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LETTER TO THE EDITOR

Newer, Longer Acting Local Anesthetics

The future of postoperative pain management looks bright

Dear Editor,

Multimodal analgesia after major surgery comprises opioids, non-steroidal anti-inflammatory drugs, various adjuvants such as gabapentinoids, alpha-2 agonists, magnesium sulphate and lidocaine infusion and regional anaesthesia (RA) techniques such as a central neuraxial block (e.g. 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 prevents the incidence of chronic postoperative pain syndrome. 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 elastomeric pumps filled with the desired volume of LA.

This led to the development of liposomal bupivacaine marketed as Exparel® (Pacira Pharmaceuticals Inc., Parsippany, New Jersey, USA) which was approved by the US- Food and Drug Administration (FDA) as wound infiltration for providing postoperative analgesia. Exparel® (Pacira Pharmaceuticals Inc.) is available for injection in the form of vesicles of bupivacaine loaded in the aqueous chambers using DepoFoam® technology (Pacira Pharmaceuticals Inc., San Diego, California, USA). Each particle in the preparation is composed of a honeycomb-like structure with numerous internal aqueous chambers which contains encapsulated bupivacaine. Kaye *et al.* comprehensively 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.[1] 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 (Durect Corp., Cupertino, California, USA) and HTX-011 (Heron Therapeutics Inc., San Diego, California, USA).

SABER®-bupivacaine (Durect Corp.) is sucrose acetate isobutyrate extended-release bupivacaine. The biodegradable sucrose acetate isobutyrate biolayer stores bupivacaine and thus acts as a depot. Upon injecting at the incision site, there is a slow and sustained release of LA at the infiltrated site.[2] In a double-blinded, randomised controlled trial, Hadj *et al.* infiltrated 5 mL of SABER®-bupivacaine (Durect Corp.) into patients undergoing open inguinal hernia repair.[3] 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 randomised controlled study investigating SABER®-bupivacaine (Durect Corp.). This drug has not been approved by the US-FDA.

HTX-011 (Heron Therapeutics Inc.) 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 (Heron Therapeutics Inc.) has been approved by the US-FDA in 2021.[4] After injection at the wound site, there is controlled hydrolysis of the polymer leading to sustained release of both bupivacaine and meloxicam for the next 72 hours. It was earlier demonstrated that in acidic pH environments, 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 normalising the pH at the site of injection and thus retains the efficacy of polymerised bupivacaine. In a phase II clinical study in patients undergoing bunionectomy, Ottoboni *et al.* recruited 237 patients to investigate HTX-011 (Heron Therapeutics Inc.).[5] They found that those who received HTX-011 (Heron Therapeutics Inc.) 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 two sequential cohorts. Patients in both cohorts received HTX-011 (Heron Therapeutics Inc.) prior to wound closure. Patients in cohort two received intraoperative dose of ketorolac in addition to HTX-011 (Heron Therapeutics Inc.) infiltration. During analysis, the 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 (Heron Therapeutics Inc.) tolerated wound infiltration well.[6]

Apart from HTX-011, these novel formulations are still not approved by the 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 a game-changer in managing postoperative pain. Pain physicians and perioperative physicians would be eager to add these to their armament of multimodal analgesia depending on its availability and cost-effectiveness.

AUTHORS' CONTRIBUTION

Both authors contributed equally to the drafting of this manuscript. Both authors approved the final version of the manuscript.

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