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Novel Local Anesthetics in Clinical Practice: Pharmacologic Considerations and Potential Roles for the Future

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Abstract

The treatment of pain, both acute and chronic, has been a focus of medicine for generations. Physicians have tried to develop novel ways to effectively manage pain in surgical and post-surgical settings. One intervention demonstrating efficacy is nerve blocks. Single-injection peripheral nerve blocks (PNBs) are usually preferred over continuous PNBs, since they are not associated with longer lengths of stay. The challenge of single injection PNBs is their length of duration, which at present is a major limitation. Novel preparations of local anesthetics have also been studied, and these new preparations could allow for extended duration of action of anesthetics. An emerging preparation of bupivacaine, exparel, uses a multivesicular liposomal delivery system which releases medication in a steady, controlled manner. Another extended-release local anesthetic, HTX-011, consists of a combination of bupivacaine and low-dose meloxicam. Tetrodotoxin, a naturally occurring reversible site 1 sodium channel toxin derived from pufferfish and shellfish, has shown the potential to block conduction of isolated nerves. Neosaxitoxin is a more potent reversible site 1 sodium channel toxin also found in shellfish that can also block nerve conduction. These novel formulations show great promise in terms of the ability to prolong the duration of single injection PNBs. This field is still currently in development, and more researchers will need to be done to ensure the efficacy and safety of these novel formulations. These formulations could be the future of pain management if ongoing research continues to prove positive effects and low side effect profiles.

Keywords: Exparel, Neosaxitoxin, Tetrodotoxin, HTX-011, Meloxicam, Novel Local Anesthetics, Peripheral Nerve Blocks, Postoperative Pain

1. Context

The treatment of pain, both acute and chronic, has been a focus of medicine for generations. Opiate medications have been the mainstay of pain management, but for the past 30 years, their use and abuse have risen dramatically (1-3). Scientists and clinicians have attempted to develop novel ways to battle pain in surgical and post-surgical settings (4-7). Chronic pain can result from surgery in about 10% of patients (8). At present, it is believed that pain can transition from acute post-surgical to chronic if not well controlled after surgery (9). Research into this transition has led to new pharmacological interventions to try to better control pain after surgery (10, 11).

One intervention used to control pain after surgery is regional nerve blocks (12, 13). This is the delivery of local anesthetic into the area of interest to block the transition of pain signals by nerves (14). Sasso et al. looked to see if a regional block could help treat chronic post-surgical pain (15). They looked at the local site pain after anterior lumbosacral fusion. They found that persistent pain was usually found in about 15 - 39% of patients undergoing this type of procedure for at least two years. Their prospective study looked at 202 patients, and 43% had persistent pain that only occurred after their surgery at six months, and 33% at one year (15). Black et al. looked at the use of a transversalis fascia plane (TFP) block to help decrease the development

of this chronic pain at the donor site (16). They found that persistent pain at the donor site was reported in only 4.3% of all patients at six months and 6.5% at 12 months (16).

This raises the question of whether a peripheral nerve block (PNB) can help with acute and chronic pain management. The results of the above studies show that it can be useful, but how long should the block last? In this regard, there are single injection PNBs and continuous PNBs. Continuous PNBs involve the insertion of a catheter to deliver the anesthetic to its intended target (12). This can be associated with a longer time to discharge, so single injection PNBs are generally preferred (17). The challenge of single injection PNBs is their length of duration, which is their major limitation. Most have a duration of only 24 - 48 hours (17).

Researchers have worked to find ways to prolong the length of duration of single-shot PNBs (18). This has led to looking at adjuvants that could be added to the local anesthetic to increase the length of their block provided (19). Adjuvants are useful at reducing pain after the surgical operation, additional analgesic requirements, duration of hospitalization, and total health cost (20-24). Many adjuvants are still not FDA approved for use, and more research is needed to determine their safety.

Novel preparations of local anesthetics have also been studied. These new preparations allow for the extended duration of action of local anesthetics (25). One example is the preparation of bupivacaine with a liposomal bilayer, which allows for sustained release of local anesthetic for at least 72 hours after the injection, and this has the potential for decreasing opioid consumption in the postoperative period (25). This manuscript, therefore, aims to look at these novel preparations and their potential role to help reduce postoperative pain and the development of chronic pain states.

1.1. Exparel

Bupivacaine is a commonly used local anesthetic delivered by local infiltration or pain pump (6, 7). The efficacy of this anesthetic method is limited by its short duration of action and nonstandard management approaches (26). Increasing the dose to prolong drug activity is not recommended due to the increased risk of toxicity (27). An emerging technique for administering bupivacaine, called exparel, uses a multivesicular liposomal delivery system that releases medication in a steady, controlled fashion. The liposomal structure is formed in a way that allows slow degradation, as mentioned in the introduction (27). The FDA approved exparel for use in local infiltration analgesia. Its use in numerous peripheral and neuraxial nerve blocks is still under investigation (28). This new technique can increase bupivacaine's duration of action from 10 hours to 72 - 96 hours (29, 30). Exparel has been shown, especially in a multimodal pain control strategy, to provide adequate relief during recovery after surgery and during post-op visits (31). When compared to a bupivacaine pain pump, liposomal bupivacaine increases time of pain relief (31, 32). Liposomal bupivacaine also provides similar or better safety and side effect profiles when compared to standard bupivacaine (28). Local anesthetic toxicity is still a risk when using exparel. Patients must be monitored for cardiotoxicity and neurotoxicity. However, the slow-release mechanism of exparel allows it to subvert some of the risks involved with bupivacaine toxicity (33). Caution must be used when using exparel in patients with hepatic disease, a primary site of its metabolism (33).

1.2. HTX-011

Another extended-release local anesthetic, HTX-011, consists of a combination of bupivacaine and low-dose meloxicam. Meloxicam is added to decrease local inflammation and stabilize the pH of bupivacaine. This is thought to enhance bupivacaine's effectiveness (34). The polymer used to encapsulate HTX-011 is a polymer designed to be hydrolyzed slowly, thus releasing bupivacaine and meloxicam at a gradual and sustained rate (35). HTX-011 provides better pain relief when compared to bupivacaine (36). In Study 301/EPOCH 1, 29% of patients did not require additional opioids for 72 hours post-surgery. Total opioid use was decreased by 25%, and pain scores were decreased by 18% in comparison to bupivacaine (37). In Study 302/EPOCH 2, 51% of patients given HTX-011 did not need opioid in the first 72 hours. This is in comparison to 40% in the bupivacaine group. Pain scores were reduced 23% when compared to the standard of care (36). A study on open inguinal herniorraphy showed opioids were not used in 90% of patients given HTX-011 in the first 72 hours. Common side effects include nausea, hypoxia, and headache (34). Safety has been shown to be equivalent to either bupivacaine or placebo (36, 37).

1.3. Tetrodotoxin

Tetrodotoxin, a naturally occurring reversible site 1 sodium channel toxin derived from pufferfish and shellfish, has shown the potential to block conduction of isolated nerves. Tetrodotoxin has been shown in preliminary animal studies to significantly prolong block duration when used in conjunction with bupivacaine (38). Other similar studies show tetrodotoxin, usually known to cause muscle paralysis, to have minimal commonly seen local anesthetic adverse effects of myotoxicity and neurotoxicity (39). A polymer conjugate of tetrodotoxin can further broaden its therapeutic index to further safety (40). Mechanical hyperalgesia has also been shown to be inhibited

after administration of tetrodotoxin (41). Capsaicin liposomes, chemical permeation enhancers, and epinephrine has also been shown to prolong the duration and improve the effectiveness of tetrodotoxin. Capsaicin liposomes have the added benefit of decreasing drug toxicity (42, 43).

1.4. Neosaxitoxin

Neosaxitoxin is a more potent reversible site 1 sodium channel toxin also found in shellfish that can block nerve conduction. Neosaxitoxin preferentially targets sodium channels in the periphery compared to the myocardium improving its safety profile (44). Severe adverse effects of respiratory and cardiac toxicity are rare. More common side effects include facial paresthesias and respiratory insufficiency are seen when using high doses (45). Combined with bupivacaine, neosaxitoxin has a prolonged duration of effect compared to bupivacaine, neosaxitoxin, and placebo independently (46).

1.5. SABER-bupivacaine

SABER-bupivacaine is a depot formulation that produces a sustained release of bupivacaine. The active component bupivacaine 12% is an experimental pain-relieving medication, and is in the form of a capsule in a biological degradable structure. It is designed for surgical infiltration to achieve a long-term post-operative analgesia, reduce opioid consumption and improve post-surgical recovery (47). Bupivacaine is slowly released over several days following injection.

1.6. INL-001

INL-001 is a biodegradable resorbable collagen matrix impregnated with bupivacaine. It is directly deposited in the surgical site and provides extended delivery of bupivacaine directly at the site. Once deposited it provides an immediate and extended release of the bupivacaine.

2. Clinical Studies: Safety and Efficacy

2.1. Exparel

In a by Surdam et al., they compared 20 mL of 1.3% liposomal bupivacaine mixed with 40 mL of saline injected into the periarticular tissues versus femoral nerve block (FNB) consisting of 40 mL of 0.5% bupivacaine with epinephrine for total knee arthroscopy (TKA). The initial target was inpatient pain management, and latter target included range of motion, nausea and vomiting, narcotic consumption, and length of stay. The pain control and also nausea, vomiting, and narcotic consumption between the two groups, demonstrated not significant difference (48). Their findings demonstrate that liposomal bupivacaine provided equal pain relief compared to femoral block while not affecting inpatient rehabilitation after arthroplasty (48).

Another study done by Hyland et al. examined patients undergoing TKA with the use of liposomal bupivacaine (49). In their study, those in the control group received a periarticular injection (PAI) including a mixture of ropivacaine, ketorolac, methylprednisolone and morphine during surgery. The case group received the same injection but containing liposomal bupivacaine. The number of physical therapy sessions required for discharge, total opioid consumption, pain scores, and adverse events were not difference between two groups (49).

Vandepitte et al. showed that adding liposomal bupivacaine to interscalene block reduced the pain score in the first postoperative week (50). However, they note these findings were only modest and did not show significant data in pain compared to baseline, reductions in opioid consumption, or sleep quality (50).

Furthermore, Namdari et al. examined pain scores and analgesic consumption after shoulder arthroplasty performed by adding intraoperative liposomal bupivacaine to preoperative interscalene nerve block (51). The pain score was not significance between these groups (51). Surprisingly, postoperative total narcotic consumption was more than interscalene nerve block alone (51). They further explain this may be due to a "dual rebound" phenomenon in which patients experienced rebound pain both after the effect of the interscalene nerve block eliminated and after the effect of the liposomal bupivacaine reduced, leading to increased opioid consumption (51).

Optimal postoperative pain management remains to be a concern in heart operation (52, 53). In the study done by Lee et al., they looked at the efficacy of liposomal bupivacaine as a single dose in a multi-level parasternal nerve block. The median postoperative pain scores were not significant reductions among two groups (53). However, overall pain scores in the case group showed less pain scores. Additionally, required analgesic reported in morphine equivalents did not show a significant reduction in opioid consumption (53).

2.2. HTX-011

In a recent double-blinded, randomized, placebo-controlled, and active-controlled phase 3 study (EPOCH 1), they examined the safety and efficacy of HTX-011. A three-arm group undergoing a bunionectomy with group (A) receiving HTX-011 (bupivacaine 60 mg/ meloxicam 1.8 mg), (B) bupivacaine 0.5%, 50 mg, and (C) saline placebo. The primary outcome examined the mean area under the curve of the pain intensity (numeric rating scale) within three days (37). The first group showed a reduction in mean

pain scale over three days compared with saline and bupivacaine group (37). Total analgesic utilization was significantly reduced in those who received HTX-011 when compared with placebo and vs. those who received bupivacaine (23, 37). Overall, 29% of HTX-011 patients were opioid-free in the first 72 hours compared with 11% in the bupivacaine and in the control group.

In the EPOCH 2 study, they examined patients undergoing herniorrhaphy. A double-blinded, randomized, placebo-controlled, and active-controlled phase 3 study (EPOCH 2) was designed to assess the pain relief effect of HTX-011 administered at the surgical site compared with bupivacaine and placebo (36). Group (A) receiving HTX-011, 300 mg/9 mg (bupivacaine/meloxicam), (B) bupivacaine 0.25%, 75 mg, and (C) placebo. The primary outcome again was the mean area under the curve of the numeric pain score within three days for each group (36). Subjects in the first group showed reduction in mean pain score over three days compared with both placebo and bupivacaine groups (36). Total analgesic utilization within three days in the first group was significantly decreased compared to the saline when compared with bupivacaine (36). Even more significantly, 51% of HTX-011cases did not need opioid within three days vs 40% for second and 22% for placebo groups.

2.3. Tetrodotoxin

In a study done by Brau et al., they examined a variety of drugs used to treat chronic pain in rats. Na^+ currents were studied mainly from dorsal root ganglion cells (54). At E of -90 mV, mexiletine, lidocaine, carbamazepine, amitriptyline, and memantine, reversibly inhibited tetrodotoxin-resistant Na^+ current (54). Current inhibition was dependent to concentration and at high concentrations was complete (54).

Furthermore Berde et al examined dose-duration following local nerve block with tetrodotoxin with bupivacaine 0.25% with or without epinephrine in rats (55). Thermal nociception blocked was evaluated using a hot plate test (55). This method raised the rat upright and lowered the rat, so the lateral aspect of a single hind paw was touching a hot plate at 56°C (55). The time it took the animal to pull out its paw was calculated with a stopwatch.

The combination of bupivacaine and tetrodotoxin showed a prolonged block duration. With the addition of epinephrine to tetrodotoxin and bupivacaine, the block was prolonged by 1.6 - 1.9 fold for 50% recovery and 1.7-2-fold for 100% recovery (55).

2.4. Neosaxitoxin

A study conducted by Rodriguez-Navarro et al. comparing neosaxitoxin to bupivacaine for laparoscopic cholecystectomy. The neosaxitoxin group was given 100 μg of neosaxitoxin, and in the bupivacaine group, they were given 50 mg for wound infiltration before insertion of working ports (56). Patients in the neosaxitoxin group reported lower scores for incisional pain versus bupivacaine, and with movement (56).

2.5. SABER-bupivacaine

In another trial, the safety and efficacy of SABER-bupivacaine in patients undergoing open inguinal hernia repair were evaluated. SABER-bupivacaine was found to be safe without significant complications compared with Placebo. SABER-bupivacaine in the dose of 5 mL decreased the area under the curve (AUC) for mean pain score on movement from 1 to 72 hours and decreased the number of patients requiring supplemental opioids when compared to SABER-Placebo. However, the 2.5 mL dose did not achieve the same results (57).

To date, the above-mentioned study is the only published randomized controlled trial that examines the use of SABER-bupivacaine (25). Currently it remains an experimental medication and it is not used in clinical practice. In 2013 FDA did not approve Saber-bupivacaine due to incomplete evidence of safety.

2.6. INL-001 (Bupivacaine Collagen Implant)

In two phase III double-blind studies MATRIX-1 and MATRIX-2 studies. Patients undergoing surgical inguinal herniorrhaphy were divided to receive three INL-001 100-mg bupivacaine HCl collagen-matrix implant or three placebo collagen-matrix implants during surgery. When compared to placebo, in both studies patients who received INL-001 had significant less pain score and analgesic within the first post-operative day. In both studies, most patients who received INL-001 did not take any opioid during the first three post-operative days. Among patients who required analgesic, subjects in the INL-001 arm received lesser opioids than those in the placebo arm.

Most of the reported side effects were mild or moderate, and bupivacaine toxicity was not observed (58).

In another study patients which scheduled for surgical inguinal hernioplasty, received three INL-001 implants, and 16 patients received local infiltration of 0.25% bupivacaine HCl 175 mg.

INL-001 plasma kevel showed a longer time to maximum plasma level and terminal elimination half-life. Maximum plasma level with INL-001 was comparable to bupivacaine and much lower than the levels related to systemic toxicity (59).

There were no side effects associated to the implant. Most of the reported adverse events were associated with general anesthesia and post-surgical care (59).

3. Conclusions

In clinical studies, exparel was not found to improve pain measurements, opioid consumption, PT sessions needed, or time to mobilization. HTX-011 improves pain scores and opioid consumption in groups that received saline or bupivacaine. Tetrodotoxin has shown some promise in animal studies as it has been shown to prolong nerve blocks when used with bupivacaine. Neosaxitoxin has shown the same prolonging effects when used with bupivacaine.

There was only one published study for SABER-bupivacaine and even though it has shown good efficacy, it has failed to demonstrate a complete evidence of clinical safety. Bupivacaine collagen matrix INL-001, two independent phase 3 studies have demonstrated statistical and clinical significance in pain intensity reduction in addition to lowering opioids requirement. A third study has shown good tolerability in patients with no major adverse events.

These novel formulations show great promise in terms of the ability to prolong the duration of single injection PNBs. This field is still currently in development, and more clinical trials will necessary to be done to ensure the efficacy and safety of these novel formulations. These formulations could be the future of pain management if more research continues to prove their positive effects and low side effect profiles.

Footnotes

Authors' Contribution: Study concept and design: ADK, ANE, EMC, CJF; Analysis and interpretation of data: AJK, MAA, ADP, AAC, RJS; Drafting of the manuscript: ANE, JYY, AJK, ADP, RJS, BMD, AS, EMC; Critical revision of the manuscript for important intellectual content: ADK, ANE, JYY, AS, EMC, CJF; Statistical analysis: AAC, RJS, BMD.

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