | 64.13 (59.97) | 0.3773 |
| Mean (SD) opioids, mg MEDD, 3 days total | 210.53 (175.06) | 159.25 (82.60) | 0.3253 | 193.03 (179.89) | 176.06 (101.11) | 0.6697 |
| PCA used, n (%) | 8 (50%) | 10 (71%) | 0.2320 | 17 (53%) | 14 (54%) | 0.9556 |
| Mean (SD) time to first opioid use, min | 224.91 (61.47) | 260.08 (123.27) | 0.4000 | 388.81 (320.7) | 426.42 (593.51) | 0.8172 |

Abbreviations: BMI, body mass index; DOS, day of surgery; LOS, length of stay; MEDD, morphine-equivalent daily dose; PCA, patient-controlled analgesia; PO, postoperative; POD, postoperative day.

a peripheral nerve block for TKA have also been reported to experience increased incidence of neuropathic pain and neurologic sequelae from the nerve block.[13]

## EXPAREL®—An Alternative to Nerve Blockade for Some Procedures

For many patients, the use of peripheral nerve blocks has now been superseded by EXPAREL® (bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc., San Diego, California), an extended-release anesthetic that can be injected into the surgical site to produce effective postoperative analgesia. EXPAREL® is infiltrated by the surgeon, as part of a multimodal regimen, to block nociceptive pain at the site of initiation of surgical trauma.[8] EXPAREL® offers some important clinical and economic benefits over nerve blocks.

### Clinical Benefits

EXPAREL® is an attractive alternative to peripheral nerve blocks because it produces no motor blockade, and patients are therefore able to mobilize faster and participate fully in physical therapy immediately after surgery.[14] Furthermore, in clinical trials, EXPAREL® has been shown to provide continuous and effective analgesia for up to 72 hours, and to reduce opioid requirements.[14]

The relative effectiveness of EXPAREL® versus sciatic nerve blockade is currently being compared in a pilot study (OrthoCarolina, Charlotte, North Carolina). A preliminary analysis of the data from that study has shown a noticeable reduction in the average pain score at rest with EXPAREL®, compared with sciatic nerve blockade, following both THA and TKA, as well as a reduction in the 6- to 12-hour pain score following THA (**Table 1**; OrthoCarolina, Charlotte, North Carolina; unpublished data). The study also found a significant reduction in overall opioid use, measured in morphine equivalents, compared with other modalities.

### Economic Benefits

The replacement of nerve blockade with EXPAREL® has also resulted in substantial cost savings. The direct cost of medication and equipment required to perform a sciatic nerve block totals approximately $527 (**Table 2**). In comparison, the cost of a vial of EXPAREL® alone—no additional equipment is needed—is approximately $299. This difference represents a direct saving of around 47%, and does not include anesthesiologist costs associated with administering the nerve block or other indirect costs.

The preliminary analysis of data from the pilot study comparing EXPAREL® with sciatic nerve blockade revealed a $411 reduction in the cost of TKA and a $348 reduction in the cost of THA (**Table 3**). Furthermore, it has been possible to eliminate 1 full-time employee position (anesthesiology

**Table 2. Direct Costs of Elastomeric, Continuous Peripheral Nerve Blockade (CPNB), Single-Shot Sciatic Nerve Block, and EXPAREL®**

| Cost | On Q Ball-Elastomeric | CPNB | Selective Femoral Nerve Catheter Plus Single-Shot Sciatic Block | EXPAREL® |
|---|---|---|---|---|
| Anesthesia | 0 | $25 | $25 | 0 |
| Ball | $171.5 | $265 | $265 | 0 |
| Tubing | $58.6 | $26.35 | $26.35 | 0 |
| Medication | $22.92 | $94.51 | $94.51 | $299 |
| Ultrasound | 0 | $100 | $100 | 0 |
| Immobilizer | $16.36 | $16.36 | $16.36 | 0 |
| **Total Costs[a]** | **$269.38** | **$527.22** | **$527.22** | **$299** |

[a]Does not include anesthesia charges ($900-$1200).

**Table 3. Comparison of the Total Cost of Total Knee and Total Hip Arthroplasty Using Femoral and Sciatic Nerve Blocks (Control) Versus Using EXPAREL®**

| Total Knee Arthroplasty | Control | EXPAREL® |
|---|---|---|
| Average total charges | $58,222 | $55,548 |
| Average expected payment | $18,259 | $25,159 |
| Average direct cost less implants | $7,019 | $6,608 |
| **Total Hip Arhroplasty** | **Control** | **EXPAREL®** |
| Average total charges | $55,935 | $52,810 |
| Average expected payment | $20,180 | $19,988 |
| Average direct cost less implants | $6,198 | $5,850 |

**Table 4. Compatibility of EXPAREL® With Other Commonly Used Medications and Implant Materials[a]**

**EXPAREL® demonstrates no significant interaction with:**

- Epinephrine
- Corticosteroids
- Antibiotics
- Tranexamic acid
- NSAIDs
- Bupivacaine HCl (up to 2:1 ratio)
- Opioids
- Stainless steel
- Titanium
- Polypropylene
- Silicone

[a]From Kharitonov.[16]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

nurse), and the reduction in opioid use observed to date has resulted in fewer call codes for respiratory sedation.

## Administration of EXPAREL® in Hip and Knee Arthroplasty

EXPAREL® incorporates bupivacaine with DepoFoam (Pacira Pharmaceuticals, Inc.), a proprietary drug delivery technology that uses multivesicular liposomes to encapsulate the bupivacaine and release it over an extended period of time.[15] Although 3% of the bupivacaine in EXPAREL® is not bound in the liposomes, and therefore is not immediately available, bupivacaine HCl is commonly used to provide additional short-term analgesia until the bound bupivacaine begins to be released from the DepoFoam. Generally speaking, experienced users recommended administration of 20 mL EXPAREL® (1 vial), together with a local injection of 30 mL 0.25% bupivacaine HCl/epinephrine. If more volume is needed, up to 50 mL preservative-free normal saline can be added, depending on the joint being infiltrated.

EXPAREL® has been shown to be compatible with many other medications and implant materials that are commonly used in total joint arthroplasty (**Table 4**).[16] There are, however, some limitations: EXPAREL® should not be used in conjunction with ropivacaine, and infiltration of EXPAREL® should be delayed for at least 20 minutes following injection of lidocaine. In addition, bupivacaine HCl may impact the pharmacokinetics of EXPAREL® if the milligram bupivacaine dose in bupivacaine HCl (Marcaine) exceeds 50% of the bupivacaine in the EXPAREL® dose (266 mg).

## Summary

The introduction of the extended-release anesthetic, EXPAREL®, represents another important advance in hip and knee replacement surgery. Clinical studies have clearly demonstrated that EXPAREL® effectively controls postoperative pain for up to 72 hours, reduces opioid consumption, improves early mobility, and lowers the overall cost of these procedures. Whereas peripheral nerve blockade was once the gold standard in multimodal analgesia and the management of postoperative pain, for many patients EXPAREL® can now be used in its place to achieve superior clinical and economic outcomes.

Dr. Springer is an orthopedic surgeon at OrthoCarolina Hip and Knee Center, Charlotte, North Carolina.

*Am J Orthop*. 2014;43(10 suppl):S6-S9. 

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# Local Infiltration of Liposome Bupivacaine in Foot and Ankle Surgery: Case-Based Reviews

Steven A. Herbst, MD

## Abstract

Foot and ankle surgical procedures, ranging from simple procedures, such as bunionectomy and correction of hammer toe, to more complex surgery, such as ankle fusion and ankle replacement, are extremely painful. Moreover, there is increasing interest in performing these procedures in an outpatient setting. Nerve blocks are extensively used in foot and ankle surgery, and commonly used techniques include sciatic nerve block with saphenous nerve augmentation; ankle block; and local, digital, or field block. Whereas more extensive blocks are associated with increased medical risk, higher cost, and delayed ambulation, more local approaches may not provide an adequate duration of effect.

EXPAREL® (bupivacaine liposome injectable suspension) is an extended-release local anesthetic that can be infiltrated directly into the surgical site by the orthopedic surgeon to provide continuous and effective analgesia at the site of surgical injury for up to 72 hours. Two cases that illustrate the use of EXPAREL® in foot and ankle surgery are described. The first case involves ankle replacement in an active 58-year-old man with a 20-plus-year history of arthritis. The second case involves a young woman undergoing surgery for a talar neck fracture-dislocation with an open injury, dislocated subtalar joint, avascular talus, and considerable deformity. Both patients reported excellent control of postsurgical pain.

Although foot and ankle surgery has some unique needs from an anesthesia standpoint, it shares 2 overriding concerns with other lower limb surgical procedures. First, orthopedic lower limb surgeries are associated with prolonged pain following the procedure, resulting in a greater need for multimodal analgesia and anesthesia. From simpler procedures, such as bunionectomy or correction of hammer toe, to more complex ones, such as ankle fusion or ankle replacement, foot and ankle surgery is painful. Second, similar to hip and knee replacement surgery, there is considerable interest in performing foot and ankle procedures in an outpatient setting.

Nerve block selection for foot and ankle procedures depends on the extent of the surgery, and at our facility we predominantly employ 3 options. For more extensive procedures involving the ankle—hindfoot/midfoot/forefoot reconstructions, arthroscopy, etc—the standard technique is a sciatic nerve block with saphenous nerve augmentation, either in the infragluteal region or closer to the knee, in a popliteal approach. For simple, less painful, soft-tissue procedures around the ankle or in the foot itself, an ankle block is preferred. Although this approach does not last quite as long as the sciatic nerve block with saphenous nerve augmentation, it does not result in significant motor paralysis. This characteristic makes it the preferred block for patients who are going to be weight-bearing. Finally, a local, digital, or field block is used for procedures involving isolated Morton neuromas, hammer toes, ganglions, etc.

Each of these approaches, of course, is associated with specific challenges. Although for extensive procedures an indwelling catheter can control pain, the benefit must be weighed against the cost, associated complications, and inconvenience, especially in outpatients.[1] At many facilities, an anesthesiologist skilled in specific blocks may not always be available, so getting a catheter correctly placed can be a challenge, and a block room may not always be available either. Conversely, because the ankle block typically lasts for only around 6 hours, patients who are undergoing less extensive procedures and who therefore receive this type of block frequently complain about pain when the medication wears off.[2] Nevertheless, in these less extensive cases, a catheter would (a) be overkill from a procedure standpoint, (b) introduce excessive risk and cost, and (c) limit ambulation.

The optimal solution in patients undergoing foot and ankle surgery would be to provide catheter-like duration of effect, without either the risk or practical issues associated

**Author's Disclosure Statement:** The author reports that he is a speaker and/or consultant for Acumed, LLC, Pacira Pharmaceuticals, Inc., and Zimmer.

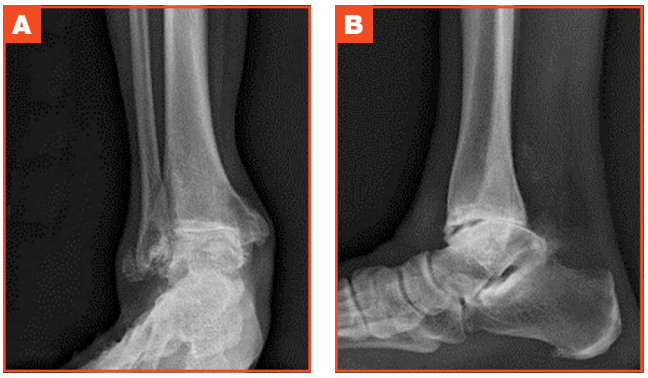


Figure 1. Case 1: (A) Anteroposterior and (B) lateral radiographs showing extensive arthritic change to the ankle with posterior subluxation to the talus.

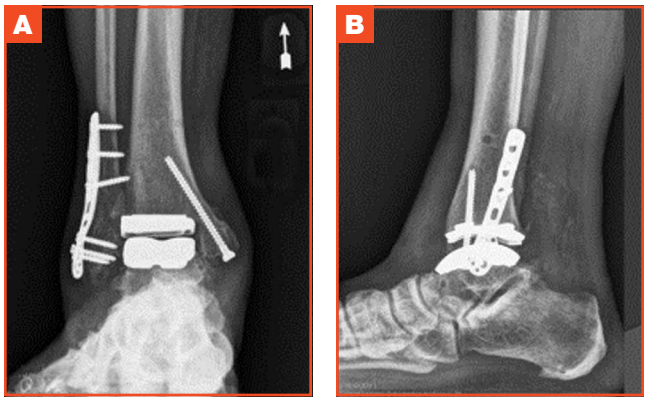


Figure 2. Case 1: (A) Anteroposterior and (B) lateral radiographs showing ankle replacement after surgery.

with inserting a catheter. EXPAREL® (bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc., San Diego, California) is an extended-release local anesthetic that can be infiltrated directly into the surgical site by the orthopedic surgeon. This medication, which can provide continuous and effective analgesia at the site of surgical injury for up to 72 hours,[3] has been shown to provide the long-acting pain control that foot and ankle patients typically need without the impaired mobilization of an indwelling catheter.[4] The 2 following cases illustrate the use of EXPAREL® in foot and ankle surgery and show the effects that this new agent can have on anesthesia and on the patient experience.

## Case 1: Ankle Replacement

### Patient Presentation and History

This first case involved ankle replacement in a 58-year-old man who was very active. He had a 20-plus-year history of arthritis but was otherwise healthy and a nonsmoker. X-ray imaging revealed extensive arthritic changes to the ankle with some posterior subluxation to the talus (**Figure 1**). The rest of his foot appeared to be healthy overall. Because the patient did not want to stay overnight in the hospital, the decision was made to perform the procedure on an outpatient basis. The patient was presented with the option of a sciatic nerve block with an indwelling catheter or injection of EXPAREL® into the deep soft tissue of the capsule and periankle area, where there are a number of small peripheral nerves.

### Analgesia Technique

One vial (20 mL) of EXPAREL® was mixed with 20 mL of 0.25% bupivacaine, without epinephrine in this particular situation because of the proximity of the surgical location to certain blood vessels of the foot and ankle that were close to the anterior-posterior bundles.

Of the total 40-mL volume, 10 mL was injected into the anterior and posterior capsule; the remaining 30 mL was injected into the peri-ankle area—adjacent to the 5 peripheral nerves of the ankle. This approach would technically not be classified as a nerve block because the nerves at this level are smaller and ultrasound guidance is not necessary.

### Postoperative Course

**Figure 2** shows anteroposterior and lateral views of a total ankle replacement. This particular ankle replacement (Zimmer Trabecular Metal Total Ankle; Zimmer, Warsaw, Indiana) is done through a lateral exposure and fibular osteotomy. The patient reported very mild postoperative pain beginning at 12 hours (end of single-shot sciatic block), and he also noted a slight increase in pain at 72 hours that was likely due to the waning effects of EXPAREL® at that point. Nevertheless, the patient was totally satisfied with the level of pain relief following surgery.

## Case 2: Talar Neck Fracture-Dislocation

### Patient Presentation and History

The second case was a young woman being treated as part of Operation Walk 2014 in Nicaragua (an orthopedic mission effort to provide hip/knee replacement and foot/ankle reconstruction in Central America). The patient had a partially treated talar neck fracture-dislocation with an open injury, dislocated subtalar joint, avascular talus, and considerable deformity (**Figure 3**). There was no active infection.

### Analgesia and Surgical Technique

The challenge of completing complex reconstruction without the use of multiple screw sizes and implants without fluoroscopy is rewarding (**Figure 4**). For the management of postoperative pain in this patient, a multimodal regimen that included EXPAREL® was also used. The EXPAREL® was infiltrated into areas of the deep soft tissue in a manner that was very similar to the approach described for Case 1.

### Postoperative Course

At 30 hours after surgery, the patient reported a pain level of 0 on a scale of 0 to 10 (**Figure 5**). Although this level of pain control is not observed in all patients, it is not uncommon.


Figure 3. Case 2: Radiographs showing open talar neck fracture-dislocation.

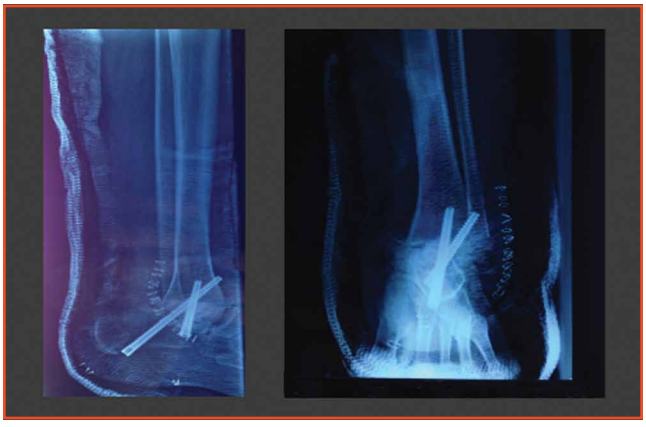

Figure 4. Case 2: Radiographs showing repair postoperatively.

Figure 5. Case 2: Patient 30 hours postoperatively with 0/10 pain score.

It is important to note that success with EXPAREL® is very technique-dependent, and following the prescribed protocol contributes to achieving consistent results.

## Future Directions

In early 2014, it was announced that a phase 3 clinical trial assessing the safety and efficacy of EXPAREL® in femoral nerve block for total knee arthroplasty had met its primary efficacy endpoint.[5] This pivotal trial evaluated 183 patients randomized to receive either EXPAREL® or placebo, with all patients offered rescue opioids as needed. The results demonstrated statistical significance in favor of EXPAREL® for cumulative pain scores over 72 hours. The preliminary safety analysis was comparable between both groups.

Based on these results, an application for a nerve block indication has been filed with the US Food and Drug Administration. This is exciting news from the standpoint of foot and ankle procedures, as patients who have extensive foot and ankle surgery are unable to walk immediately after surgery; therefore, whether or not their ankle moves after surgery is of less importance than, for example, whether a patient is able to walk soon after knee surgery. With complex foot and ankle surgery, the focus is instead on maintaining postoperative analgesic activity in the foot and ankle for as long as 72 hours. At some point in the future, it may be possible to achieve such a duration of sciatic nerve block without the need for an indwelling catheter.

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*Am J Orthop*. 2014;43(10 suppl):S10-S12. 

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# Local Infiltration of Liposome Bupivacaine in Orthopedic Trauma Patients: Case-Based Reviews

Hank L. Hutchinson, MD


## Abstract

Orthopedic trauma surgery is often associated with considerable postoperative pain, which can result in a cascade of direct and indirect clinical consequences. Patients undergoing orthopedic trauma surgery are at risk for the development of chronic postsurgical pain, which may persist for 2 years or longer. Effective approaches to reducing postoperative pain in orthopedic trauma surgery patients include the use of minimally invasive procedures and multimodal analgesia.

Infiltration of the surgical site with EXPAREL® (bupivacaine liposome injectable suspension), an extended-release local anesthetic, represents an advance in the multimodal management of postoperative pain. As part of a multimodal regimen, EXPAREL® has been shown to provide effective, safe, and efficient analgesia across a range of surgical procedures.

Two cases that illustrate the use of EXPAREL® in orthopedic trauma are described. The first case involves repair of a subtrochanteric nonunion in a 63-year-old woman with a history of bisphosphonate use and prior treatment with a cephalomedullary nail. The second case involves a young woman undergoing outpatient surgery for repair of a fractured clavicle. Both patients experienced good control of postsurgical pain, supporting the clinical utility of EXPAREL® in orthopedic trauma surgery.


Although orthopedic trauma surgery is associated with considerable postoperative pain, data are lacking regarding the effects and management of postoperative pain in patients undergoing procedures for repair of orthopedic trauma injuries. It is now well established that a cascade of direct and indirect clinical consequences can occur secondary to inadequate control of postoperative pain, including delayed and less robust participation with physical therapy, increased anxiety, delays in recovery of normal function and lifestyle, poor sleep, gastrointestinal and urinary dysfunction, reduced quality of life, increased cost of care, increased risk of pulmonary morbidity (including pneumonia) and thrombosis, cardiac and hemodynamic compromise, and increased mortality.[1-5] Moreover, patients undergoing orthopedic trauma surgery have an especially high risk for the development of chronic postsurgical pain,[6] which may persist for 2 years or longer.

Effective approaches to reducing postoperative pain in orthopedic trauma surgery patients include the use of minimally invasive procedures[7] and multimodal analgesia.[8] Infiltration of the surgical site with a long-acting local anesthetic represents an exciting advance in the multimodal management of postoperative pain that offers effective, safe, and efficient analgesia across a range of surgical procedures.[1]

EXPAREL® (bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc., San Diego, California) is an extended-release local anesthetic that has been shown to provide continuous and effective analgesia at the site of surgical injury for up to 72 hours.[9] EXPAREL® can be infiltrated by the surgeon to block nociceptive pain at the site of surgery, while the anesthesiologist employs other anesthetics and complimentary analgesic modalities (such as peripheral nerve and/or neuraxial blockade) to achieve complete management of perioperative pain.[1]

In various soft-tissue and orthopedic procedures, EXPAREL® has been shown to significantly reduce the need for opioid use.[10] In the general inpatient surgery population, where much of the current clinical data on outcomes can be found, this medication has also been shown to reduce costs and length of hospital stay.[11,12]

The following 2 cases illustrate the use of EXPAREL® in

**Author's Disclosure Statement:** The author reports that he is a consultant and/or speaker for Pacira Pharmaceuticals, Inc., and Smith & Nephew PLC.

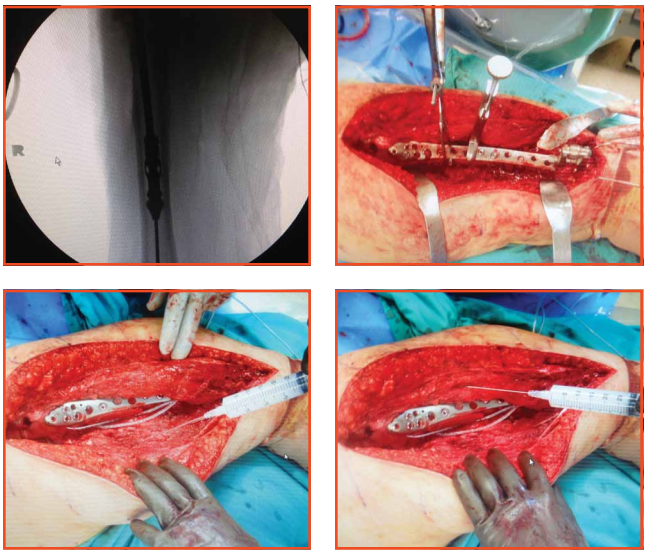

Figure 1. Case 1: Images showing lateral approach for the procedure. Buttocks are to the left, and knee is to the right; also visible is a proximal femoral locking plate with the articulating tensioning device down at the distal end by the knee, which was used for compression after the knee was reduced.

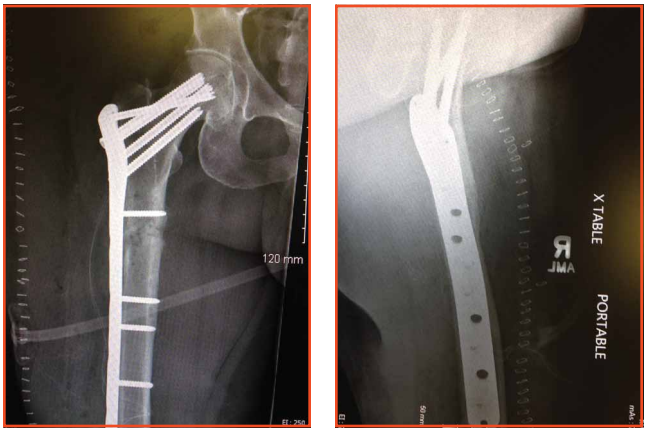


Figure 2. Case 1: Postoperative radiographs showing subtrochanteric fracture repair.

the setting of orthopedic trauma surgery and highlight the impact that this new agent can have on perioperative and postoperative pain.

## Case 1: Open Repair of Subtrochanteric Nonunion

### Patient Presentation and History

This case involves a 63-year-old obese woman with a history of bisphosphonate use and prior subtrochanteric fracture. The fracture had been treated 3 years previously with a cephalomedullary nail; however, the patient continued to have pain with weight-bearing and was referred to our institution for evaluation. A metabolic workup was obtained to rule

Figure 3. Case 1: At 30 hours postoperatively, the patient is able to elevate her leg.

out the presence of calcium and vitamin D disorders, as well as other potential metabolic disorders. Ultimately, the patient was diagnosed with a varus subtrochanteric nonunion, and surgery was scheduled once the vitamin D level had been optimized.

### Treatment Approach

The nail and locking screws were removed percutaneously and the Synthes Reamer/Irrigator/Aspirator system (Synthes, West Chester, Pennsylvania) was then used to obtain autograft from the intramedullary canal. An extensile lateral approach to the proximal femur was performed, and saucerization and mobilization of the nonunion site were performed. The varus deformity was corrected and proximal fixation was achieved with a proximal femoral locking plate. The plate was then clamped distally, and an articulating tensioning device was used to compress the fracture nonunion site. The autograft was then packed around the nonunion and covered circumferentially with a large collagen sponge impregnated with bone morphogenetic protein 2 (BMP-2).

### Analgesia Technique

No preoperative or postoperative nerve or neuraxial blocks were performed. Prior to closure, 20 mL of EXPAREL® was diluted to 100 mL total volume with preservative-free normal saline owing to the large size of the wound and to achieve even distribution. A 22-gauge spinal needle was used to inject the drug. In our experience, an 18-gauge needle is too large and the drug can be seen actually coming back out of the needle hole instead of remaining in the tissue where it was intended to stay. The quadriceps musculature was injected systematically with the drug, in order to try to evenly distribute 75% of the anesthetic all along the subfascial tissue anteriorly (**Figure 1**). The remaining drug was injected posteriorly and evenly distributed. Fifty mL of 0.25% bupivacaine with epinephrine was then diluted to 100 mL total volume with normal saline and injected in the same pattern. Our technique is typically not to inject into the subcutaneous layer. A high incidence of incisional pain has not been seen with this approach.

### Postoperative Course

**Figure 2** shows the postoperative radiographs for this patient. Patients who have undergone similar procedures of-

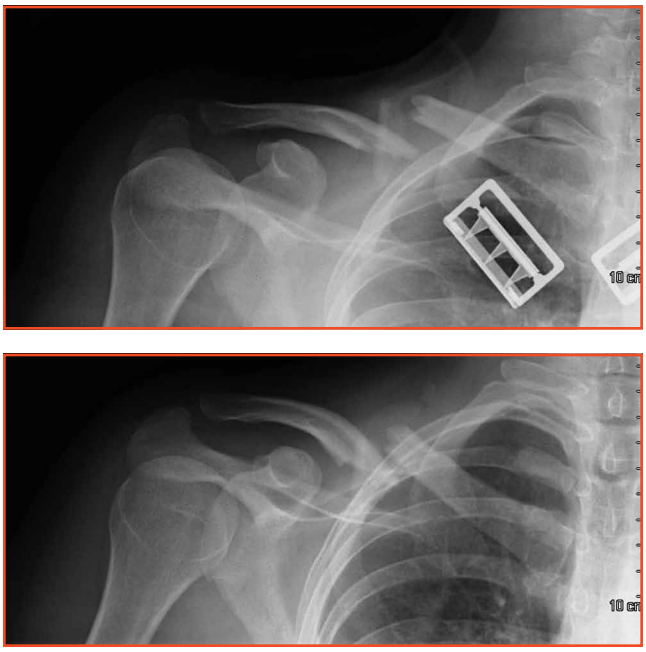

Figure 4. Case 2: Radiographs showing fracture of right clavicle.

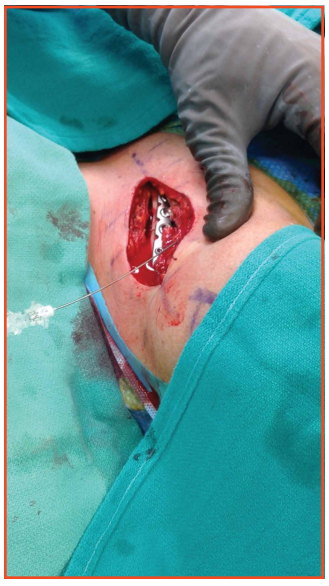

Figure 5. Case 2: Infiltration technique for liposomal bupivacaine. Head is to the bottom and body is to the top in this image.

ten require significant oral and intravenous (IV) opioids on day 1 for pain control and have difficulty participating with physical therapy and mobilizing. At 30 hours postoperatively, however, this patient was awake, alert, and able to perform an unassisted straight leg raise and actively flex her knee to 45° (**Figure 3**). This postoperative course is typical of similar cases that have been performed, in which patients who receive local infiltration with EXPAREL® not only preserve motor function but also are relatively pain-free and active—sitting up soon after surgery; interacting with their families; reading, eating, etc; and not requiring patient-controlled analgesia use for IV opioids.

### Follow-up

There were no perioperative complications, and, at 12 weeks, the patient was walking without assistive devices. By 16 weeks, radiographic healing was complete.

Such outcomes provide a strong case for use of EXPAREL® in controlling postsurgical pain in the setting of nonunion, deformity, and trauma surgery.

## Case 2: Clavicle Fracture

### Patient Presentation and History

This second case was a 32-year-old right-hand–dominant woman, mother of 3 children, who tripped and fell while out of town. She presented with a closed, comminuted, midshaft clavicle fracture with 200% displacement (**Figure 4**).

### Analgesia and Surgical Technique

No preoperative or postoperative nerve or neuraxial blocks were performed. A superior approach was used, and a standard lag screw and anterior/inferior plating technique were used for reduction and fixation. To provide adequate coverage of a wound of this size, 20 mL EXPAREL® was diluted to a total volume of 60 mL with preservative-free normal saline and carefully injected into the platysma, pectoralis, trapezius, and deltoid musculature to a depth of 2 to 3 cm, using a 22-gauge spinal needle (**Figure 5**). The injection procedure was repeated with 30 mL of 0.25% bupivacaine with epinephrine. Keeping in mind the location of the neurovascular structures just deep to the inferior clavicular periosteum and the close proximity of the lung, care must be taken to avoid these areas. The needle was directed parallel to the skin to avoid these structures and the area directly inferior to the clavicle was not injected. The wound was then closed in a standard fashion.

### Postoperative Course

The patient was discharged home the day of surgery and reported very little pain for about 3 days. She reported that after 2 to 3 days she began to have some soreness that was manageable for the first week with nonsteroidal anti-inflammatory drugs and occasional doses of oral opioid. After this period, she no longer required any opioids.

### Follow-up

There were no perioperative complications, and the fracture healed in 6 weeks. At 12 weeks, the patient had regained full strength and range of motion of the shoulder.

This surgical technique, using EXPAREL®, has been employed in approximately 20 patients with operative treatment of clavicle fractures with equal success and no complications.

## Practical Considerations in the Use of Liposome Bupivacaine

When using EXPAREL®, infiltration technique is important. For example, when repairing tibial plateau fractures through an anterolateral approach, our technique is to dilute 20 mL of EXPAREL® with saline to 60 mL total volume and inject systematically throughout the entire wound, staying out of the joint. EXPAREL® should be injected into the anterior compartment musculature just adjacent to the incision, and not posterior to the tibia or deep to the fibula. All of the pericap-

sular tissue at and above the knee joint should be injected, taking care not to inject into the knee joint itself. EXPAREL® should remain extracapsular just as plain bupivacaine should. Although patients with tibial plateau fractures typically experience a great deal of postoperative pain, it is possible to eliminate patient-controlled analgesia in almost all of the patients, particularly those with Schatzker type II fractures and even in some with type V and VI fractures.

For various types of trauma procedures, including subtrochanteric fractures, clavicle fractures, tibial plateau fractures, and others, our protocol is to dilute 20 mL of EXPAREL® with preservative-free normal saline to 40 to 100 mL total volume, depending on the size of the wound. Injection is performed using a 22-gauge needle. In addition, 30 to 50 mL of 0.25% bupivacaine with epinephrine is infiltrated into the same pathways as the EXPAREL®.

## Summary

Another major area where use of EXPAREL® can have a substantial impact is hip fractures. At our institution, we are currently following a protocol in which EXPAREL® and 0.25% bupivacaine are infiltrated into the pericapsular area for femoral neck fractures after hemiarthroplasty. The result has been a dramatic impact on postoperative days 0 to 3: Instead of suffering the effects of heavy opioid infusions postoperatively, patients are much more active, typically sitting up in bed, reading, talking to their families, and starting rehabilitation sooner.

Based on our experience, EXPAREL® has clinical utility not only in the outpatient setting, but also in the inpatient setting. Its impact on outcomes in the trauma setting, such as shorter hospital stay, reduction in opioid-related adverse events, reduction in both inpatient and outpatient opioid usage, and lower total cost of treatment will be important areas for future investigation.

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*Am J Orthop*. 2014;43(10 suppl):S13-S16. 

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