DEAR EDITOR,

Multimodal analgesia after major surgery comprises opioids, non-steroidal anti-inflammatory drugs (NSAIDs), various adjuvants like gabapentinoids, alpha-2 agonists, magnesium sulphate, lidocaine infusion, and regional anaesthesia (RA) techniques which could be a central neuraxial block like continuous epidural analgesia, a peripheral nerve block or the fascial plane blocks. Although single-shot RA techniques work well for a certain period of time, a continuous infusion provides opioid-sparing analgesia, facilitates early rehabilitation, and also prevents the incidence of chronic postoperative pain syndrome (CPPS). Continuous infusion is facilitated by placing catheters in the epidural space, around the targeted peripheral nerves or in the desired fascial plane for continuous local anesthetic (LA) infusion. The continuous LA infusion is delivered via syringe pumps or via elastomeric pumps filled with the desired volume of LA. Clinicians found this cumbersome as there were several incidences of accidental catheter removals, infections and that also interfered with patient ambulation.

This led to the development of liposomal bupivacaine marketed as Exparel (Pacira Pharmaceuticals, Inc., Parsippany, N.J.) and also approved by US-FDA as wound infiltration for providing postoperative analgesia. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022496s9lbl.pdf). Exparel is available for injection in the form of vesicles of bupivacaine loaded in the aqueous chambers using DepoFoam® technology (Pacira Pharmaceuticals Inc, San Diego, CA). Each particle in the preparation is composed of a honeycomb like structure with numerous internal aqueous chambers which contains encapsulated bupivacaine. In the comprehensive review by Kaye et al, authors reviewed the existing literature in which liposomal bupivacaine was used as a component of multimodal analgesia and concluded that when used there was prolonged...
analgesia, opioid-sparing effect and was better than placebo or conventional bupivacaine infiltration. Researchers have also used liposomal bupivacaine in pediatric patients although it is not approved for use in pediatric patients. The success of liposomal bupivacaine encouraged the researchers to develop better liposomal products which can be used in clinical practice. This led to the development of SABER-bupivacaine and HTX-011.

SABER-bupivacaine is sucrose acetate isobutyrate extended-release bupivacaine (DURECT Corporation, Cupertino, California, USA). The biodegradable sucrose acetate isobutyrate biolayer stores bupivacaine and thus acts as a depot. On injecting at the incision site, there is a slow and sustained release of LA at the infiltrated site. In a double-blinded, randomized controlled trial by Hadz et al, authors infiltrated SABER-bupivacaine (5 ml) in patients undergoing open inguinal hernia repair. They found that there was good pain relief, lesser analgesic consumption postoperatively and the infiltration did not interfere with wound healing. Till date, this is the only randomized controlled study investigating SABER-bupivacaine.

HTX-011 is an extended-release, fixed-ratio agent which consists of bupivacaine along with low-dose meloxicam, which is a cyclooxygenase-2 inhibitor, to enhance the effectiveness of infiltrated bupivacaine. This preparation is integrated into a bioerodible polymer (Biochronomer). HTX-011 has been developed by Heron Pharmaceuticals and is still awaiting US-FDA approval. After injection at the wound site, there is controlled hydrolysis of the leading to sustained release of both bupivacaine and meloxicam for the next 72 hours. It was earlier demonstrated that in acidic pH which is present at the incision site due to inflammation, the efficacy of infiltrated bupivacaine is reduced. Meloxicam thus plays a dual role in this preparation. Meloxicam helps in normalizing the pH at the site of injection and thus retains the efficacy of polymerized bupivacaine. In phase II clinical study in patients undergoing bunionectomy, Ottoboni et al recruited 237 patients to investigate HTX-011. Authors also found those who received HTX-011 infiltration after undergoing bunionectomy had significantly lower pain scores over the first 24, 48, and 72 hours compared to patients who received HTX-002 (bupivacaine alone), HTX-009 (meloxicam alone), and placebo (saline). Singla et al divided patients undergoing herniorrhaphy into 2 sequential cohorts. Patients in both cohorts received HTX-011 prior to wound closure. Patients in cohort 2 received intraoperative dose of ketorolac in addition to HTX-011 infiltration. On analysis, authors found that more than 90% of patients did not receive any opioids as rescue analgesia
for 72 hours, and that the addition of ketorolac did not confer any additional benefit. All patients who received HTX-011 tolerated wound infiltration well.6

These novel formulations are still not approved by US-FDA for clinical use and are thus not marketed yet. However, on reviewing their unique mechanism of action, sustained-release properties, safety and opioid-sparing effects once available these products could be game-changer in managing postoperative pain. Pain physicians and perioperative physicians would be eager to add them in their armamentarium of multimodal analgesia depending on its availability and cost-effectiveness.

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References


