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Advanced Pain Management Techniques

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Improving Patient Outcomes through Advanced Pain Management Techniques in Total Hip and Knee Arthroplasty

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Abstract

Pain following orthopedic surgery is common and often suboptimally managed, with many patients reporting acute moderate to severe pain following surgery. Opioids are often used to manage this pain, yet this can result in significant side effects and complications, including constipation, nausea, vomiting, respiratory distress, and other central nervous system issues. Multimodal therapy that includes surgical site infiltration with extended release local anesthetic has been seen as a new way to minimize this pain for patients, which can result in improved quality of life and shorter length of hospital stay. This article examines the use of bupivacaine liposome injectable suspension (EXPAREL®; Pacira Pharmaceuticals, Inc., San Diego, California), a non-opioid product for pain management. Liposomal bupivacaine uses DepoFoam® technology that allows for the extended release of injected drugs. When used as the foundation of a multimodal regimen, it is effective in reducing postsurgical pain for up to 72 hours while reducing the need for opioids for pain relief.

Introduction

Pain is a complex phenomenon that is perceived by the patient based on his or her biological, psychological, and social factors (see ***Causes of Postsurgical Pain*** on next page).[1] Now considered the fifth vital sign, pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1,18,19] Nearly 80% of patients undergoing surgery report moderate to extreme pain in the first 2 weeks following surgery.[2-4]

More than 1 million hip and knee arthroplasty procedures are performed in the United States annually.[20] Orthopedic surgeons are well aware of the postoperative pain their patients experience as a result of these procedures and the impact this pain can have on recovery. Optimal pain control results in earlier mobilization, ambulation, and return of normal gait and promotes optimal range of motion, which can be reduced when joints are splinted as a result of pain.[21] Suboptimally treated pain from hip and knee arthroplasty can become chronic and impede functional recovery.[22]

Patients may anticipate pain as result of surgery and as a result, many patients frequently delay needed surgery.[22] Moreover, postoperative pain is now viewed as a major health care issue.[23]

The purpose of this article is to describe a novel approach to pain management using infiltration therapy with the long-acting local anesthetic, liposome bupivacaine (EXPAREL®; Pacira Pharmaceuticals, Inc., San Diego, California), as part of a multimodal pain management program.

Defining the Unmet Need

Despite evolving strategies in regional anesthesia and multimodal therapies, postoperative pain continues to be a complication of orthopaedic surgery, with more than half of postoperative hip or knee arthroplasty patients experiencing acute, unacceptable levels of pain.[21] Acute, severe pain has become a predictor of chronic pain and disability; up to 20% of patients have moderate to severe pain 1 year following knee arthroplasty, which may be related to the failure of acute pain management.[24,25] Inadequate pain control also results in increased cardiovascular and pulmonary pathophysiology, which can lead to shortened or missed rehabilitation sessions, decreased quality of life, increased cost of care, and prolonged pain.[26-29]

Guidelines are available for the management of acute pain; however, they do not provide a procedure-specific approach to pain management.[17,30] The guidelines rely heavily on the use of intravenous and oral opioids, which can lead to opioid-related adverse effects, as well as the real risks of opioid abuse, addiction, and diversion (**Table 1**).[31-35] Additionally, the guidelines are not proactive, as the patient usually must experience pain before therapy is initiated.

Table 1. Adverse Events Associated with Opioids[31-35]

Common
Constipation
Vomiting
Sedation/drowsiness
Nausea
Less Common
Dysphoria/delirium
Myoclonus/seizures
Respiratory depression
Nightmares/hallucinations
Pruritus/urticaria
Urinary retention

Continued on page S5

Causes of Postsurgical Pain

More than 90 million surgical procedures are performed every year in the United States (almost 35 million ambulatory procedures and 56 million inpatient procedures) and according to several national surveys, approximately 80% of patients undergoing surgery report pain that is moderate, severe, or extreme in intensity during the first 2 weeks postprocedure.[2-4]

The incidence and severity of acute postsurgical pain is primarily determined by the type and duration of the surgery and the type of pain control given postsurgically.[5-8] Estimates indicate that more than 98% of US patients undergoing surgery receive opioids for postsurgical pain management.[9]

Postsurgical pain may be of 3 types:

- Somatic – arising from injury to skin, muscle or bone
- Visceral – arising from injury to or manipulation of organs within the chest or abdomen
- Neuropathic – arising from damage or dysfunction within the nervous system[10]

The type of pain that predominates depends on the type of surgery the patient has undergone; many patients experience more than 1 type of pain after surgery.[10] Pain results not only from the initial assault (surgery), but from ongoing stimuli during the recovery phase, when inflammatory and pain mediators sensitize the nociceptors of the normally silent primary afferent neurons.[10,11] Sensitization in the periphery and central nervous system (with increased activity of spinal dorsal horn neurons) can heighten a patient's pain sensitivity, causing hyperalgesia.[10,11]

No single analgesic is able to target all types of pain—for example, local anesthetics target somatic pain by local infiltration—which contributes to the challenge of effective postsurgical pain control and provides a rationale for a multimodal approach to pain management.

Pain is most intense during the first or second day postprocedure.[12-15] For example, approximately 25% to 40% of day surgery patients report moderate (Visual Analog Scale [VAS] score 4-6) to severe (VAS score 7-10) pain within the first 24 hours following a procedure.[12,13,15] For inpatients undergoing more extensive surgery, the acute phase of pain management may last for approximately 2 weeks, with 80% to 90% of patients experiencing moderate to extreme pain during this timeframe.[3,4]

After discharge, pain can continue to interfere with daily activities, such as sleep and work, for several days.[12,16] Unrelieved acute pain not only causes unnecessary patient suffering, but it can also lead to other health problems, thus delaying recovery from surgery and resulting in higher health care costs.[17]

Controlling acute postsurgical pain is also important because the intensity of acute pain is a predictor of ongoing chronic pain postsurgery.[5,7]

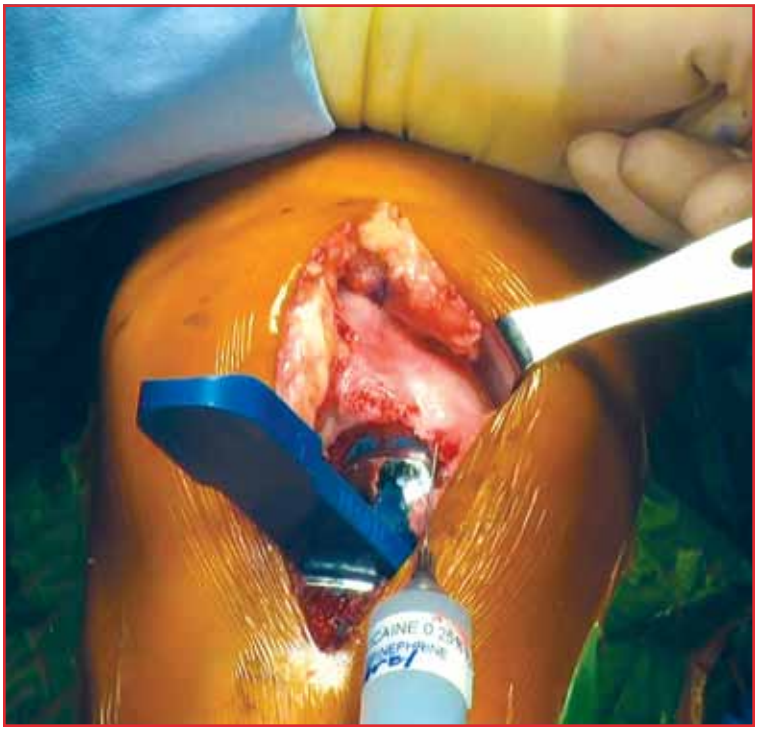

Figure 1. Soft tissue injection technique for liposomal bupivacaine

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In addition, the guidelines do not address supplemental analgesia to cover potential analgesic gaps, such as when the patient is transferred between services (eg, post-anesthesia care unit to the surgical unit), when the type of analgesia is switched (eg, regional anesthesia to patient-controlled analgesia [PCA] pump or PCA pump to oral analgesia), and when the patient is receiving physical therapy.[27,37]

Regional anesthesia—epidural, spinal, or peripheral nerve blocks—have been promoted to reduce the adverse effects of general anesthesia (particularly nausea and vomiting). Data, however, suggest that regional analgesia has significant drawbacks for orthopedic surgery patients, including postoperative hypotension and motor weakness.[27]

A multimodal approach to analgesia is

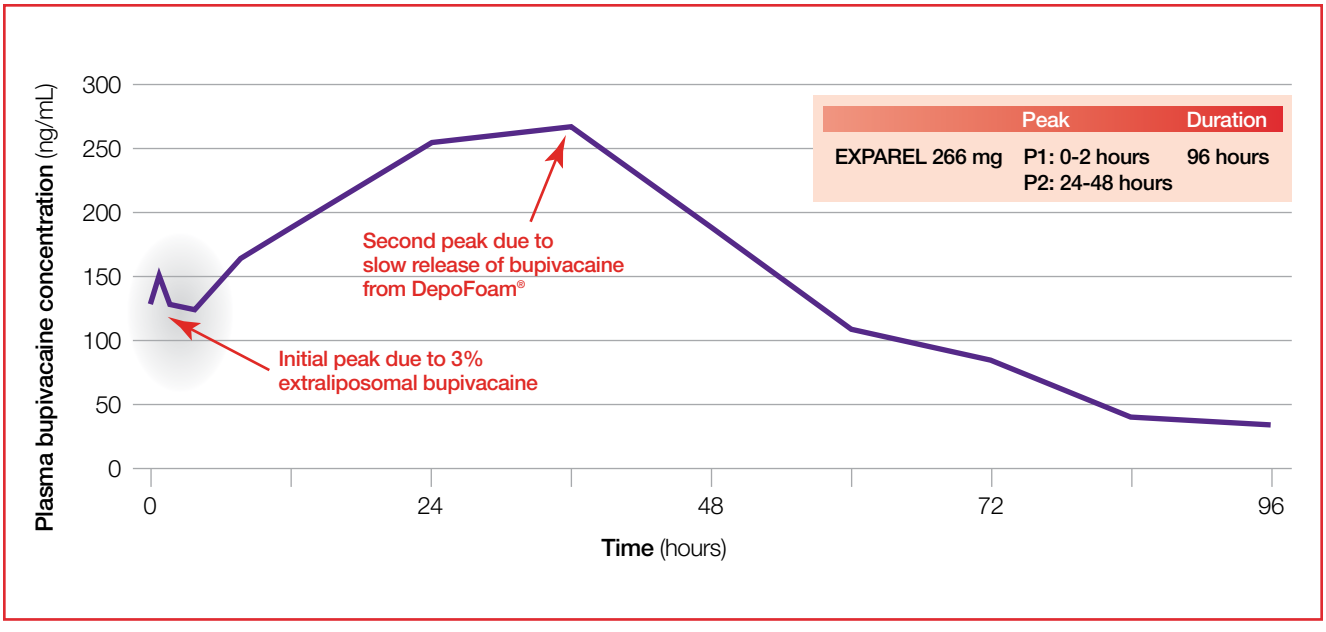

Figure 2. Absorption profile of liposomal bupivacaine following local infiltration in patients undergoing total knee arthroplasty[44]

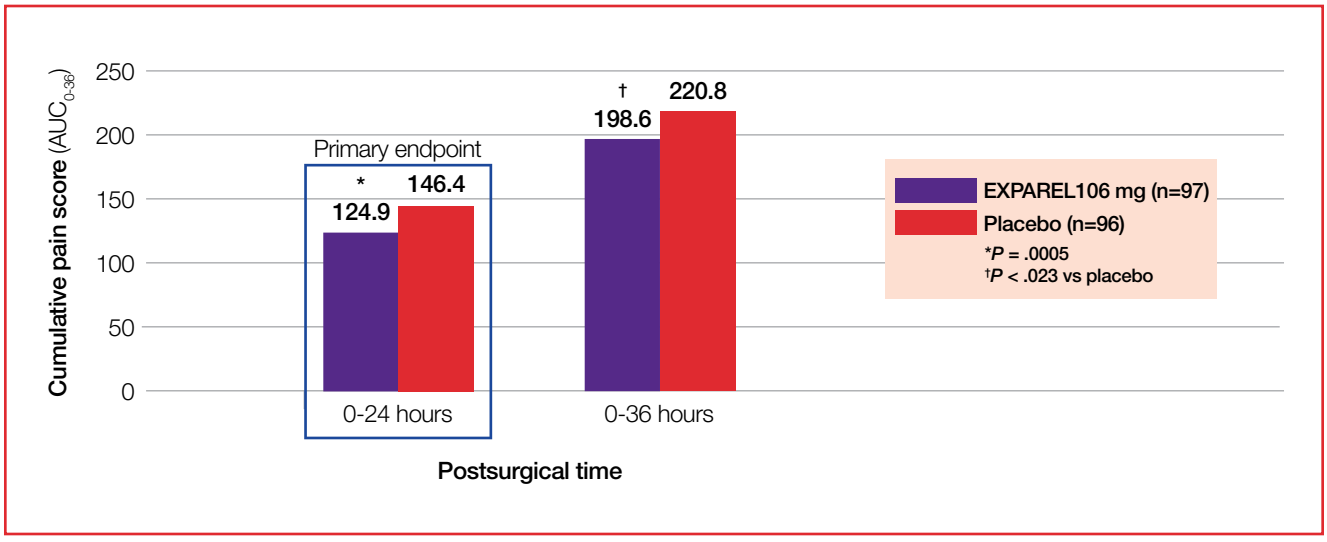

Figure 3. Cumulative pain intensity scores from infiltration through 24 and 36 hours in pivotal phase III bunionectomy clinical trial[46]

gaining favor. However, there is no single protocol and the variations in analgesics used, doses, and techniques mean that results can be inconsistent.[27]

The authors have experience with numerous approaches to pain management in their hip and knee arthroplasty patients.

Dr Dalury is a proponent of using pericapsular injection of a drug "cocktail" as part of a multimodal pain management approach.[38] A study he and his colleagues recently published in *The Journal of Arthroplasty* showed lower pain scores, less opioid use, and improved functional outcomes (active extension, active flexion, walking distance) among patients who received an injected cocktail consisting of ropivacaine, ketorolac, epinephrine, and clonidine compared with patients who received different drug cocktails.[39] In all cases, the drug cocktail was injected subcutaneously into the capsule, the periosteum, and the posterior capsule.

Dr Dalury developed this approach after trying many others, including general anesthesia plus a PCA pump, spinal analgesia plus a PCA pump, intrathecal morphine, peripheral blocks, epidurals, and peripherally indwelling catheters. All were methods that did not effectively manage his patients' pain throughout the postoperative period.

Advances in Multimodal Pain Management

The multimodal pain management approach adopted by Dr Dalury and the other authors is the current trend in postoperative pain management. This approach combines analgesic agents with differing modes of action so that they work synergistically to manage pain. The type and number of analgesics used should be procedure- and patient-specific, with an emphasis on promoting early ambulation and physical therapy.

The goals of multimodal pain management are to:

- Reduce postoperative pain
- Avoid therapy-related complications
- Improve outcomes
- Accelerate postoperative care
- Reduce hospital length of stay
- Improve patient satisfaction[40]

As part of a multimodal pain management approach, the authors advocate infiltrating local anesthetics into the skin,

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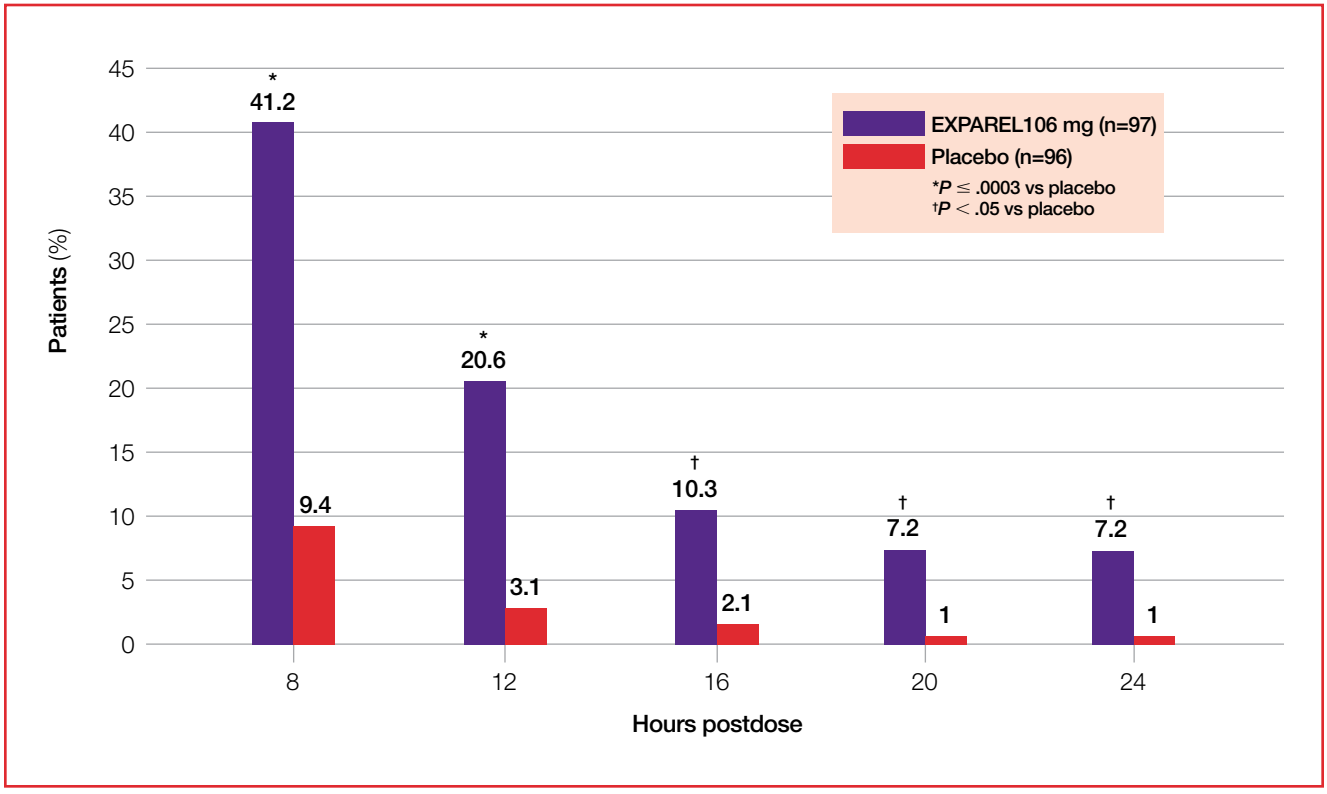

Figure 4. Proportion of patients receiving no opioid rescue medication in pivotal phase III bunionectomy clinical trial[46]

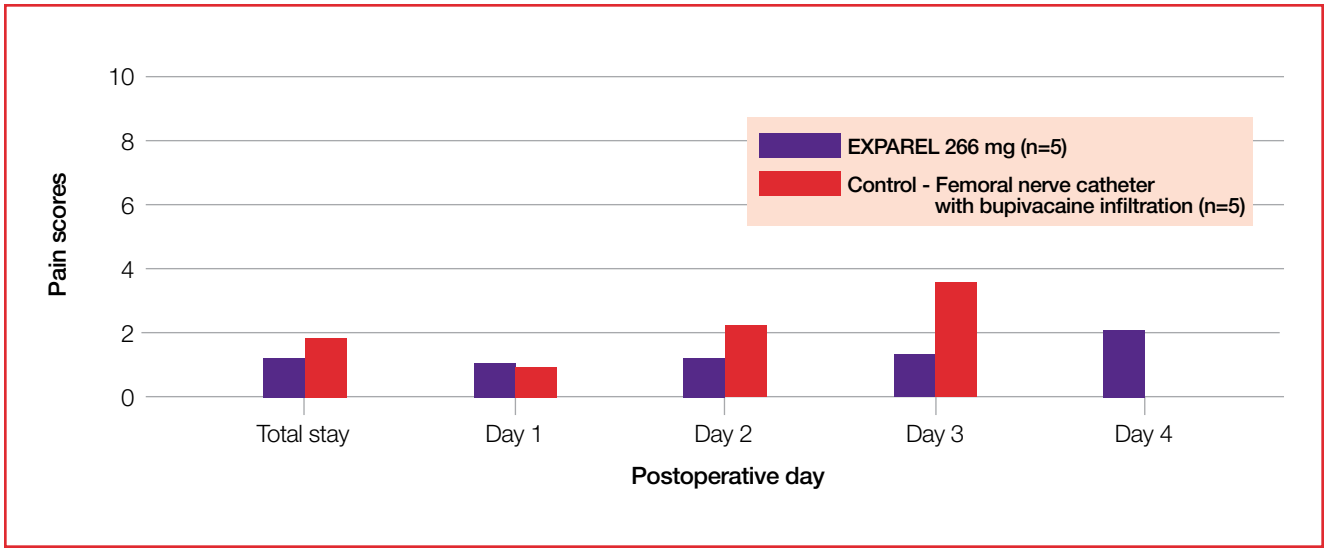

Figure 5. Average pain scores in patients undergoing unicondylar knee arthroplasty with and without liposomal bupivacaine

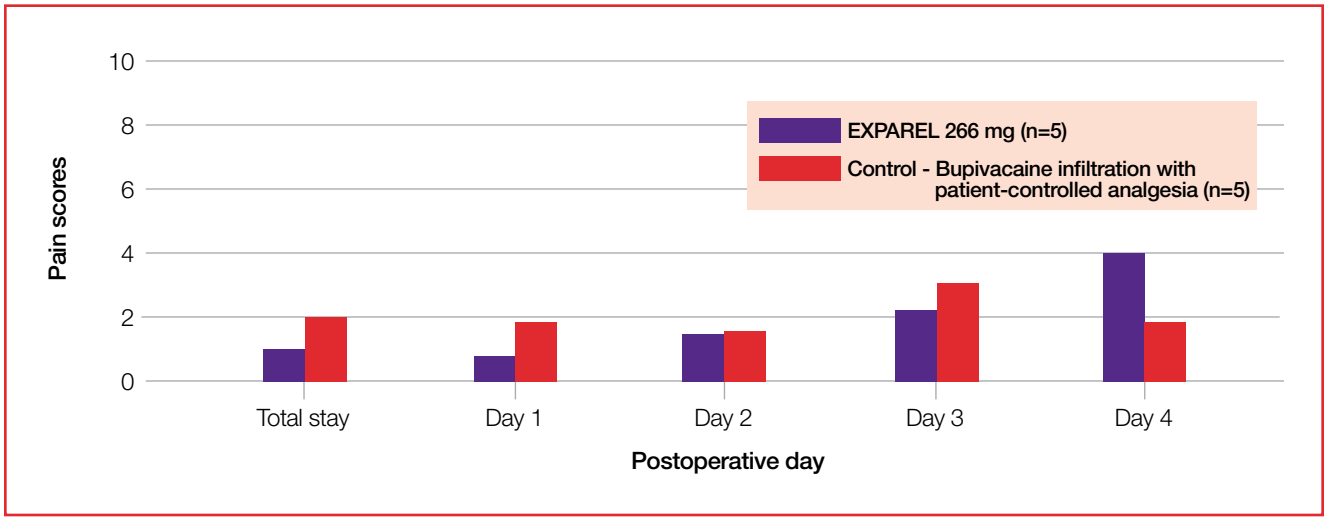

Figure 6. Average pain scores in patients undergoing total hip arthroplasty with and without liposomal bupivacaine

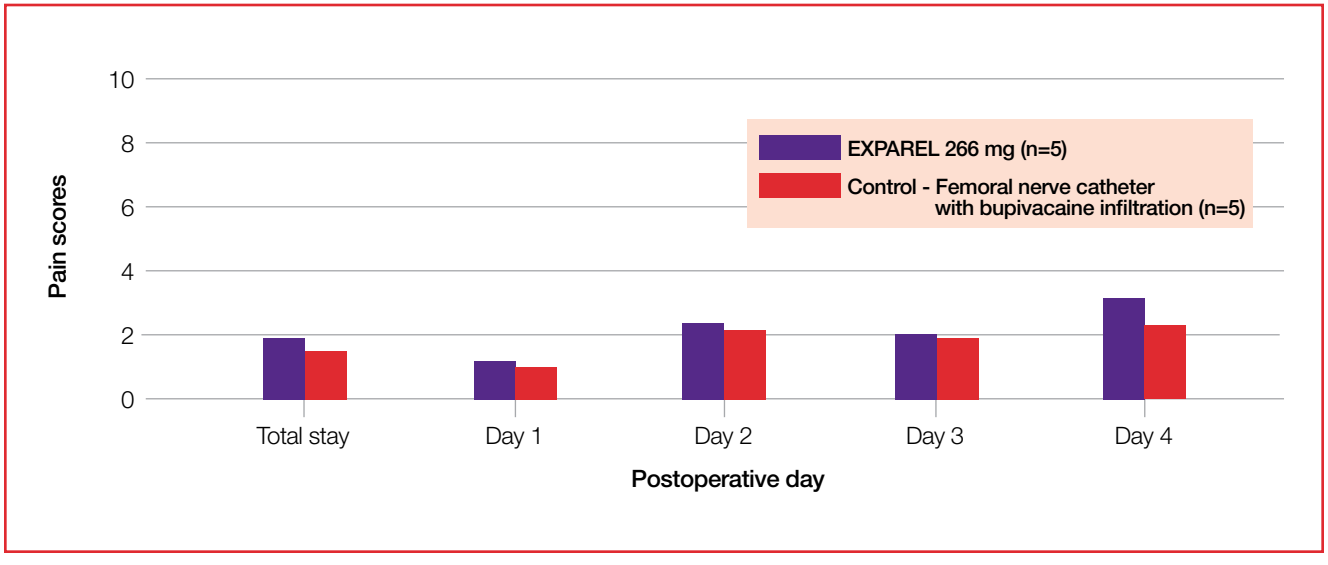

Figure 7. Average pain scores in patients undergoing total knee arthroplasty with and without liposomal bupivacaine

Continued from page S6

subcutaneous tissue, and deeper soft tissue prior to surgical wound closure. The benefits of local wound infiltration have been documented, and this technique is considered to be safe, with few side effects and a low risk of toxicity.

One issue, however, is which local anesthetics to use. For most short-acting anesthetics such as bupivacaine HCl, the duration of action is 7 hours or less.[41] This can be problematic, as that time frame does not adequately

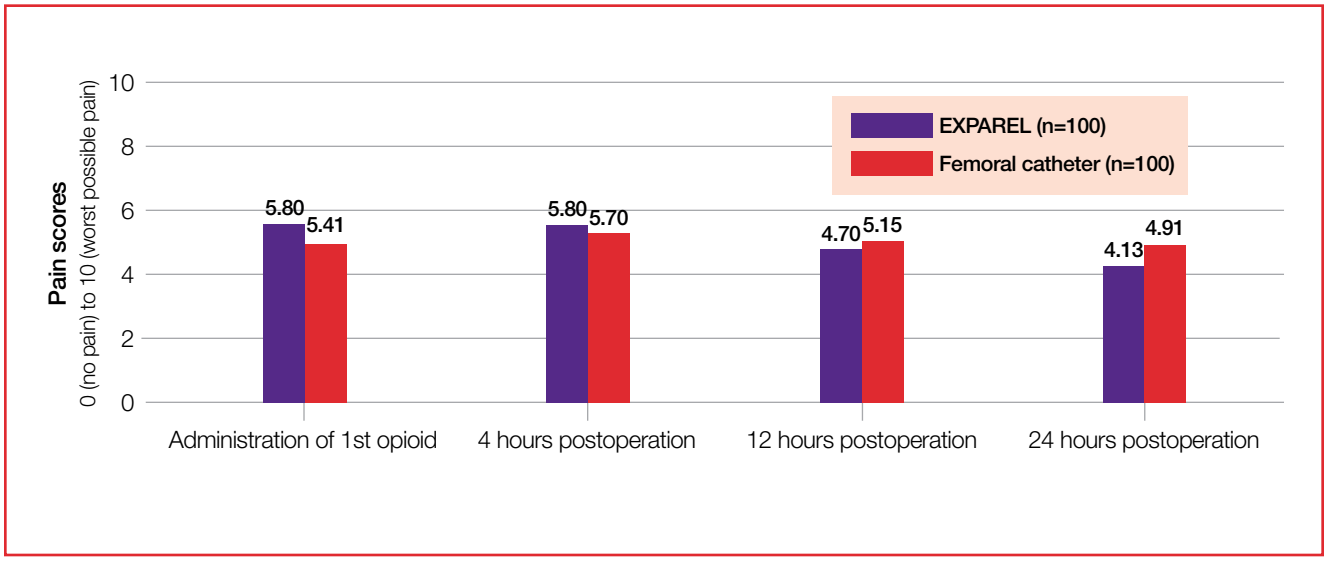

Figure 8. Resting pain scores, 0 to 24 hours, liposomal bupivacaine vs femoral nerve catheter with ropivacaine infiltration

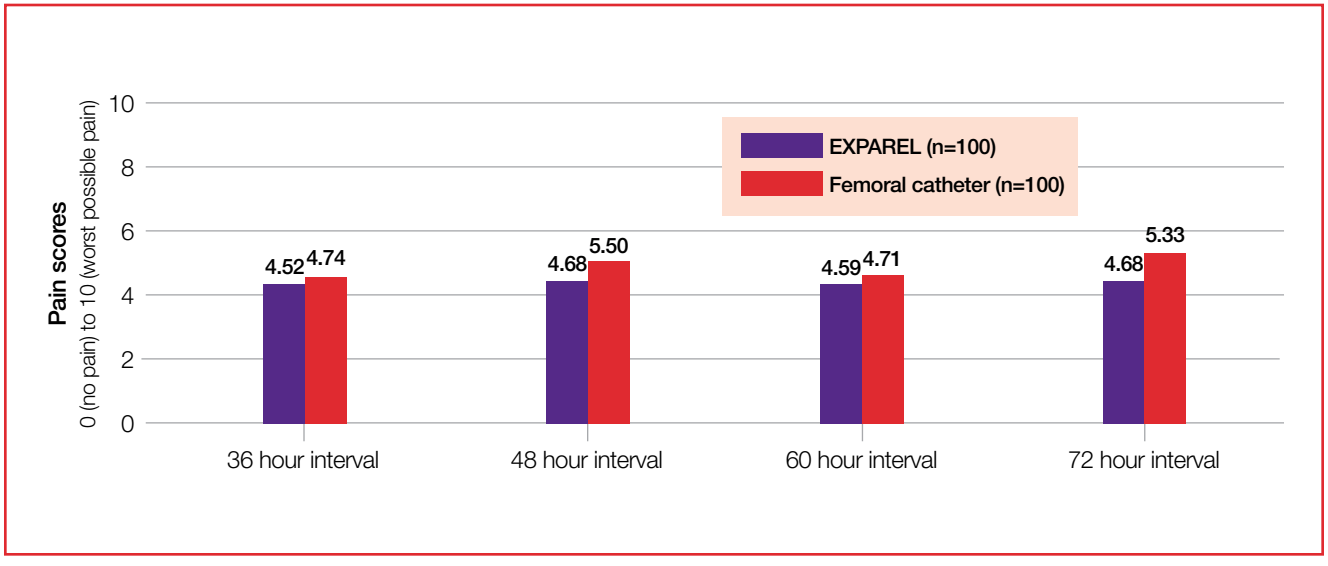

Figure 9. Resting pain scores, 36 to 72 hours, liposomal bupivacaine vs femoral nerve catheter with ropivacaine infiltration

cover the patient's pain management needs throughout the postoperative period.

Liposomal bupivacaine (EXPAREL®; Pacira Pharmaceuticals, Inc., San Diego, California), a local analgesic using the delivery platform DepoFoam®, has been shown to provide a longer duration of action, with up to 72 hours of pain relief.[42]

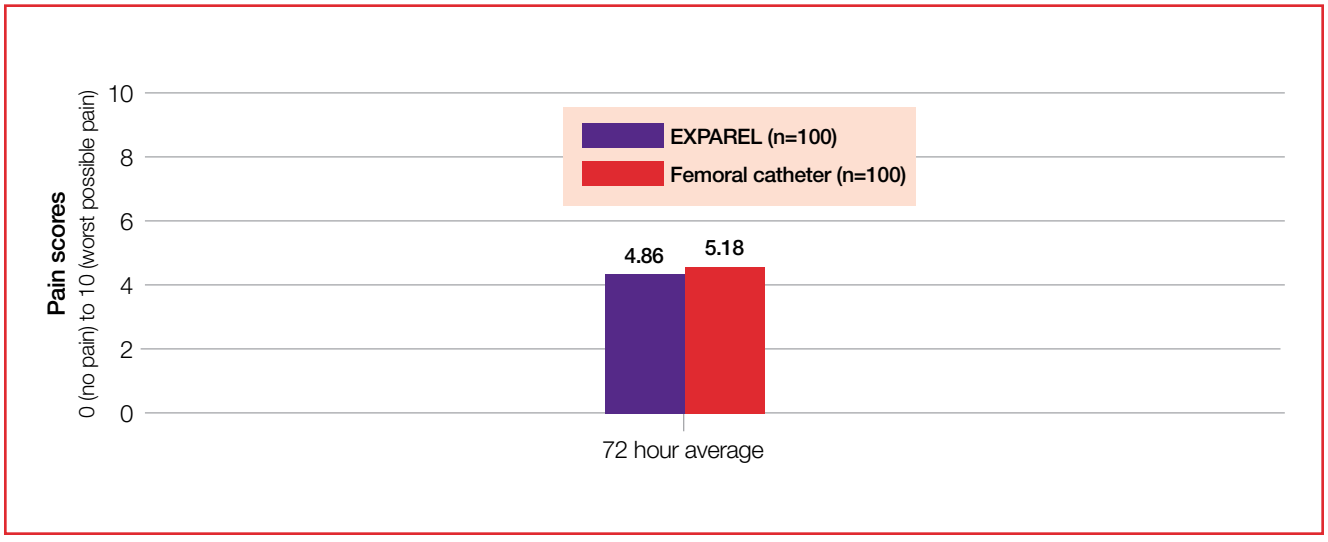

Figure 10. Average resting pain scores, liposomal bupivacaine vs femoral nerve catheter with ropivacaine infiltration

Injection Technique

Liposomal bupivacaine is typically mixed with normal saline, 20 mL of each, for a total of 40 mL. This admixture is injected into the surgical site prior to wound closure, with the drug equally divided between each side of the surgical wound.[42] The surgical wound is slowly injected multiple times, using recommended smaller needles (22- or 25-gauge) and a moving-needle technique to evenly deposit the drug into the soft tissues. Frequent aspirations reduce the risk of accidental intravascular injection.[41-43]

Starting at the level below the fascia, the drug should be administered along 3 horizontal layers (**Figure 1**):

- Just below the fascia
- Just above the fascia
- In the upper portion of the subcutaneous tissue/skin

This technique ensures proximity of the drug to the small sensory nerve fibers that penetrate through these layers, from deep to superficial.

In the case of hip and knee arthroplasty, the admixture should be placed in all capsular layers as well as the periosteum. For the knee in particular, it is important to inject the posterior capsule, staying away from the midline and carefully aspirating before injection to avoid an intravascular injection. If the aspiration draws blood, the needle should be moved to a different location.

Research with Liposomal Bupivacaine

Liposomal bupivacaine is released from multivesicular liposomes over a period of time, resulting in markedly prolonged plasma levels and analgesia for up to 72 hours, allowing for reduced postoperative use of opioids (**Figure 2**).

This was demonstrated in 2 multicenter, randomized, double-blind studies of patients undergoing soft tissue (hemorrhoidectomy) and orthopedic (bunionectomy) surgical procedures. Liposomal bupivacaine was shown to be effective and safe, with extended pain relief and decreased opioid use (**Figures 3** and **4**).[45,46] Additional studies are underway to further demonstrate the safety and efficacy of liposomal bupivacaine for other procedures.

The safety of liposomal bupivacaine has also been evaluated in 8 active controlled Phase II and Phase III studies. In these studies, the drug was administered into

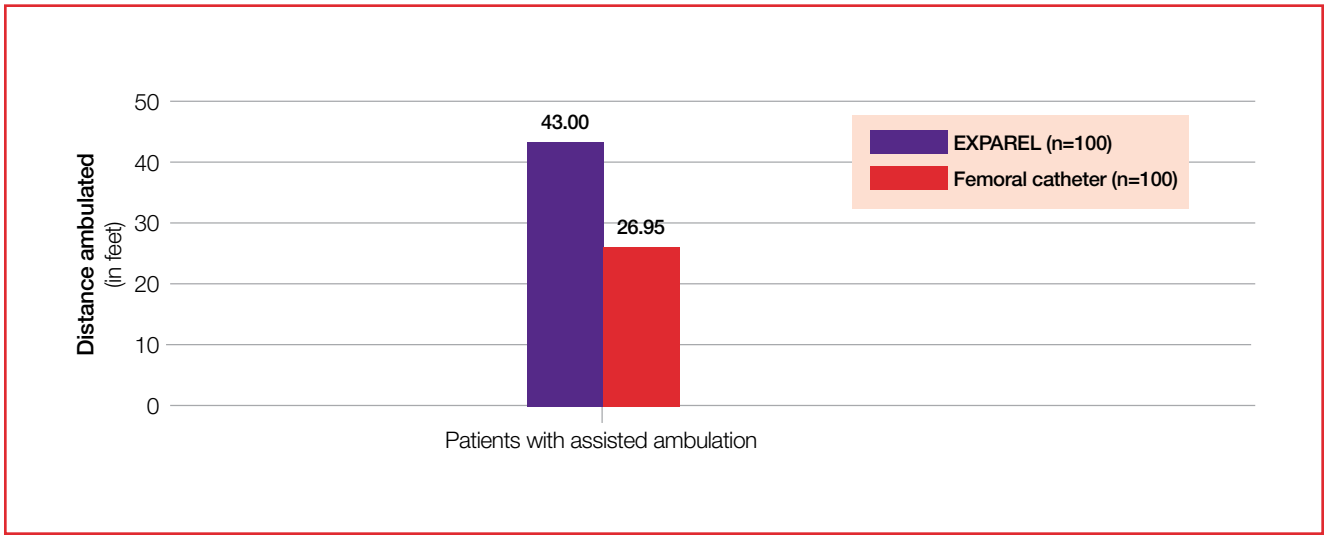

Figure 11. Assisted ambulation, day 0 postoperation, liposomal bupivacaine vs femoral nerve catheter with ropivacaine infiltration

the surgical wounds of patients undergoing hemorrhoidectomy, inguinal hernia repair, breast augmentation, and total knee arthroplasty.[47,48] These studies have shown that when liposomal bupivacaine is injected in all tissues from the open surgical site, the result is effective postoperative analgesia.[45]

A recently published analysis of pooled efficacy data from 10 randomized, double-blind liposomal bupivacaine clinical studies found that the drug was associated with lower pain scores, reduced opioid use, and greater patient/provider satisfaction with postoperative analgesia.[49] It was also well tolerated.

Surgeon Experience with Liposomal Bupivacaine

At a recent symposium on pain management in orthopaedic patients, 4 of the authors discussed our experiences with using liposomal bupivacaine with hip and knee arthroplasty patients.[50-53]

Dr Barrington noted that adding liposomal bupivacaine to a multimodal pain management approach is very beneficial in reducing nausea and vomiting from opioids, the primary cause of missed physical therapy.[50] Early mobilization may be the most important factor in preventing venous thromboembolism after orthopedic surgery.[54]

A pain management approach that does not rely on nerve blocks or opioids also reduces the risk of falls in the postoperative period, Dr Emerson reported. At his facility, the Texas Center for Joint Replacement in Plano, Texas, 14 orthopedic patients experienced an "unplanned descent to the floor" in the first 9 months of 2012.[51] In the fourth quarter of 2012, liposomal bupivacaine was added to the pain management protocol; femoral nerve blocks were eliminated and opioids were used for rescue only. Following implementation of the new protocol, only 1 patient fell in the fourth quarter of 2012 and no patients had fallen in the first quarter of 2013.[51]

Dr Emerson also conducted a pilot study with 30 patients on the orthopedics unit at his facility, in which epidurals were not used and all patients' surgical sites were infiltrated with liposomal bupivacaine as part of a multimodal pain management approach (**Figures 5-7**).

EXPAREL® COST	$273*
REDUCED COSTS	
Anesthesia professional fees	$1450
Anesthesia technician	$230
Full-time equivalent physical therapist	$180
Femoral nerve catheter drug administration	$148
TOTAL REDUCED COSTS	**$2008***
TOTAL SAVINGS	
Added costs using EXPAREL®	273
Reduced costs	($2008)
TOTAL SAVINGS	**($1735) per surgery***

* Estimates from 2012 total knee arthroplasties at Greenville Hospital System

Figure 12. Preliminary cost analysis, liposomal bupivacaine vs femoral nerve catheter

The unicondylar knee and total knee control groups had an indwelling femoral nerve catheter, pain pump, and periarticular bupivacaine infiltration. The data show that the liposomal bupivacaine group had equivalent pain relief. Of significance, all patients could do a straight leg raise in the recovery room because they had not had a nerve block, which impacts fall risk.[51]

At the Steadman Hawkins Clinic of the Carolinas, Greenville, South Carolina, Dr Hawkins' colleagues evaluated the use of liposomal bupivacaine in 100 patients versus the use of a 2-day femoral nerve catheter in 100 patients; all 200 patients were undergoing total knee arthroplasty.[52]

Dr Hawkins noted that a femoral nerve block with an indwelling catheter for 2 days with initial ropivacaine infiltration was the preferred method of analgesia for surgeons at the Steadman Hawkins Clinic due to the sustained delivery of the local anesthetic drug. However, femoral catheter use has several downsides, one of which is the loss of quadriceps function while the block is in place. Others include increased risk of patient falls, decreased participation in physical therapy, loss of sensation to the leg, and inability to move the leg.

In the study, resting pain scores were about equal in both groups, although trending favorably toward the liposomal bupivacaine group (**Figures 8-10**).[52] The real differences were seen in ambulation and time to discharge: patients in the liposomal bupivacaine group were out of bed sooner and with less assistance and they went home sooner than the patients in the continuous femoral nerve catheter group (**Figure 11**).[52]

Of note, patients in the liposomal bupivacaine group also received injections of short-acting 0.5% bupivacaine HCl with epinephrine (Marcaine; Hospira, Inc., Lake Forest, Illinois) in the same anatomic layers as the liposomal bupivacaine injection.[52] This allowed for rapid onset of pain control in addition to the long-acting effects of liposomal bupivacaine. The combination of these 2 medications provided excellent pain relief after surgery.

Dr Stulberg said that because total knee arthroplasty procedures are known to be painful, achieving 48 to 72 hours of pain control makes a significant difference in patients' early recovery and their perception of their surgical intervention.[53]

He admitted that he was initially skeptical of infiltration techniques with local anesthetics, but after hearing Dr Dalury speak on the topic, Dr Stulberg decided to try

liposomal bupivacaine with a patient who had severe osteoarthritis of the left knee and wanted a knee replacement procedure.

Postoperatively, the patient's pain never rose above a 3 in the 72-hour postoperative period, even after physical therapy. The patient returned to full activity within 3 months, with no pain, 130° range of motion, and no complaints about the procedure.[53]

Potential Economic Benefits of Liposomal Bupivacaine

The issues of economic efficiency and patient outcomes with liposomal bupivacaine cannot be overlooked, as hospitals continue to face pressure to contain costs and improve care. Pain management becomes an economic consideration when patient satisfaction is tied to hospital reimbursement. In addition, patient care involves a variety of expenses aside from drugs.[31] Strategies that help to reduce those expenses optimize the hospital's reimbursement level.

At the Steadman Hawkins Clinic of the Carolinas, Dr Hawkins and his colleagues reviewed expenses related to the use of liposomal bupivacaine versus femoral nerve catheter. In terms of personnel, an anesthesia technician was used to monitor the continuous femoral nerve catheter, but was not required when liposomal bupivacaine was administered instead. Postoperatively, a patient with a femoral nerve catheter required 2-person assistance, crutches, and a knee immobilizer to ambulate. A patient who received liposomal bupivacaine could ambulate without crutches or a knee immobilizer and needed minimal assistance from 1 person.[52]

Overall, Dr Hawkins estimated a savings of $1735 per total knee arthroplasty procedure for the Greenville (South Carolina) Hospital System, where the Steadman Hawkins Clinic surgeons practice (**Figure 12**).[52] Applying that savings to the 500 000 total knee arthroplasty surgeries performed annually in the United States could result in savings of nearly $1 billion a year, Dr Hawkins said.[20,52]

Conclusion

Studies have shown that postoperative pain in total knee and hip arthroplasty is poorly managed. Optimal management can lead to earlier mobilization, shortened hospital stay, reduced hospital costs, increased patient satisfaction, lower rates of 30-day readmission, and lower mortality rates. Pain regimens should take into account the medical, psychological, and physical condition of the patient; the age of the patient; the patient's level of fear and anxiety; his or her personal preferences; tolerance to opioid analgesics, and each patient's response to pain treatment.

A multimodal pain management approach that includes surgical site infiltration with a local anesthetic is becoming more accepted due to the effectiveness of the technique. The use of liposomal bupivacaine, as the local anesthetic of choice, allows the creation of a new protocol for postoperative pain, with less reliance on opioids and fewer side effects that can extend hospital stays, increase hospital costs, decrease patient satisfaction, and lead to higher readmission rates.

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Dr Barrington discloses that he is a consultant to Angiotech Pharmaceuticals, Inc., Biomet, Inc., Medtronic, Inc., and Pacira Pharmaceuticals, Inc.

Dr Dalury reports that he has nothing to disclose.

Dr Emerson discloses that he is a consultant to Biomet, Inc., Medtronic, Inc., and Pacira Pharmaceuticals, Inc.

Dr Hawkins discloses that he is founder and chairman of the Hawkins Foundation, which has received support from Arthrex, Inc.; ArthroCare Corporation; Arthrosurface; Breg, Inc.; DJO Surgical, a DJO Global, Inc. company; Ferring Pharmaceuticals, Inc., on behalf of Euflexxa; Greenville Hospital System; Neurotech, a division of Bio-

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Dr Joshi reports that he has nothing to disclose.

Dr Stulberg discloses that he is a consultant to Exactech, Inc.; Pacira Pharmaceuticals, Inc.; and Stryker Corporation. He receives royalties from Exactech, Inc. He is a member of the ICJR Faculty Panel.

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NOTES

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