By Holly Wall, MD, FACS, and Simeon Wall, MD, FACS

EXPAREL for Post-Op Pain Management

One practice's experience investigating liposomal bupivacaine long-lasting analgesic for postsurgical pain management.

For plastic surgeons who primarily perform elective aesthetic procedures, patient comfort after surgery is of vital importance to patient satisfaction, word-of-mouth referrals and long-term retention. After a successful surgical outcome, effectively managing pain and minimizing analgesic-related adverse events (AEs) not only impacts timely ambulation and recovery, but also shapes the patient's overall experience with the surgeon. In fact, a recent Cedars-Sinai study[1] found that postsurgical pain scores were highly correlated with reports of overall patient satisfaction during hospital stays, underscoring the need for surgeons to optimize treatment of post-op pain.

Ask a patient contemplating surgery to list common concerns and, more often than not, you will find anxiety regarding postsurgical discomfort at the top of the list. Despite this fact, many surgeons remain reluctant to proactively set expectations about the postsurgical recovery period during the preop consultation for fear of increasing patient anxiety or hesitancy to undergo the procedure. This can lead to an uninformed patient who may not be aware of the various analgesic treatment options that can help mitigate discomfort and opioid-related AEs during the recovery process.

The Evolving Pain Treatment Landscape

Until recently, the standard approach to postsurgical analgesia consisted of opioids (intravenous and oral), local anesthetics either infiltrated at the time of surgery or supplied via elastomeric pumps, and nonsteroidal anti-inflammatory drugs (NSAIDs) for breakthrough pain. Opioids, while effective analgesics, are associated with moderate to severe AEs, such as respiratory depression, nausea, constipation and urinary retention, which reduce quality of life, prolong the recovery period, require additional post-op care staff and increase the cost burden on the healthcare system.

Local anesthetics, while safer and more tolerable than opioids, have limitations associated with duration of action and delivery methods. Traditional local anesthetics infiltrated at the wound site only provide up to eight hours of analgesia, requiring supplemental or rescue opioids for the crucial few days after surgery. Delivery of local anesthetics via elastomeric pumps has been reportedly associated with safety issues ranging from inconsistent infusion-rate accuracy and clogging and/or leaking of the pump catheter to premature emptying of the medication reservoir and technical pump failure.

In 2011, the U.S. Food and Drug Administration (FDA) approved a liposomal bupivacaine for infiltration analgesia, known as EXPAREL (bupivacaine liposome injectable suspension). Unlike its predecessor standard bupivacaine—which had a six to eight hour duration of action—liposomal bupivacaine claimed analgesic effects lasting up to 72 hours after administration.

Wary of the "new is better" approach to medical treatment, we held off shifting our current pain management approach until we had seen some substantive clinical and practical evidence to

support the value and benefit of liposomal bupivacaine for patients. We were then invited, along with six of our esteemed peers from across the country, to participate in a Phase 4, multicenter, prospective, observational study to examine the impact of liposomal bupivacaine in patients undergoing breast and abdominal surgeries—procedures that are associated with significant postsurgical pain and consequent risk of opioid-related AEs.

Evaluating the Clinical Value of Liposomal Bupivacaine

The study, known as EXCLAIM (Assessing the Impact of **EX**PAREL On Patient Out**C**omes and Ease Of Use When Administered By Infi**L**tration In Subjects Undergoing Breast **A**ugmentat**I**on **M**ammoplasty, Breast Reduction and Abdominoplasty Surgeries), evaluated 49 patients—34 underwent breast surgery and 15 underwent abdominoplasty. Surgeries were performed according to each surgeon's usual technique, and short-acting opioids were administered intraoperatively according to the surgeon's usual practice.

Prior to surgical closure, liposome bupivacaine 266mg was administered via infiltration into the surgical site. For breast surgeries, liposome bupivacaine 266mg was given undiluted (20mL) or diluted with 0.9% saline to a total volume of up to 100mL (dilution volume was at the investigator's discretion) and administered in equal volumes to the left and right breast surgical sites as per the surgeon's normal practice. For abdominoplasty, liposome bupivacaine 266mg (20mL) was diluted to a volume of 40-100mL (at the investigator's discretion) and administered to the surgical site as per the surgeon's normal practice. For subjects who underwent concomitant abdominoplasty and breast surgery, dilution volume and amount of study drug administered across surgical sites was left to the discretion of the surgeon.

Following surgery, pain intensity was assessed using an 11-point numeric rating scale (NRS: 0=no pain, 10=worst possible pain) when the subject awoke and then hourly until discharge. The type, dosage and time of administration of any postsurgical analgesics were recorded until discharge. Acetaminophen and/or NSAIDs were administered as needed for minor pain (NRS score ≤4). For moderate to severe pain (NRS score >4), intravenous (IV) morphine sulfate, hydromorphone HCl and/or orally administered opioid combinations were given as needed until subject discharge.

Analgesic consumption was recorded postoperatively on the day of surgery. In addition, each subject completed an overall benefit analgesic score (OBAS)[2] assessment daily from day of surgery through postoperative day (POD) 3.

Outcome measures included postsurgical pain intensity (NRS) and OBAS through POD 3, total volume of liposome bupivacaine plus diluent administered, duration of surgery, duration of stay in the post-anesthesia care unit (PACU), time of first postsurgical opioid use, total postsurgical opioid use (expressed as the number of opioid analgesic tablets), number and purpose of postsurgical subject calls and/or unscheduled visits to the surgeon's office or surgical center, and postsurgical AEs observed or reported through end of study (POD 3).

Following surgery, pain intensity was assessed using an 11-point numeric rating scale when the subject awoke and then hourly until discharge.

For analysis purposes, the breast surgery group included subjects who underwent breast augmentation or breast reduction procedures. The abdominoplasty with or without breast surgery group included subjects for whom abdominoplasty was the primary surgical procedure, whether or not they underwent breast surgery.

Reduced Opioid Requirements and Improved Patient Satisfaction

From discharge through POD 3, mean and median NRS pain intensity scores were consistently reflective of low to moderate pain intensity (3 to 5) across both surgery groups. Scores for the abdominoplasty

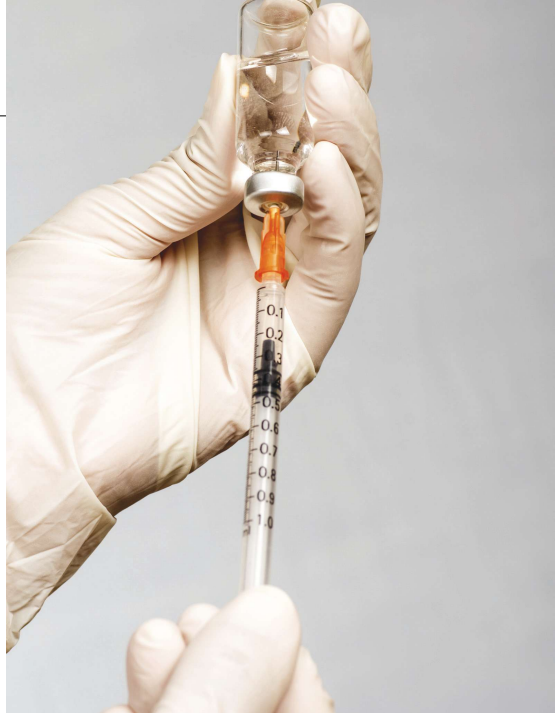
with or without breast surgery group were generally slightly higher than for the breast surgery group, consistent with the investigators' experience that abdominoplasty is typically a more painful procedure than breast surgery. The between-group differences decreased with time after surgery.

Postsurgical consumption of opioid analgesics was also low, with the median daily dose peaking at approximately three to four tablets/day on POD 1 and declining to approximately two to three tablets/day on PODs 2 and 3. These amounts are substantially lower than the amount of postsurgical opioids typically prescribed in the investigators' practices (approximately six to 12 tablets/day). The amount of opioids consumed was similar between surgical procedure groups, a somewhat unexpected finding given the investigators' experience (supported by pain intensity scores in this study) that abdominoplasty is typically a more painful procedure than breast augmentation or breast reduction surgery.

Total OBAS remained low throughout the study, indicating satisfaction with analgesia and a low burden of opioid-associated side effects. Individual mean domain scores for pain intensity and opioid-associated side effects were low throughout the study, and mean scores for the "Satisfaction with Pain Management" domain were greater than 3 throughout the study, with a single exception (on POD 1 in the abdominoplasty with or without breast surgery group).

From Bench to Bedside: Clinical Implications

Integrating liposomal bupivacaine into our suite of pain management tools has been transformative for our patients and practice. Having a single-shot, local analgesic do the heavy lifting during the critical few days post-op means cutting back on narcotics, having patients alert and out of bed sooner; which in turn reduces the burden on our post-op care staff who used to actively monitor pain pump functioning and accuracy while tackling opioid-induced GI and GU side effects. And while the cost of liposomal bupivacaine is higher than some other commonly used analgesics for perioperative pain (e.g., opioids, standard formulations of local anesthetics), in our experience, the incremental cost is typically offset by improved outcomes, such as better pain relief, lower opioid consumption and improved patient satisfaction, therefore resulting in higher retention rates and increased patient-to-patient referrals.



Offering patient education on pain management options has increased conversions.

Not surprisingly, more of our abdominoplasty consultations convert to surgery after we educate them on the benefits of liposomal bupivacaine in improving their postoperative pain. Based on the EXCLAIM data and our clinical experience, we are optimistic about the potential of liposomal bupivacaine to drive a major shift in the traditional opioid-centric approach to managing postsurgical pain, and we hope our colleagues take the opportunity to experience the value of this game-changing analgesic. ❖

Holly Wall, MD, FACS, and **Simeon Wall, MD, FACS**, are the founders of The Wall Center for Plastic Surgery, Shreveport, LA. Contact them at wallcenter.com.

1. American Academy of Pain Medicine (AAPM). "Postsurgical pain control linked to patient satisfaction with hospital experience." ScienceDaily, 6 March 2014. <www.sciencedaily.com/releases/2014/03/140306211038.htm>.

2. The OBAS questionnaire is a validated, multidimensional tool that assesses pain intensity, opioid-related AEs and subject satisfaction. It includes questions on the following items: pain intensity (scale: 0=minimal pain; 4=maximal pain), opioid-associated adverse effects (vomiting, itchiness, sweating, freezing and dizziness; scale: 0=not at all; 4=very much), and overall subject satisfaction with pain treatment (scale: 0=not at all; 4=very much). The overall OBAS score is derived by summing the scores for questions 1 through 6 and adding "4 minus the question 7 score." In addition, a single-question assessment of the impact (of pain) on normal daily activities (IONDA; "On a scale of 0 to 10, please enter the number that best describes the impact of your surgical pain on normal daily activity") was administered on the day of surgery and postoperative days 1, 2 and 3 (scale: "0=none, I am doing everything I did before surgery; 10=I am not able to do any activities I did before surgery").