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In search of the Holy Grail: Poisons and extended release local anesthetics

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Regional anesthesia has been advocated as adjunct to a multimodal analgesia regimen. The limited duration of the action of available local anesthetics limits their application. Catheters, perineural or IV adjuvants, or repetition of blocks are modalities available to prolong the analgesic benefit of LRA. All of these approaches have their shortcomings. New extended release local anesthetic formulations may provide time-efficient and longer duration of analgesia with a single injection. Available data on liposomal bupivacaine are promising, and more recently, it has been FDA approved for use in interscalene brachial plexus block but not for other nerve blocks at this time. Several other new formulations and compounds, such as HTX-011, Neosaxitoxin, and SABER-Bupivacaine, are also being developed and tested for their safety and analgesic potential.

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Introduction

Acute pain management is of clinical, economical, and even ethical importance. Poorly managed postoperative pain can delay recovery and prolong hospitalization. Likewise, pain also has an impact on cardiovascular, pulmonary, and gastrointestinal systems [1]. Adequately controlled postoperative pain may decrease the risk of thromboembolic events and septic complications [2]. Moreover, adequate pain treatment may lower mortality in high-risk patients and decrease the incidence of persistent postoperative pain [3–5].

Locoregional anesthesia could significantly contribute to a more optimal acute pain management with longer acting pharmacologic formulations. The rather short duration of action of single shot techniques and the subsequent rebound pain has been a cause for concern [6]. Higher doses or concentrations of local anesthetics can prolong the duration of peripheral nerve blocks but may increase the risk for systemic toxicity of the local anesthetic and possibility of neurotoxicity. Furthermore, currently available long-acting local anesthetics result in prolonged motor block, which impedes early rehabilitation, may increase length of stay (LOS), and interfere with enhanced recovery programs [7]. Pronounced motor block and muscle weakness also carry a risk of falls [8]. Adjuvants such as dexamethasone [9] prolong the duration of action of local anesthetics but appear to have a systemic rather than nerve-specific effect [10]. The use of perineural catheters theoretically allows for more control, but this is very difficult to accomplish in actual practice, is time-consuming, and requires substantial expertise that may not be ubiquitously available [11]. Moreover, catheter programs require additional equipment for follow up and can be cost-prohibitive to run. Moreover, primary and secondary failures due to anatomical abnormalities, dislodgement, and leakage are common, yet costly and time-consuming to troubleshoot [12]. Consequently, there have been continuing efforts to develop new pharmacologic agents and formulations to prolong the duration of local anesthetics [13,14]. This article aims to review the available data on new local anesthetic formulations for the use in LRA, predict their role in practice, and suggest future research needed before their adoption.

Neosaxitoxin

Neosaxitoxin is a neurotoxin derivative, found in shellfish that reversibly blocks voltage-gated sodium channels [15]. (Fig. 1) It blocks neural conduction, impeding the propagation of nerve impulses like most other local anesthetics do. On the other hand, neosaxitoxin's affinity for sodium channels Nav 1.7 and Nav

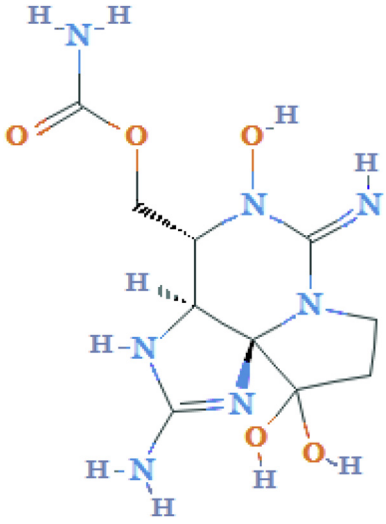

Fig. 1. Neosaxitoxin.

1.8 specifically found in peripheral nerves is much higher in relative comparison to the cardiac sodium channels Nav 1.5 [16,17]. This low affinity for sodium channels in the myocardium may make neosaxitoxin considerably safer. Moreover, neosaxitoxin is a site 1 sodium channel blocker, meaning that it does not need to cross the phospholipid bilayer of the cell membrane to block the Na channel. Although neosaxitoxin - unlike saxitoxins in general - does not cross the blood–brain barrier (BBB), it can produce facial paresthesias and respiratory insufficiency at high doses [18,19].

A human safety study in healthy volunteers already [20] documented efficacy and prolonged duration of action that was also proven for port site infiltration during laparoscopic surgery and cutaneous anesthesia [21,22].

Further research in dosing is needed to have a good understanding of its safety profile as well of its potential benefits. It was suggested that tetrodotoxin and all derivate toxins should be used in combination with a vasoconstrictor and other local anesthetics (e.g., epinephrine and bupivacaine) to confine its high potency to the region of interest [23]. Adding bupivacaine to saxitoxin allows to lower the administered doses of both drugs as additive/synergistic effects are achieved.

In one available study, a combination of bupivacaine and epinephrine resulted in lower frequency and severity of systemic symptoms caused by neosaxitoxin, while producing nearly five-fold prolongation of clinical cutaneous anesthesia [23]. Although the potentially better cardiovascular safety profile of Neosaxitoxin makes it attractive, more research is absolutely essential to establish its role in LRA [24].

HTX-011

HTX-011 is a formulation containing slow release bupivacaine in combination with a low fixed dose of an anti-inflammatory drug, meloxicam [25]. (Fig. 2) Both drugs are encapsulated in a bioerodible polymer (Biochronomer®). The polymer family contains an orthoester linkage and has been specifically designed for controlled, sustained drug delivery [26]. Although the Biochronomer has been developed and commercialized for several other slow release drugs, HTX has not yet been marketed. Initiated by A.P Pharma, it is currently under development by Heron Therapeutics, Inc. San Diego, California, United States (Heron). The same company also developed a formulation containing mepivacaine in the same polymer carrier called APF112.

HTX-011 is specifically designed to reduce postoperative pain for extended time and reduce opioid consumption. The polymer delivery system undergoes slow and controlled hydrolysis once administered in the target tissues and gradually releases bupivacaine over the course of approximately 72 h [27,28]. Two phase III trials have been concluded at this time (EPOCH 1/2).

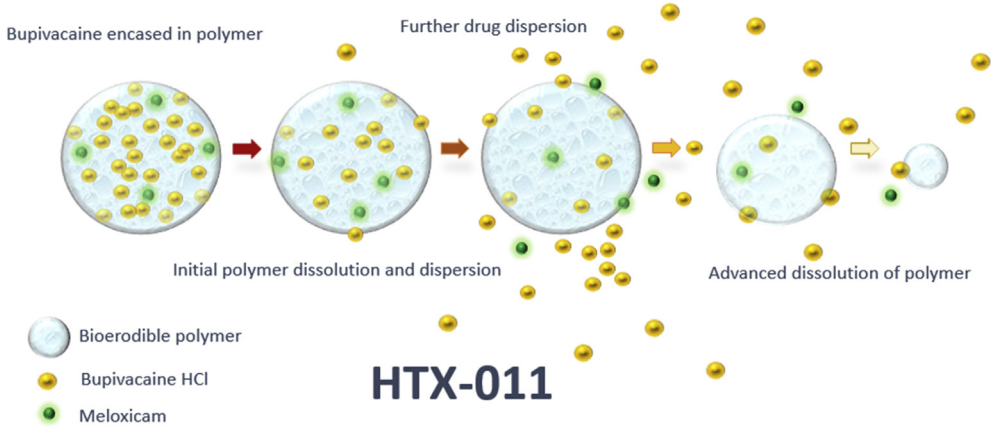

Fig. 2. Mechanism of working of HTX-011.

Study 301/EPOCH 1

Study 301/EPOCH 1 enrolled 412 patients following bunionectomy surgery in a three-arm randomized double-blind fashion. The experimental arm received 60 mg of HTX-011 solution injected locally, and the control group was treated with an injection of bupivacaine HCl 50 mg while the third group received placebo for surgical wound infiltration.

In this study, 29% of the patients receiving HTX-011 did not require any opioids for up to 72 h in contrast with 11% in the bupivacaine group ($P = 0.0001$) and 2% in the placebo group ($P < 0.0001$). The amount of total opioid intake was reduced by 37% compared to the placebo group (>0.0001) and still 25% less compared to the bupivacaine group ($P = 0.0022$).

Injection of HTX-011 also reduced the area under the curve (AUC) of up to 27% ($AUC_{0\text{-}72}$, $P < 0,001$) for pain outcome compared to placebo. Researchers also registered a 18% decrease in pain in comparison with the Bupivacaine group ($P = 0.0002$).

Study 302/EPOCH 2

This randomized, placebo- and active-controlled study involved 418 patients undergoing unilateral open inguinal herniorrhaphy with mesh under general anesthesia. HTX-011 was given at a much higher dose (300 mg), and it was again compared to bupivacaine (75 mg) and placebo. Primary outcome was AUC of the NRS and pain intensity scores with activity (NRS-A) for HTX 011 compared with saline placebo. Secondary outcomes included the following:

- AUC of the NRS-A pain intensity scores for HTX 011 compared with bupivacaine HCl.
- Total postoperative opioid consumption for HTX 011 compared with saline placebo.
- Mean total postoperative opioid consumption and proportion of subjects who were opioid-free for HTX 011 compared with bupivacaine HCl.

EPOCH 2 met all primary and secondary outcomes. In the HTX-011 group, opioid consumption decreased by 38% compared to placebo ($P < 0.0001$) and by 25% in comparison to bupivacaine ($P = 0.02$). An overall 51% of the HTX-011 group had no need for opioids at all in the first three days. In the bupivacaine group, however, also 40% of the patients did not use rescue opioids during that same period ($P = 0.0486$). In contrast, the placebo group had only 22% of total opioid free 72 h ($P < 0.0001$) The reduction of pain intensity again measured in $AUC_{0\text{-}72}$ in the HTX-011 group was 23% versus placebo ($P = 0.0004$) and 21% versus bupivacaine ($P < 0.0001$).

Ongoing research

In 2018, 220 patients were enrolled in study 209, a randomized placebo- and active-controlled, double-blind, phase IIb clinical study in patients undergoing primary unilateral total knee arthroplasty. It seems as if all primary and secondary endpoints were met.

Study 211 investigated patients undergoing augmentation mammoplasty, had several arms in which HTX was given in doses ranging from 60 mg, 120 mg, 240 mg up to 400 mg compared to bupivacaine and placebo. HTX-011 was used as pure infiltrative technique but also for nerve blocks infiltrating lateral and medial pectoral nerves. In the HTX-011,400 mg nerve block part, the reduction in opioid usage was tripled in comparison with the bupivacaine nerve block. All pain reduction targets were met. Study 211 was also important in testing the safety profile of HTX-011 at higher doses. No severe or other adverse events were noted; furthermore, there were no withdrawals or even effects on wound healing in the high dose infiltrative arm of the study.

In summary, HTX-011 is a promising formulation combining two well-known drugs in a unique way to prolong pain control for at least 72 h. More research is needed to define the minimum effective dose for the perineural safety of meloxicam when HTX-011 is used as nerve block and to compare the effect and adverse events to other slow release anesthetics.

SABER-bupivacaine, sucrose acetate isobutyrate extended-release bupivacaine

As opposed to HTX-011 and liposome bupivacaine, SABER-Bupivacaine is intended for infiltrational use as extended release formulation of bupivacaine. POSIMIR or POSIDUR is developed by DURECT Corporation (Cupertino, California, USA) in a partnership with Sandoz AG (Basel, CH). Bupivacaine is stored in a biodegradable depot composition. This structure is composed of sucrose acetate isobutyrate (SAIB), which can store bupivacaine at high concentrations. It also consists of benzyl alcohol (which explains why SABER-Bupivacaine should not be used perineurally) and bupivacaine base in a concentration of 13.2% (132 mg per ml). Commonly used doses are 5 mL, which contains 660 mg of bupivacaine base (about 743 mg of bupivacaine HCl equivalent), and 2.5 mL, which contains 330 mg bupivacaine base. SABER-Bupivacaine releases its content faster than liposomal bupivacaine and diffuses within a couple of minutes after injection into the infiltrated tissue. It slowly discharges bupivacaine in a constant rate of approximately 10 mg/h for 72 h thereafter.

In two phase II investigations, POSIMIR significantly reduced postoperative pain and opioid use compared with placebo over the first 72 h after surgery. The first one investigated 79 patients undergoing open mesh hernia repair and revealed reductions in mean pain intensity of 31% ($P = 0.003$) and median opioid use of 80% ($P = 0.009$). The second phase II trial examined 78 patients undergoing shoulder arthroscopy, showing reductions of 20% ($P = 0.012$) and 67% ($P = 0.013$), respectively, in the same parameters as the first study.

PERSIST

In a phase III randomized, multicenter parallel-group, double-blind, placebo-controlled trial, in patients undergoing laparoscopic cholecystectomy, the efficacy, and safety of SABER-bupivacaine were evaluated. In part one, POSIMIR was tested against a placebo group; in part two of that same trial, it was compared to bupivacaine HCl. In total, 296 patients were enrolled. The primary efficacy endpoint (pain intensity on movement over 0–72 h after surgery) showed a positive trend but did not reach statistical significance.

SABER-bupivacaine RCT's

Since the phase III trial, there have been a few randomized control trials using SABER-Bupivacaine. In 2012, Hadj et al. presented their findings in a double blind placebo-controlled study in which 124 patients for inguinal hernia repair were randomized to get either SABER-Bupivacaine 2.5 mL (330 mg bupivacaine base), SABER-Bupivacaine 5 mL (660 mg bupivacaine base), or SABER-Placebo [29]. SABER-Bupivacaine appeared safe with no difference in the incidence of side effects compared with SABER-Placebo. Discoloring of the instillation site was seen in approximately 5% of patients. The 5.0 mL dose reduced the AUC of pain intensity on movement compared with SABER-Placebo ($P = 0.0033$) and decreased the number of patients requiring supplemental opioids by 26%. Although the latter was not statistically significant, the mean cumulative opioid was reduced with nearly 80% ($P = 0.009$). The time to first opioid use was also prolonged in a very convincing way (from 2.7 h up to 131.8 h $P = 0.017$).

All the other papers involving the instillation of SABER-Bupivacaine in herniorrhaphy, arthroscopic subacromial decompression, or other abdominal surgeries reported comparable results, showing a decrease in overall opioid consumption or time to first need for rescue opioids. To our knowledge, none made it to a full paper. However, abstracts and poster presentations are available [30–33].

EXPAREL, bupivacaine liposome injectable suspension

Introduction

There is currently only one extended release local anesthetic that is approved by the US Food and Drug administration (FDA). EXPAREL (Pacira Pharmaceuticals, Parsippany, New Jersey, USA) consists of the well-known active local anesthetic bupivacaine HCl, which is encapsulated in multivesicular

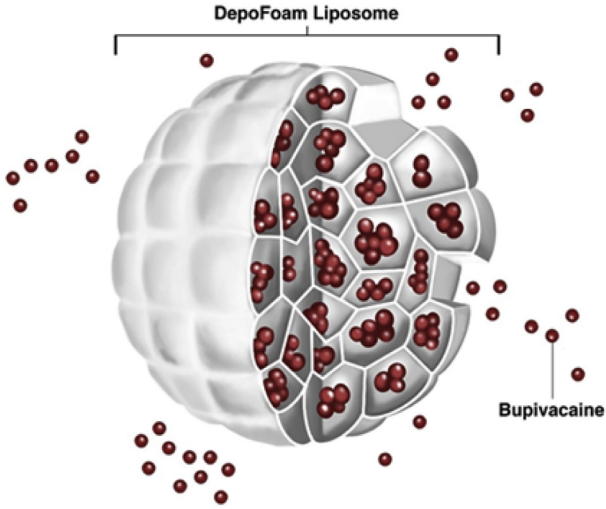

Fig. 3. Structure of liposomal bupivacaine.

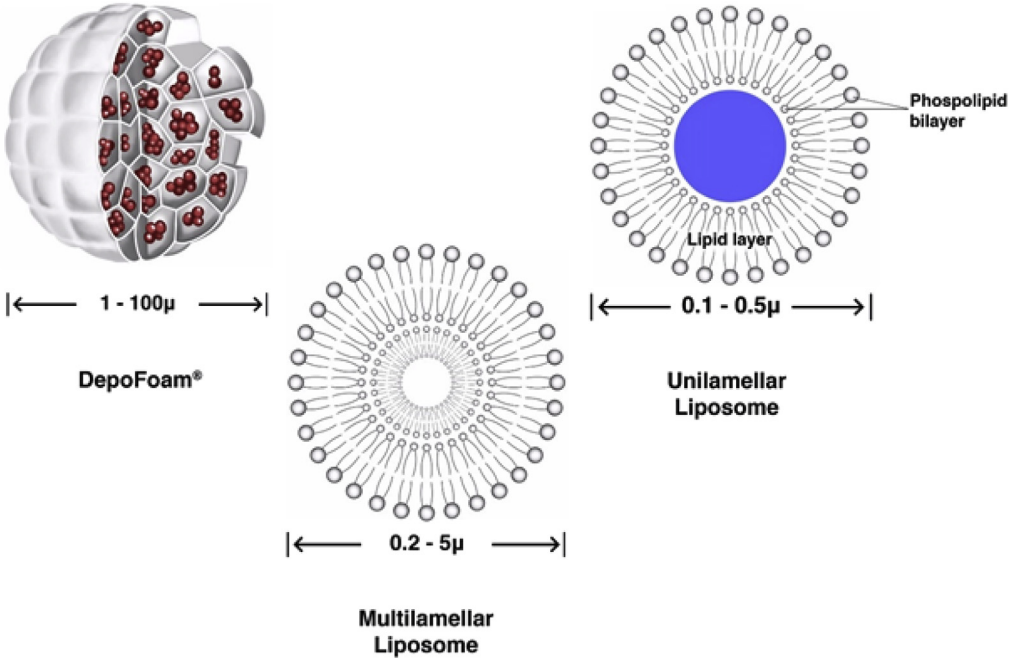

Fig. 4. Multivesicular liposome structure versus uni-en multilamellar liposomes.

liposomes (DepoFoam) (Fig. 3). These liposomes form a steady and stable mixture that releases the active local anesthetic in a very consistent way.

DepoFoam has a molecular structure that is quite similar to unilamellar and multilamellar liposomes (Fig. 4). Unilamellar liposomes are made of a single phospholipid bilayer, and multilamellar liposomes are made of concentric versions of that phospholipid bilayer. Although concentric structures

degrade in very predictable and fast fashion, nonconcentric forms go through processes of internal fusion and division and degrade slowly. The nonconcentric shape of the DepoFoam nature explained may provide a mechanism for the slow degradation of the active substance, bupivacaine, resulting in significantly longer duration of analgesia than that of bupivacaine HCl (72 + hours) [34,35].

The active component of EXPAREL, bupivacaine, is an amide-type local anesthetic. Bupivacaine exerts its neurally blocking action through inactivation of voltage-gated sodium channels. It is metabolized in the liver by microsomal P450 enzymes through a hydroxylation and N-dealkylation. Bupivacaine is a very potent local anesthetic with high lipid solubility and 95% protein binding. Its lipid solubility allows for readily crossing the BBB and causing central nervous system toxicity. Bupivacaine is cardiotoxic, with the toxicity manifesting in severe arrhythmias, heart block, and cardiovascular arrest. The approximate half-life of bupivacaine is long at approximately 2.7 h. Increasing the dose to prolong the duration of analgesia is not recommended because of its toxicity [36]. However, encapsulating bupivacaine in a dense liposomal structure prevents crossing the BBB and prolongs the duration of the blockade without the added risk of toxicity.

Richard et al. studied the toxicity of repetitive dosing of liposomal bupivacaine by repeated subcutaneous injections in rabbits and dogs. Dogs tolerated high doses of up to 30 mg/kg mixed with bupivacaine HCl using injections twice weekly [37]. Liposomal bupivacaine in incremental doses administered as incision wound infiltration demonstrated no negative effect on wound healing and - apart from some local granulomatous inflammation - was proven to be safe [38].

In another follow-up, Richard et al. injected incrementally larger doses of liposomal bupivacaine ranging from 9 mg/kg up to even 30 mg/kg in the interscalene brachial plexus of rabbits and dogs assessing clinical signs and analyzing samples of the brachial plexus, surrounding muscle and connective tissue to determine any muscular, neuronal, or other tissue toxicity. The only effect seen was minimal to mild granulomatous inflammation of adipose tissue around the nerve roots in brachial plexus sites [39].

In 2011, The FDA approved Liposomal Bupivacaine, but only for infiltration into surgical field (see picture 3) In the meantime, research was performed to evaluate its safety and efficacy in peripheral regional blocks. It took another 7 years to get FDA approval for the use of EXPAREL in interscalene brachial plexus infiltration [40]. For all other nerve blocks, the use of EXPAREL is still strictly an off-label use. Although it is not a surgical field infiltration in a strict sense, the FDA approved TAP application with liposomal bupivacaine under the field infiltration name [41]. To the best of our knowledge, there is no data, except a few case-reports on other fascia blocks such as PECS, serratus, Quadratus lumborum blocks, and should be considered as off-label too [42,43].

Liposomal Bupivacaine itself has been examined thoroughly for both its pharmacodynamical and pharmacokinetical properties in clinical and nonclinical studies. Plasma levels of EXPAREL usually follow a bimodal distribution. A single plasma level peaks at the start of the first injection, followed by a secondary late peak at approximately 12–36 h late [44,45]. Because there is only a small amount of free bupivacaine HCl in the suspension and the initial peak of release is modest, it is recommended to add a dose of plain bupivacaine to help early analgesia. However, this dose should not exceed 50% of the liposomal dose. It is also very important not to use other local anesthetics in sequence or in an admixture at the same site of infiltration. Doing so would possibly result in a rapid increase of free unencapsulated bupivacaine. For lignocaine for example, it is recommended to wait at the very least 20 min before injecting after administration of EXPAREL (see FDA highlights of prescribing information 37).

Like all local anesthetics, the systemic absorption depends on the local blood flow, hence also on the site of injection (Fig. 5). Addition of epinephrine can cause a local vasoconstriction, prolong the working mechanism of bupivacaine, and decrease systemic absorption. Epinephrine works, however, far more efficient for short-acting local anesthetics. It will certainly not be helpful in the presence of a slow releasing form of bupivacaine nor will it reduce its systemic toxicity [46,47].

The first RCT's published in 2011 using EXPAREL showed the efficacy of liposomal bupivacaine versus placebo sodium chloride in infiltrative techniques of bunionectomy and hemorrhoidectomy (Table 1). [48,49].

In 2012, a second wave of RCT's followed, this time focusing on the efficacy of liposomal bupivacaine versus plain bupivacaine. These publications demonstrated that liposomal bupivacaine was as effective

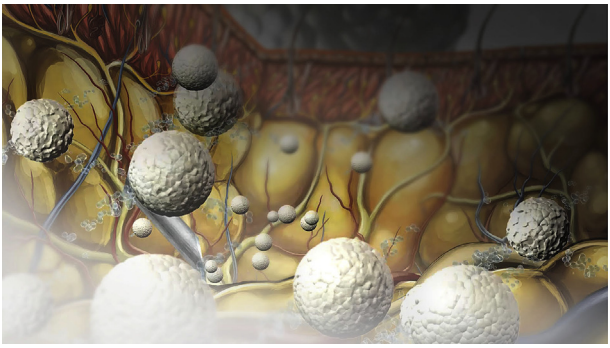

Fig. 5. Liposomal bupivacaine dispersal in vivo.

Table 1
Initial research on liposomal bupivacaine.

Gorfine et al., 2011 [47] **Dis Colon Rectum**	RCT	Hemorrhoidectomy	Liposomal bupivacaine 300 mg compared to placebo	NRS outcome scores significantly lower in liposomal bupivacaine group
Golf et al., 2011 [48] **Adv Ther**	RCT	Bunionectomy	Liposomal bupivacaine 120 mg compared to placebo	NRS outcome scores significantly lower in liposomal bupivacaine group
Smoot et al., 2012 [49] **Aesthet Surg J**	RCT	Mammoplasty	Liposomal bupivacaine 600 mg compared to bupivacaine 200 mg with epinephrine 1:200,000	No statistical difference between groups for NRS 0 −72 h
Bramlett et al., 2012 [50] **Knee**	RCT	TKA	Liposomal bupivacaine 133, 266, 399, and 532 mg compared to bupivacaine 150 mg with epinephrine 1:200,000	No statistical difference between all liposomal groups and bupivacaine for NRS 0–96 h
Cohen et al., 2012 [51] **J Pain Res**	Cohort study	Colectomy	Liposomal bupivacaine 366 mg versus postoperative opioid-based PCA	Opioid consumption, hospitalization cost, and length of stay significantly reduced in which group?

as but not superior to infiltration with bupivacaine in TKA and mammaplasty operations [50,51]. In that same year, Cohen et al. performed a cohort study in which they enrolled 42 patients receiving open colorectal surgery [52].

Neuraxial use

Liposomal bupivacaine is to our knowledge the only long-lasting slow release local anesthetic that has been already injected in the epidural space. Already in 1997, Boogaerts et al. performed the very first study injecting liposomal bupivacaine in the epidural space. Twenty-four patients receiving major surgery received a postsurgical epidural injection. The control group received bupivacaine 50 mg with 1/200,000 epinephrine, while the treatment group was administered 50 mg liposomal bupivacaine. The sensory block was approximately double as long as in the liposomal group and lasted on average 6 h. In a subset of patients undergoing abdominal aorta surgery, the analgesia even seemed to last even five times longer than in the control group. There was no motor block in the liposomal group. No neuro-or cardiotoxicity was recorded. Neither were other adverse events noted [53].

In a phase I study performed by Viscusi et al., the safety and pharmacokinetic and -dynamic effects of single bolus liposomal bupivacaine injections into the epidural space were evaluated [54]. A bolus of

89 mg, 155 mg, or 266 mg liposomal bupivacaine or bupivacaine HCL 50 mg were injected in 30 volunteers in a double-blinded fashion. There was a clear relationship between the dose of liposomal bupivacaine and bupivacaine plasma concentrations. Even with 266 mg, the peak plasma concentration did not exceed the initial peak concentration in the plain bupivacaine group. The latter group also demonstrated the highest proportion of motor block followed by the 266, 155, and 89 mg liposomal groups. There was absolutely no motor blockade at all in the 89 mg group. It is very interesting to note that even in the liposomal group of 266 mg the motor block was significantly weaker than in the bupivacaine HCL group. Half-lives were similar across the three liposomal groups and were roughly three to four times longer than for the bupivacaine HCL group.

Sensory block characteristics were also tested in this study, using pinprick and cold methods. While the 89 mg group had a sensory loss roughly half the extent of the normal bupivacaine HCl 50 mg group, the 155 mg group had about the same duration. It is only in the 266 mg group that there was a very significant increase in sensory block, roughly 6 times longer than in the plain bupivacaine group. There were no serious adverse events in this study. Injection site pain was reported; however, it was comparable in both the liposomal and the bupivacaine groups. Headaches were also reported and one of the cases was deemed related to the 266 mg dose. There was one accidental intravascular injection also in the 266 mg group. No systemic toxicity was noted; however, orthostatic hypotension was seen, which resolved without further problems.

To the best of our knowledge, no further neuraxial studies have been performed yet. It is our honest opinion that this line of research is very promising, especially in the light of modern-day enhanced recovery programs. Prolonged sensory block without the added disadvantage of catheters and the low chance of motor block could certainly add a new dimension to the use of epidural analgesia. However, catheter placement and withdrawal is a well-known risk for the development of epidural hematomas. The knowledge that the incidence of epidural hematomas could be much higher than previously suspected has been one of the biggest reasons for the diminishing use of thoracic epidurals in contemporary anesthesia and analgesia [55].

Perineural use

Femoral nerve block (FNB)

In 2013, a small study was performed where bilateral single-injection femoral nerve blocks were administered in healthy volunteers injecting different dose to each side in a blinded fashion. The endpoints were maximum voluntary isometric contraction (MVIC) of the quadriceps femoris muscle and tolerance to cutaneous electrical current in the femoral nerve distribution. Although the study demonstrated the ability of liposomal bupivacaine to give prolonged sensory and motor block (>24 h) for the highest doses injected, there was a striking high variability of block magnitude among subjects and an inverse relationship of dose and response [56].

In 2016, a two-part multicenter double-blinded RCT was conducted studying liposomal bupivacaine for femoral nerve block [57]. In the first part, 101 patients undergoing a total knee arthroplasty received an ultrasound-guided femoral nerve block with liposomal bupivacaine (single shot, with the insertion of a femoral nerve catheter for possible backup in case of serious pain). There were three groups getting either 67 mg, 133 mg, or 266 mg of EXPAREL. The primary outcome looked at the AUC for NRS score for pain intensity at rest throughout 72 h (AUC NRS-R_{0-72}). The researchers also took blood samples for pharmacokinetic analyses. There was a three-step rescue approach with the first step being a single IV bolus of hydromorphone 0.5 mg. If there was still need for rescue medication because of severe pain after that first step, an on-demand IV bolus of morphine or hydromorphone was provided, which was administered using a patient-controlled analgesia pump for the remaining 72-h study period. In the third step, the previously inserted “dry femoral catheter” was used to administer bupivacaine HCl 0.125% (1.25 mg/mL) at a rate of 8 mL/h for up to 12 h. If these three steps failed to produce satisfactory pain relief, the patient was excluded from the study and treated for pain according to the institute's protocols.

In the second part of this big multicenter study, 196 patients (none of which took part in the previous study) were enrolled, of whom 99 received a single dose of 266 mg of liposomal bupivacaine

versus a placebo group of 97 patients getting a saline block. The primary objective was to evaluate the efficacy and safety of high dose liposomal bupivacaine. With regard to efficacy, more patients were pain free and required less opioid rescue in the liposomal bupivacaine group compared to the placebo group. The time to first rescue, however, remained the same. It was theorized that not blocking the sciatic and obturator nerves by the femoral nerve block was partially to be blamed for that. Concerning safety, the same number of adverse events was seen in both groups. The incidence of nausea, vomiting, constipation, pyrexia, and pruritus was almost identical in the liposomal and placebo groups, most probably owing to the fact that reduction of opioids alone does not reduce incidence of opioid-related side-effects. There were three falls in the liposomal group, and one of the falls was deemed to be due to the liposomal bupivacaine. Partly due to the inter individual differences when using liposomal bupivacaine in femoral nerve blocks, the occurrence of falls, and the at best modest efficacy, the FDA did not vote for an approval of the use of liposomal bupivacaine in FNB.

Intercostal nerve block

Rice et al. compared liposomal bupivacaine for intraoperative intercostal nerve injections to a high thoracic epidural (HTEA) using bupivacaine HCl [58]. Under thoracoscopic guidance, a five-level posterior intercostal nerve block (PICB) was given to 54 patients undergoing video-assisted thoracoscopic surgery, robotic-assisted thoracoscopic surgery, or thoracotomy. This entailed a surgically performed percutaneous injection of 2 cc liposomal bupivacaine (13.3 mg/mL) using a 22G spinal needle. In the HTEA group ($n = 54$ patients), the epidural catheter was inserted at a level between T4 and T8. Unfortunately, neither anesthesiologists nor outcome observers were blinded.

All patients received multimodal analgesia, and pain scores were almost identical up until POD3. There were no serious adverse events or signs of cardiotoxicity in the liposomal group. No significant differences between groups with respect to cardiac, pulmonary, gastrointestinal, infectious, or neurologic postoperative complications were observed. In both groups, the same amount of postoperative hypotension was seen; however, in the HTEA group, the PCA was discontinued or basal infusion rates were changed. The thoracotomy group receiving HTEA had higher pain scores, probably since in the liposomal group, more multimodal pain management was used in comparison with the HTEA group. An unexpected finding was that the day of discharge in the liposomal group was lowered from a median of 4.5 to 3.5 days, which again could provide a significant advantage for enhanced recovery programs.

Mehran et al. published in 2017 a follow-up of this intercostal study [59]. The group looked at retrospective data covering the years 2010–2015, in which they performed intercostal injections with 266 mg of liposomal bupivacaine. In a propensity matched analysis, they included 612 patients who had received liposomal bupivacaine intercostal injections by the surgeons and compared them to 1119 subjects who had a high thoracic epidural. All patients had pulmonary surgery (minimally invasive or open), received multimodal analgesia, and had also rescue opioid options. Patients undergoing pneumonectomy, esophagectomy, and thoracic wall resection were excluded. In the epidural group, there was a higher rate of postoperative cardiovascular complications, mostly attributable to arrhythmias. These differences disappeared after a new propensity score matching because of an imbalance between minimal invasive techniques and thoracotomy. However, the liposomal group had a shorter hospital LOS (minus one day). No serious adverse events were recorded, and the authors concluded that intercostal injection with liposomal bupivacaine is a reasonable option for the treatment of postoperative thoracic analgesia.

Interscalene block (ISB)

In 2016, a phase III multicenter, randomized, double-blind, placebo-controlled study (NCT02713230) randomized patients randomly (1:1:1) to receive liposomal bupivacaine (133 or 266 mg) administered as an ultrasound-guided single-injection brachial plexus block at least 1 h before surgery, or placebo. The experimental group had significantly reduced pain intensity throughout 48 h post-surgery (- 46% as compared with placebo ($P < 0.0001$), as measured by the AUC of visual analog scale pain intensity scores). Postoperative opioid consumption through 48 h was

reduced significantly by 77% in recipients of liposomal bupivacaine versus placebo ($P < 0.0001$). Though all endpoints were met, there were also several points of criticism. Only 6% of patients had no pain at 24 h, and when testing the sensory block, only 50% of patients demonstrated a change in sensation over the shoulder.

Vandepitte et al. published their findings on the use of liposomal bupivacaine in interscalene blocks in 2017 [60]. In this paper, 52 patients were randomized into 1 of 2 study groups: The liposomal group received 5 mL of 0.25% bupivacaine HCL immediately followed by 10 mL of liposomal bupivacaine (133 mg). The standard bupivacaine group received 15 mL of 0.25% plain bupivacaine HCL, without any addition. Primary outcome was the worst pain scores in the first week. Socioemotional and functional differences were assessed as secondary outcomes including sleep quality, functionality of the surgical arm, and opioid consumption.

Although there was a modest effect on pain scores during the first week in favor of the liposomal bupivacaine group, there were no statistical differences in the secondary outcomes. Because all enrolled patients received multimodal analgesia, differences could be bigger in people having contraindications for certain analgesics. There were no serious adverse events, and the number of adverse events in total was comparable in both groups. Phrenic nerve palsy did not seem to persist even if liposomal bupivacaine was used.

It is also important to know that the functionality of the arm did not differ and that liposomal bupivacaine did not significantly prolong motor block. As such, liposomal bupivacaine does offer an alternative to adjuncts or catheters in an enhanced recovery program.

Field and/or fascial blocks

In 2014, the use of liposomal bupivacaine for TAP block was reported by Feierman et al. in a very small cohort single arm study of 13 patients. Primary outcomes were pain scores using the NRS. Based on the low pain scores and the absence of adverse events, the authors concluded that liposomal bupivacaine was both safe to use and decreased postoperative pain. There was no comparator, the sample size was low, and the use of NRS as primary outcome is debatable [61].

A prospective RCT comparing bilateral subcostal TAP blocks with plain bupivacaine and bilateral subcostal TAP blocks with liposomal bupivacaine in patients undergoing robot-assisted hysterectomies was performed by Hutchins et al. [62] The primary objective was to determine if a TAP with liposomal bupivacaine decreased total opioid use in the first 72 h as compared to a TAP with bupivacaine HCl. Secondary outcomes included pain scores, use of pain medication, length of hospital stay, nausea/vomiting, and patient satisfaction. A total of 60 patients were randomized and allocated 1:1 to each of the groups. Total opioid consumption and PONV were significantly decreased in the liposomal group. The study was not blinded, and total opioid consumption was not measured in a standardized way. The study was not powered for the secondary outcomes.

Hutchins et al. also compared the effect of a subcostal TAP block with liposomal bupivacaine to a TAP block with nonliposomal bupivacaine in 60 patients undergoing donor nephrectomy [63], receiving either 1.3% liposomal bupivacaine and normal saline or 0.25% nonliposomal bupivacaine with adrenaline. The study was observer- and patient-blinded. Primary outcomes were maximal pain scores up to 72 h after surgery. Secondary outcomes included opioid use, incidence of PONV, and LOS. Liposomal bupivacaine significantly reduced pain, opioid consumption, PONV, and also the LOS. However, the study was only partially blinded and compared 266 mg liposomal bupivacaine to 150 mg plain bupivacaine.

In another pilot study, 25 patients undergoing elective minimally invasive colorectal resection received a TAP block and surgical local peritoneal port infiltration with liposomal bupivacaine (20 mL long-acting liposomal bupivacaine, 30 mL 0.25% bupivacaine, 30 mL saline). Patients received a low dose of intraoperative opioids (<150 mcg fentanyl equivalent) and received multimodal analgesia together with the possibility of opioid rescue. The twenty-five patients were matched and compared to a historical control group. Primary outcome was perioperative opioid consumption, pain scores, and LOS. Although the liposomal group had reduced pain and opioid use, this study was not randomized and had only a small sample size [64].

Recent literature and advances

In this part, we summarize recent reviews, meta-analyses, and prospective RCT's published in 2017 and 2018.

Most of this material is surgeon-driven, and the majority of reported papers are focused on looking at alternatives for peripheral nerve blocks.

Shoulder

In a meta-analysis, Yan et al. compared local infiltration analgesia with liposomal bupivacaine in total shoulder arthroplasty (TSA) to interscalene block [65]. The authors included 5 RCTs adding up to 573 patients meeting the inclusion criteria. The meta-analysis indicated that there were no significant differences between both groups in terms of visual analog score (VAS) score at 12 h. However, the sample sizes of the included studies were small, and dosing of local anesthetic was mixed and hardly comparable. The logical conclusion was that more high quality RCTs with better blinding are needed before a definitive conclusion can be taken.

Since the publication of this meta-analysis, two more randomized controlled trials were published studying interscalene nerve blocks with plain bupivacaine versus single shot interscalene blocks with plain bupivacaine in addition to liposomal bupivacaine infiltration for prolonging [66,67]. Both papers showed excellent pain relief, cost reduction, and even less postoperative complications. Again, blinding was only partial. Until sham block catheters and complete blinding with placebo infiltration are used, all evidence on infiltration with liposomal bupivacaine on TSA will be seen in this light.

Namdari et al. looked at the efficacy of liposomal bupivacaine infiltration in prolonging pain relief after TSA in comparison with single shot interscalene blocks with ropivacaine 0.5%. There was no mention of blinding in this small RCT, which included 39 patients in each group. Interestingly, the control group had a statistically relevant morphine reduction, but VAS scores were same in both groups. The study was underpowered, periarticular infiltration (PAI) not standardized, and no recording of morphine consumption beyond the first 24 h was recorded [68].

Weller et al. published a large retrospective study looking at 214 arthroplasties, in which 156 patients had interscalene block and 58 had liposomal bupivacaine injections that were mixed with morphine, ketorolac, and 0.5% bupivacaine with epinephrine. Throughout the first 24 h, pain scores were markedly better in the interscalene group; however, there was no long-term beneficial effect. The incidence of adverse events and also the cost of indwelling catheters (up to 5 times as expensive as a single shot technique) were much higher in the interscalene group [69].

Sun et al. provided a new meta-analysis in 2018, including a total of 7 studies and 707 patients. Their results were similar to the above-mentioned meta-analysis. Although initial pain relief was better in the interscalene block, there were more adverse events, and both the liposomal infiltrative group and the nerve block group had comparable opioid consumption and general overall pain relief [70].

Knee

In a systematic review performed by Liu et al., 8 studies were included that involved a total of 2407 patients, in which a periarticular infiltration of the knee with liposomal bupivacaine was compared to standard FNB treatment [71]. There are several problems with this review as nonrandomized trials were included and as in two studies a continuous FNB was used as opposed to the other studies in which single shot femoral blocks were used. All studies were heterogeneous regarding the type, volume, and concentration of local anesthetic used in the block. The studies were also not comparable with respect to the dosing of liposomal bupivacaine. Only one of the studies mentions proper randomization, and all studies have a high risk for assessment bias. This could account for the rather peculiar conclusion that although the pain scores and opioid consumption were comparable in both groups, a decrease in LOS was observed in the FNB group.

In 2018, Talmo et al. published an observer-blinded study [72], in which FNB was compared with infiltrative liposomal PAI. The anesthesiologist was blinded to the medication used in the FNB as to the infiltrative medication used by the surgeon. All data were collected by the blinded anesthesiologist. Surgeons were blinded until the infiltrative medication was delivered to the operating room during

surgery (liposomal bupivacaine is difficult to blind because of coloring). Two groups with almost 190 patients each either received a sham placebo saline femoral and a liposomal bupivacaine PAI or an FNB with bupivacaine in combination with bupivacaine PAI of the posterior capsule. Pain scores were higher in the first 24 h in the liposomal bupivacaine group than that in the control group. Functional outcomes at 3 months after surgery were slightly better in the liposomal group, while the incidence of adverse events was comparable. This paper is important as it is one of the very few studies (if not the only) reporting a follow-up after one year. It is also significant because of the large sample size. The fact that surgeons were not blinded, the use of a tourniquet, and the decision to use an FNB instead of an ACB may hamper, however, valid conclusions.

Barrington et al. conducted a prospective multicenter three-arm randomized controlled trial, randomizing 119 patients undergoing TKA with spinal anesthesia to receive spinal anesthesia plus PAI with liposomal bupivacaine (40 patients), spinal anesthesia with bupivacaine plus intrathecal morphine (41 patients) and ropivacaine PAI, or spinal anesthesia with bupivacaine (38 patients) and the same PAI ropivacaine as in group 2 [73]. Patients and data-recording research teams were blinded to the identity of the anesthetic. The primary aim of the study was to compare the VAS for postoperative pain and analgesic use during POD1. Secondary endpoints included opioid-related side effects during hospitalization. Group 1 had the best initial VAS scores, but the results of the liposomal group were almost similar to the intrathecal morphine group. The ropivacaine only group (group 3) performed worst. An increased incidence of pruritus in group 2 convinced Barrington et al. to adopt liposomal bupivacaine as an alternative to spinal anesthesia with intrathecal morphine.

Amundson et al. performed a three-arm, nonblinded randomized trial enrolling 165 adults undergoing unilateral primary TKA to receive either a femoral catheter in combination with a sciatic nerve block, a ropivacaine-based PAI, or a liposomal bupivacaine-based PAI [74]. Primary outcome was maximal pain during postoperative day 1 using the NRS scale. Additional outcomes included opioid consumption for POD0 up to POD2. Ropivacaine-based periarticular injections delivered identical pain control comparable as the femoral catheter and single-injection sciatic nerve block. Amundson et al. did not demonstrate an advantage of liposomal bupivacaine over ropivacaine in periarticular injections for TKA.

Pichler et al. performed a retrospective database analysis in which the authors examined a total of 88,830 TKA scheduled during a period from 2013 to 2016 using the Premier Healthcare database (Premier Inc., USA) [75]. Primary outcome was inpatient opioid prescription, extracted from billing and converted to oral morphine equivalents. Secondary outcomes included LOS, total cost, and opioid-related adverse events. In 21.2% (n = 18,817) of the patients, a peripheral nerve block was complemented by infiltrative liposomal bupivacaine, which was not associated with reduction in opioid prescription, LOS, cost, or opioid-related complications.

Lower arm surgery

Only one RCT was found investigating infiltrative liposomal bupivacaine versus conventional peripheral nerve blocks in both elbow and thumb basal joint arthroplasty.

Miller et al. published the very first prospective trial studying infiltrative liposomal bupivacaine for basal thumb arthroplasty (trapeziectomy or in combination with a suspensionplasty) and compared it to two standard analgesic regimen [76]. All enrolled patients received general anesthesia for the surgical procedure and were given either a supraclavicular nerve block with 20 mL of 0.5% bupivacaine HCl, an infiltration with 20 mL of 0.5% bupivacaine at the surgical site, or a pre-incision injection of 10 mL of 0.5% bupivacaine HCl at the surgical site superseded by a post-incision injection of 10 mL of liposomal bupivacaine in the same region.

Seventy-eight patients were enrolled. A total of 27 patients were assigned to group 1, 23 patients to group 2, and 28 patients to group 3. The nerve block group was superior with respect to analgesia scores but only on the first postoperative day (POD1). Average visual analog scale pain scores were highest in group 1 after POD 2 and decreased in all groups consistently thereafter. Total opioid consumption was lowest in group 3. There are several problems with this prospective study: it was not randomized, but the pain treatment was left at the discretion of the surgeon. There was no blinding, no standardized postoperative opioid treatment, and there was self-reporting of opioid consumption of

the enlisted patients, which has significant potential to generate recall bias. Finally, the operative techniques were not standardized.

A small retrospective study by Thompson et al. reported the effects of infiltrative liposomal bupivacaine for total elbow arthroplasty (TEA) and compared it to a standard nerve block [77]. However, several flaws are obvious. First, for some reason, an ISB was commonly used for TEA, although a supraclavicular, infra, or even axillary block would have been a more appropriate choice. Second, of 28 patients receiving an ISB, 36% experienced nerve block-related problems. One of the patients even received an emergency tracheostomy for acute respiratory distress. Although most of the adverse events were minor (including catheter leakage and block failure), these numbers are certainly alarming and suggest a lack of experience with nerve blocks in this center.

Colorectal and abdominal surgery

Felling et al. performed a single-institution trial in which 200 patients scheduled for open elective or minimally invasive colorectal surgery were randomized to either receive an epidural anesthesia at T10-T11 ($N = 87$) or a TAP block with liposomal bupivacaine ($N = 92$) [78]. Their primary endpoint was Numeric Pain Scale scores (NPS) and a previously validated Overall Benefit of Analgesia Score (OBAS). Although NPS was initially better in the epidural group, this seemed to reverse on POD2. All OBAS scores were similar. There was a significant difference in total opioid usage with the epidural group receiving almost twice the amount of the TAP arm (epidural analgesia 206.84 mg vs TAP 98.29 mg, $p < 0.001$). Subgroup analysis showed that NPS was significantly higher in the midline incision group and for open surgery in the epidural group. Although these are impressive results, there are certain shortcomings in this publication. There was no blinding, and only the TAP group received a PCA with morphine, while the epidural group relied on oral morphine and fentanyl in the epidural admixture. The locoregional techniques were performed by several anesthesiologists, which may have had variable levels of expertise, and patients with a history of chronic pain were excluded.

Torgeson [79] piloted a prospective randomized trial and enrolled 87 patients undergoing open and laparoscopic colorectal surgery into an epidural analgesia ($n = 39$) or TAP ($n = 44$) group. This publication looked at enhanced recovery and studied LOS and complications as primary endpoints. LOS was shorter with TAP (postoperative day 3.3 vs 2.8; $p = 0.023$). However, postoperative nausea and vomiting rates were statistically nonsignificantly higher with TAP (14% vs 33%; $p = 0.057$). Urinary retention occurred much more frequently with epidural anesthesia (30% vs 15%; $p = 0.11$). The authors concluded that TAP blocks offer an effective alternative to epidural anesthesia in colorectal surgery.

Stokes et al. published one of the biggest retrospective studies in 2017 comparing outcomes between patients receiving TAP with a 20 mL bilateral injection of 0.25% bupivacaine and TAP blocks with 10 mL liposomal bupivacaine mixed with 10 mL of saline on each side ($n = 303$). Pain scores were similar in both groups; however, there was a significant decrease in opioid intake in the liposomal group. These differences were mostly confined to the laparoscopic and robotic surgery groups. The interpretation of the results is complicated by the heterogeneity of the anesthetists performing the block, the fact that the groups were not matched and that multimodal analgesia was not standardized [80].

Intercostal block

In 2018, Lee et al. completed a single-surgeon study including 79 patients undergoing median sternotomy for coronary revascularization [81]. Study participants were randomized to receive either liposomal bupivacaine or placebo administered as a parasternal nerve block. Postoperative pain was rated with the nonverbal pain scale or numeric rating scale. The results were disappointing, and the authors concluded that there was no opioid-sparing benefit of liposomal bupivacaine when used for a parasternal nerve block. Though the study was adequately blinded, it was, however, underpowered to detect significant differences in secondary endpoints. Liposomal bupivacaine seemed to be associated with only a marginal decrease in postoperative pain levels. Pre-emptive infiltration before surgery may have wielded more convincing results, and more study and bigger trials could shed some new light on the use of EXPAREL in cardiothoracic surgery.

Toxicity and dosage studies

In a small prospective study, 20 cc of liposomal bupivacaine (266 mg) and 30 cc of 0.25% bupivacaine (75 mg) with epinephrine were injected into each knee during 15 bilateral total knee arthroplasties. Plasma concentrations were measured and remained low and well beyond toxic levels during up until the day of discharge. There were no adverse events nor were cardiac or neurological toxicity signs reported. Whilst a total amount of more than 500 mg of liposomal bupivacaine cannot be recommended, this small article does give us insight in resulting plasma concentrations after administration of higher dosage [82].

Conclusion

Extended release local anesthetics and toxin derivatives such as neosaxitoxin could play an important role in the future of regional anesthesia. Only one of these drugs has already been approved by the FDA: liposomal bupivacaine. However, more research is still needed to define its role in enhanced recovery programs and its added value in multimodal analgesia. Infiltrative techniques in combination with single shot regional blocks should be investigated more thoroughly.

HTX-011 looks very promising and its unique double working mechanism could revolutionize the whole concept of infiltration analgesia. SABER-bupivacaine is in a late phase of development, and we are awaiting more clinical trials to evaluate its efficacy compared to the other slow release drugs.

Neosaxitoxin is still in the very early stages of development; however, it is the only drug without addition of bupivacaine and has a different mechanism of action. Because of its low affinity to cardiovascular sodium channels and its low central nervous toxicity it looks more than encouraging.

Practice points

- There is currently only one slow release local anesthetic commercially available: *Liposomal bupivacaine*.
- Liposomal bupivacaine is an extended release formulation of bupivacaine allowing for a slow release of bupivacaine HCl from its liposomes.
- The mechanism could extend the duration of this local anesthetic up to 72 h.
- If used for locoregional techniques in which a fast onset is needed, liposomal bupivacaine should be injected together with plain bupivacaine, in a ratio not more than 50% of the liposomal dosage. Do not mix with other local anesthetics or dilute with hypotonic fluids.
- The FDA has approved liposomal bupivacaine for local infiltration analgesia including TAP) and for interscalene brachial plexus nerve blocks to produce postsurgical regional analgesia.
- The recommended maximum dose of liposomal bupivacaine for local infiltration in adults is 266 mg (20 mL).
- The recommended dose of liposomal bupivacaine for interscalene brachial plexus nerve block in adults is 133 mg (10 mL).
- Common side-effects are nausea, constipation, and vomiting. When used for nerve blocks, hyperpyrexia was also observed.
- Current data suggest that liposomal bupivacaine can play a role in achieving prolonged analgesia in surgical field infiltrations.
- SABER-bupivacaine contains bupivacaine that is encapsulated in a biodegradable depot composition consisting of sucrose acetate isobutyrate. It cannot be used for peripheral nerve block infiltration. Initial studies show a potential for reducing opioid consumption.
- HTX-011 is an experimental drug combining bupivacaine with a low dose of NSAID meloxicam in a bio-degradable polymer carrier. Data on the phase III trials show promise and potential.
- Neosaxitoxin is an experimental drug and derivative of a potent toxin binding at site 1 voltage gated sodium channels.

Research agenda

- More research is needed to study the role of liposomal bupivacaine role in peripheral nerve blocks and its potential to replace adjuncts or perineural catheters.
- More high-quality clinical trials are needed with proper blinding and randomization.
- Studies are required to determine the role of liposomal bupivacaine in single shot epidurals.
- It should be studied whether different plane blocks with liposomal bupivacaine could facilitate enhanced recovery programs.
- SABER-bupivacaine infiltrations in plane blocks could be interesting but have not been investigated yet.
- More research is needed on HTX-011 to display its perineural safety profile. Clinical trials researching the safety of the low dose Meloxicam are mandatory.
- Neosaxitoxin looks very promising but needs more data on its safety and efficacy as well as its comparative efficacy.

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