Examining Liposomal Bupivacaine's Use in Dentistry

This year's Landmark Articles in Dental Anesthesiology with Commentary in Honor of Joel M. Weaver, DDS, PhD features a study by Lieblich and Danesi[1] on the analgesic efficacy and safety of liposomal bupivacaine (Exparel, bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc) for patients undergoing extraction of third molars. Used to provide prolonged local anesthetic effects, Exparel features bupivacaine encapsulated in multivesicular liposomes that slowly break down and release bupivacaine over 3 to 4 days. Exparel typically is not intended for intraoperative local anesthesia due to its slow onset, but rather administered at the end of the procedure for postoperative pain control. Its use must be timed properly as other coadministered local anesthetics, aside from bupivacaine, can cause premature rupture of the liposomal vesicles if injected into the same areas, leading to massive release and potential overdose of bupivacaine. Manufacturer recommendations stipulate that a 20-minute delay follow the use of nonbupivacaine local anesthetics (e.g., lidocaine) before Exparel is injected. Additionally, Exparel is intended to be administered via local infiltration along the surgical site rather than as a nerve block (e.g., V2, mental, or inferior alveolar nerve block). The purported benefits of liposomal bupivacaine are decreased surgical site pain, increased patient satisfaction, and decreased opioid use, among others.

Since being approved in 2011 by the US Food and Drug Administration (FDA) for "administration into the surgical site to produce postsurgical analgesia," Exparel has been used successfully in a variety of surgeries in medicine and dentistry. It even has FDA approval for use in pediatric patients 6 years of age and older as a single-dose infiltration for prolonged local anesthesia. Much of the data on the use of Exparel has supported the manufacturer's claims and suggest positive impacts on decreasing opioid use postoperatively, particularly during the first few days. Exparel is also being incorporated into contemporary Enhanced Recovery After Surgery (ERAS) protocols in several surgical disciplines, such as plastic surgery, orthopedics, and even nephrectomies, as part of a multimodal approach to improve outcomes.

Data from the reprinted study found later in this issue suggest that patients who received Exparel had significantly decreased postoperative pain scores up to 96 hours as compared with those who did not, although this trend was noted only in the per-protocol population analysis performed due to potential confounding effects from several protocol violations in both groups.[1] Interestingly, this study failed to demonstrate any significant difference in opioid use; however, the protocol only permitted opioids (oxycodone 5–10 mg) for breakthrough pain and did not utilize other common analgesics like nonsteroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen. A related study by Lieblich et al[2] in 2021 retrospectively assessed opioid prescriptions for third molar extraction patients and found that those who received Exparel had lower opioid prescription refill rates. The protocol for this study included scheduled ibuprofen use along with acetaminophen for breakthrough pain and if unsuccessful, an opioid agonist for rescue. Although many would likely consider the nonopioid postoperative analgesic management less than ideal (suboptimal scheduled acetaminophen use), the data demonstrated the Exparel group utilized few opioids and had a lower opioid prescription refill rate. Another study published in 2023 compared standard bupivacaine with Exparel and failed to demonstrate any significant difference in pain levels following uncomplicated third molar extractions.[3] However, this study's protocol used 1-mL volumes of liposomal bupivacaine per surgical site, substantially less than the volumes used in the Lieblich studies, bringing into question its clinical validity.

Aside from those mentioned previously, studies on the use of Exparel in dentistry and oral surgery are somewhat sparse. A few have evaluated its use in endodontic procedures with mixed results,[4,5] while another assessed Exparel use in full-arch implant surgery with more positive findings.[6] Its use for postoperative analgesia has also been documented in TMJ surgeries as well. One study from 2019 even utilized Exparel for surgical site infiltration in pediatric patients (age range, 8–17 years) with alveolar clefts undergoing alveolar bone grafting and found Exparel use was associated with decreased opioid requirements postoperatively.[7] After surveying the literature on Exparel in dentistry and oral surgery, the general trend that emerges seems to suggest that its use may help reduce postoperative pain for 3 to 4 days as well as decrease the need for opioids.

Given this assumption, the natural question that arises is "Why isn't Exparel being used more frequently throughout dentistry and oral surgery?" The answer is multifactorial but likely involves several usual suspects. First, it must be acknowledged that clinicians are typically rather slow to adopt to change. Exparel was approved in 2011, so many in practice since that time have likely had little to no experience with its use. Even those clinicians in residency programs from 2011 onward may not have had many opportunities to use Exparel, so its slow adoption into contemporary practice is not surprising.

Another equally critical factor is the cost of Exparel which as of today is roughly $225 for a 10-mL vial and

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$375 for a 20-mL vial. For reference, the 2017 Lieblich study protocol used a total volume of 10 mL per patient. Although there is a dental code for administering liposomal bupivacaine (D9613), most dental insurance and state Medicaid plans do not reimburse for this service, leaving either the provider or the patient to shoulder the extra financial burden. Anecdotally, I know of a large oral and maxillofacial surgery practice in California that has adopted routine use of Exparel for all third molar cases along with scheduled NSAIDs and acetaminophen, saving opioids mainly for particularly challenging cases where postoperative pain is likely to be more severe. Exparel is sterilely divided into 3 to 4 aliquots to decrease cost. Even in those rare cases where opioids are needed, the number of opioid tablets is kept to a minimum, reducing the risk of opioid abuse. This particular practice has found success with this approach as many parents are happy to pay for Exparel to minimize opioid use in their teenage sons and daughters. Parents or patients in less affluent areas of the country may not share the same sentiment or ability to handle the extra costs for Exparel. Financial considerations likely have played a major role in slowing the widespread adoption of Exparel in dental practice.

Discussion of Exparel's cost leads to the question of a generic alternative which would help remove financial barriers to more widespread use. Following the initial FDA approval in 2011, the earliest to expect a generic version of Exparel was 2026. However, in June 2021, Pacira successfully filed a new patent related to Exparel which extended that date to 2041. Pacira was then given notice in 2021 that eVenus Pharmaceutical Laboratories, Inc was seeking FDA approval for a generic version of Exparel, ultimately granted in July 2024, which prompted litigation. In response, eVenus retaliated by challenging the validity of Pacira's newly extended patent. That lawsuit that was found to have merit in August 2024, potentially opening the door for generic liposomal bupivacaine soon. However, despite the favorable ruling, continued appeals are likely, plus industry insiders have reported that eVenus's generic version wouldn't be commercially available until after 2030 at a minimum. For the time being, it appears that a generic alternative to Exparel will not be available anytime soon in the United States.

The reasons, then, behind Exparel's slow adoption throughout dentistry and oral surgery are complex. Clinicians are left to juggle several ongoing issues: rising drug costs, pressures to reduce/avoid opioids, flat or declining insurance reimbursement rates, and skyrocketing inflation to name a few. The benefits of using liposomal bupivacaine appear quite promising, but the barriers are also robust. Asking clinicians to shoulder the financial burden for using Exparel alone is most likely unrealistic. It may make more sense to present the option and associated cost for incorporating Exparel to the patient or their parents or caregivers as part of the treatment planning process, and those who see value can opt in. Looking at this from the perspective of the human cost related to the opioid pandemic, important questions may be: "What am I willing to pay for safety? Am I or my child worth $100 or $225 to help avoid/minimize opioids postoperatively?"

Exparel is yet another tool at our disposal that likely has benefits but comes at a considerable financial cost. A major responsibility we have as healthcare providers is to work with our patients to help them determine which treatment options are in their best interest. Some may find value in using Exparel while others may not. The decision should ultimately be made by patients and caregivers with as much information as possible.

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