Liposome Bupivacaine
Pharmacology, Current Uses and Future

Admir Hadzic, MD, Professor of Anesthesiology
Director, NAICE (North American Institute for Continuing Education)
Director, NYSORA (The New York School of Regional Anesthesia)
Consultant, Department of Anesthesiology, Ziekenhuis Oost-Limburg, Genk, Belgium

Goals:
- Pharmacology
- Mechanism of action
- Current clinical uses
- Systemic Toxicity Concerns
- Local tissue and Neurotoxicity
- Liposome Bupivacaine in Nerve Blocks
  - Femoral Nerve Block study
  - Interscalene Block Data
- LB in US-guided soft tissue infiltration
Disclosure

- Research grants: GSK, Baxter, Pacira
- Advisor: GE, Sonosite, BD, B Braun, LifeTech
- Consultant: Pacira Pharmaceuticals
- Royalty income: BBraun Medical
- Co-owner of Avenue-V, LLC

DepoFoam® Structure

Current Clinical use
FDA Approved
Soft tissue infiltration

Local Infiltration into Surgical Site

Local Anesthetics:
Interrupt Pain Transmission
Limitation #1
Duration of action; typically a few hours

Limitation #2
Difficult to re-administer
Original article
Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting

Abstract
Applicable

Results: Long-term efficacy of liposome-bupivacaine was superior to 0.375% bupivacaine HCl administered at a fixed 200mg/m² dose in postoperative patients.

Research design and methods: A randomized, double-blind, placebo-controlled, single-blind study compared liposome bupivacaine to bupivacaine HCl administered via the surgical site, using a single-blind intervention. The primary endpoint was the 72-hour cumulative pain score.

Figure 1: Mean (SEM) cumulative pain score (median 72 hours after surgery) in the bupivacaine group compared to the liposome group. SEM = standard error of the mean.

 ![Graph 1: Mean (SEM) total amount (mg) of opioid medication consumed through 72 hours after surgery (morphine equivalent). Data shown are least-squares geometric means. SEM = standard error of the mean.](image1)


 ![Graph 2: Percentage of patients with ≥1 DRS (defined as generalized pruritus, respiratory depressive, vomiting [no need for anti-emetic medication], or urinary retention during the 72 hours post-surgery] > 1609-15.](image2)

 Postoperative Pain and Length of Stay Lowered by Use of Expander in Immediate, Implant-Based Breast Reconstruction.


 @Author information

 Abstract

 BACKGROUND: Patients undergoing mastectomy and prosthesis-based breast reconstruction have significant acute postoperative pain, which may delay hospital discharge and impact the postoperative recovery period. Liposomal bupivacaine (LBP) is an investigational agent with a novel formulation that allows for prolonged delivery of bupivacaine by passive diffusion in the systemic circulation. However, there are limited data on the effectiveness of LBP in reducing postoperative pain.

 MTHOD: This prospective, nonrandomized, single-center trial of adult patients undergoing mastectomy and immediate implant-based breast reconstruction was conducted. Patients were randomized into one of three groups: a control group receiving bupivacaine alone, a group receiving LBP alone, or a group receiving a combination of bupivacaine and LBP. Pain scores were recorded at baseline, 4, 8, 12, 16, and 24 hours after surgery.

 RESULTS: A total of 49 patients were included in the study. There were no significant differences in baseline characteristics between the groups. The combination group had a significantly lower mean pain score at 24 hours compared to the control group (P < 0.05).

 CONCLUSION: The use of LBP in this group of patients undergoing mastectomy and breast reconstruction was associated with a reduction in postoperative pain compared to the control group, resulting in improved patient satisfaction and reduced duration of hospital stay.

 ![Graph 3: Pain scores for the combination group.](image3)
Marketing Surgical Practice with Exparel

Dr. Max Gomez: New Anesthetic Can Hold Off Pain For Days After Surgery

NEW YORK (CBSNewYork) – Imagine having a knee replacement and be able to walk on the same day with almost no pain and no narcotic pain medication.

Not only is it possible, but as CBS2’s Dr. Max Gomez reported it’s actually safer and less expensive.

Infiltration in TKA Shows Reduced Pain and LOS, Greater Knee Flexion, Higher Satisfaction

Rapid Recovery Pain Pathway for Total Knee Arthroplasty Results in Improved Pain Management, Decreased Length of Stay, and Significant Cost Savings
Plasma Levels after Rx Liposome Bupivacaine

DOI: 10.1016/j.cdi.2013.04.001

REVIEW ARTICLE

Pharmacokinetic Profile of Liposome Bupivacaine Injection Following a Single Administration at the Surgical Site

DebDee Hii - Erol Ozen - Nell Single - William G. Kravitz - Ahmad Hatice

PLASMA LEVEL OF EXPAREL AFTER SOFT TISSUE INJECTION

CNS Toxicity:
2,500 to 4,000 ng/ml
Radiolabeled Liposome Bupivacaine (Exparel)
Signal persisting through 72 hours

Inadvertent IV Injection?
IV INJECTION in dogs

CNS Toxicity:
2,500 to 4,000 ng/ml

3x

IV INJECTION in dogs

CNS Toxicity:
2,500 to 4,000 ng/ml

Inadvertent IV Injection?

Low free bupivacaine exposure
• ~ 50% remains as intact EXPAREL particles
• ~45% Bupivacaine associated with lipid fragments
• ~ 5% Free Bupivacaine
• Free bupivacaine releases slowly from liposomes after IV Injection

Safety and Side Effect Profile of Liposome Bupivacaine (Exparel) in Peripheral Nerve Blocks

Systemic safety profile: Better than Bupivacaine

and myelosuppression are well recognized in bupivacaine therapy. In one study, the incidence of at least one adverse event was 2.5% in the bupivacaine group and 12% in the control group. High-dose intrathecal bupivacaine hydrochloride may cause systemic toxicity, including hypotension, respiratory depression, and death. Inadvertent IV injection of bupivacaine can cause serious systemic toxicity, requiring the immediate administration of resuscitative measures.
>1,000,000 Patient-exposures without LAST

Nerve Blocks Not FDA Approved

Exparel 4 Femoral Nerve Block
- Phase 3 clinical study completed
- 266 mg Exparel in Femoral block in TKA
- Data collection over 72 hours
- Multi-institutional trial, USA-wide

Hadzic et al. 2014 Manuscript currently in review
Exparel in FNB for TKR

184 Patients TKR

92 pts
266 Exparel
92 pts
NaCl 0.9%

All blocks preoperatively through catheter
All patients received GA or Spinal for surgery
VAS scores, Opioids, 20 m walk test, drug-related AE, DRAE

Hadzic A et al. 2015, manuscript in revision

Phase 3 Femoral Nerve Block: NRS-R

Phase 3 Femoral Nerve Block: Proportion of Subjects Able to Complete 20-meter Walk Test
Exparel in ISB for Shoulder Sx

40 Patients
Rotator Cuff Sx

20 pts
Bupivacaine 0.25%

20 pts
Exparel 80 mg

All blocks preoperatively within 30 min of Surgery
All patients received GA for surgery
Onset times, VAS scores, Sleep, Opioids at home

Gadsden J, Hadzic A, Shariat A, Vandepitte C, 2015, in review

Percent VAS ≤ 3 (no to mild) for 40 patients in study of Exparel compared to bupivacaine for post shoulder surgery analgesia
Neurotoxicity of perineural vs intraneural extradural injection of liposomal bupivacaine in the perine model of sciatic nerve block

J. Davanlou, D. Gupta, A. Haddix, A. Majd, F. De Cousey, K. Bhaskar

Introduction
Liposomal bupivacaine is a prolonged-release local anesthetic, the neurotoxicity of which has not yet been determined. We used quantitative histopathologic and immunohistochemical analyses to evaluate the neurotoxic effect of liposomal bupivacaine after perineural and intraneural injection in the sciatic nerve in mice. In this randomized, prospective, blinded trial, 14 effusion-liposomal bupivacaine 0.7% was injected either perineurally or intraneurally. Half of the mice received a control injection of saline. The sciatic nerves were harvested at 4 days after injection. The nerves were processed for histology, immunohistochemistry, and electron microscopy. The results were compared to those of control nerves not exposed to injection. No differences were found between the groups. The neurotoxic effects were assessed using a 4-point scale (1 point for no abnormality, 3 points for severe abnormalities). The sciatic nerves were evaluated for histopathologic abnormalities.

Neurotoxicity
NO Neurotoxicity

Figure 2: Histological analysis of the sciatic nerve. Staining with toluidine blue. Scale bar: 100 µm. (a) Cross section of the sciatic nerve in 4 days after intraneural (extradural) injection of liposomal bupivacaine demonstrating no pathological changes of nerve structure. The outer border of large (red) and small (green) nerve fibres were circumscribed. (b) In large fibres, the inner borders of myelin was circumscribed (yellow). Using morphometric software, several parameters were assessed: (1) percentage of fascicle area per nerve; (2) number and density of nerve fibres; (3) percentage of large fibres per nerve; (4) nerve fibre diameter; (5) axon diameter; and (6) myelin width.
Table 2: Number of immunopositive cells 14 days after intraneural (intrathecocurcular) and periureal injections of liposomal bupivacaine and intraneural (intrathecocurcular) injection of saline. Values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Total number of immunopositive cells</th>
<th>Lymphocytes per mm²</th>
<th>Macrophages per mm²</th>
<th>Granulocytes per mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraneural liposomal bupivacaine</td>
<td>29 (46)</td>
<td>13 (2)</td>
<td>7 (1)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Intraneural saline</td>
<td>9 (6)</td>
<td>8 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.012</td>
<td>0.538</td>
<td>0.011</td>
<td>0.008</td>
</tr>
<tr>
<td>p-value†</td>
<td>0.598</td>
<td>0.185</td>
<td>0.063</td>
<td>0.199</td>
</tr>
</tbody>
</table>

*Comparison between intraneural liposomal bupivacaine and intrathecocurcular saline.
†Comparison between periureal liposomal bupivacaine and intrathecocurcular saline.
Exparel in Addition to Bupivacaine

Pharmacokinetics in Femoral Block

Hadzic et al, 2015, in press
Other Uses?

TAP Block?
Infiltration for hemorrhoidectomy (Standard anal block)

Infiltration for abdominal surgery (TAP infiltration)

= SURGICAL SITE
Hemorrhoidectomy
abdominal wall

Take Home
• Possible Revolution in Acute Pain Rx
• Will catheters be replaced - NO
• Best consider as an additive to LA?
• More RCT needed
• Dose-ranging studies needed
• Best sites for injection?
• Mixture with other LAs studies needed
• Future - Exciting