Bupivacaine Versus Liposomal Bupivacaine for Postoperative Pain Control after Augmentation Mammoplasty: A Prospective, Randomized, Double-Blind Trial

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Abstract

Background: The long-acting preparation of bupivacaine, liposomal bupivacaine (EXPAREL, Pacira Pharmaceuticals, Inc., San Diego, CA), was approved by the Food and Drug Administration in October 2011 and has been shown to be safe in breast augmentation. It remains to be established if liposomal bupivacaine provides superior pain control in this setting.

Objectives: This study compares liposomal bupivacaine and standard bupivacaine for postoperative pain control.

Methods: Thirty-four patients undergoing cosmetic primary subpectoral breast augmentation were recruited. Each patient was treated with bupivacaine in one implant pocket and liposomal bupivacaine in the other prior to closure in a randomized fashion. Both patient and surgeon were blinded. A brief pain inventory was administered by telephone every 12 h up to 72 h postoperatively.

Results: Liposomal bupivacaine demonstrated a statistically significantly lower pain score at the 12, 36, and 48 h time points in the worst pain category, at the 24, 36, 48, and 60 h time points in the least pain category, at the 12, 24, 36, 48, 60, and 72 h time points in the average pain category, and at the 24, 48, and 72 h time points in the pain rated at the time of the survey. These differences, however, were small, ranging from 0.08 to 0.98 using a 10-point pain scale. When asked if the additional charge for the liposomal bupivacaine would have been worth the benefit, 70% of the patients surveyed said "no."

Conclusions: Although there is a statistically significant decrease in postoperative pain with the use of liposomal bupivacaine, this may not translate to an appreciable clinical benefit that justifies the additional cost.

Level of Evidence: 3

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Augmentation mammoplasty is the second most common cosmetic surgery performed in the United States, with 286,694 cases performed in 2014.1 Patients experience a variable amount of postoperative discomfort, with the mainstay of pain management including oral narcotics. Given the extensive side effect profile of narcotic pain medication,
including nausea, vomiting, constipation, respiratory depression, and dependence, it is unsurprising that plastic surgeons continue to utilize a variety of techniques to minimize postoperative discomfort and narcotic use. Multiple studies indicate a reduction in postoperative pain with the instillation of the local anesthetic bupivacaine into the implant pocket.\(^7\,^6\)

In keeping with this literature, our current practice is to instill bupivacaine into each implant pocket just prior to closure. In October 2011, Pacira Pharmaceuticals, Inc. (San Diego, CA) received Food and Drug Administration approval for a long-acting bupivacaine utilizing liposome technology. This liposomal bupivacaine product has successfully suppressed postoperative pain in bunionectomy and hemorrhoidectomy surgeries with a half-life of 34.1 and 23.8 h, respectively.\(^7\,^8\)

Two industry-funded studies of liposomal bupivacaine used in augmentation mammoplasty have recently been published in the plastic surgery literature. The first was a two-year observational safety study.\(^9\) This determined there was no compromise of implant integrity, changes in sensation, or otherwise abnormal findings associated with the use of liposomal bupivacaine. The second study compared two sets of patients, one set receiving liposomal bupivacaine in each pocket and the other set receiving standard bupivacaine in each pocket. This showed a trend toward less pain in the liposomal bupivacaine group, but the study was terminated early and did not reach statistical significance.\(^10\) There is no published study comparing the products in the same patient, allowing each patient to serve as their own control.

This prospective, randomized, double-blind trial compares postoperative pain scores of each breast after submuscular augmentation when using bupivacaine in one pocket and liposomal bupivacaine in the other. The study was designed to evaluate postoperative pain control of each of the products up to 72 h postoperatively. The secondary outcome is to determine whether the additional cost is justifiable (bupivacaine costs $1.15 per 20 cc of product vs liposomal bupivacaine, which costs $285 per 20 cc of product).

**METHODS**

**Study Design**

After obtaining approval from the Institutional Review Board at Riverside Methodist Hospital (Columbus, OH), a prospective, randomized, double-blind study was conducted on 34 patients who underwent primary submuscular augmentation mammoplasty from October 2012 to March 2013. Our power analysis indicated that 25 subjects were necessary to achieve an expected power level >80%. This was calculated using the Power and Sample Size program from the Department of Biostatistics, Vanderbilt University School of Medicine (Nashville, TN).\(^11\) This was based on a beta value of 0.8 and a clinically significant difference in pain scores on a scale of 0-10 to be two points with a standard deviation of one. All patients satisfied the inclusion criteria of hypomastia. Each enrolled patient provided informed consent for the study and the surgical procedure. Exclusion criteria included any concomitant surgical procedure, significant breast ptosis, constricted breast deformity, previous chest wall irradiation, previous breast surgery, known allergy to bupivacaine or liposomal bupivacaine, current use of antiplatelet or anticoagulation therapy, and significant medical comorbidities.

Each patient received 10 mL of 0.5% bupivacaine with 1:200,000 epinephrine in one breast implant pocket as a control. The contralateral side was treated with the study drug, liposomal bupivacaine. A computer-generated randomized list (Microsoft Excel, Microsoft Corp., Redmond, WA) was created that specified which breast pocket would be treated with the liposomal bupivacaine according to the patient’s assigned study number. This list was maintained by the circulating nurse, who helped the scrub nurse or technician to prepare the vials and label them as right and left. The syringes were covered with tape to prevent identification by the surgeon, as the liposomal bupivacaine has a characteristic cloudy appearance. After the study was completed this list was made available to the data analysis team. All operations were performed by the senior author (Dr Vasko) and two of her partners at the Riverside Outpatient Surgical Center (Columbus, OH). All operating surgeons are board certified by the American Board of Plastic Surgery.

Beginning at 12 h postoperatively and at an interval of 12 h for a total of 72 h, a brief pain inventory using a 0-10 scale for each breast was collected by phone interview. The phone interview was conducted by the authors of the article (Drs Nadeau, Saraswat, and Vasko) and the same individual called the patient for each time period. The brief pain inventory, a validated pain survey tool, queried patients regarding their pain in each breast over the previous 12 h.\(^12\) Patients were asked to rate their pain on average, at its worst, at its least, and at the time of the survey. Data was collected out to 72 h, or two half-lives of liposomal bupivacaine versus 26.7 half-lives of bupivacaine. At the completion of data collection (May 2013), the results were unblended and ranged from 1-6 months postoperatively for all patients. The patients were contacted by the senior author (Dr Vasko) and asked if the pain relief difference would have been worth an additional $250 charge. Twenty-three of the 34 patients could be queried in this manner.

**Surgical Technique**

Under general anesthesia, a standard submuscular breast implant pocket was dissected through an inframammary...
incision. Hemostasis was achieved, the pocket was irrigated, and the implants were inserted. Just prior to closure, 100 mg of bupivacaine was instilled into one breast pocket and 130 mg of liposomal bupivacaine into the other breast pocket according to the syringes, labeled right and left. The incisions were then closed in layers and dressed with surgical tape.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2013 for PC (Microsoft Corp, Redmond, WA). The t test was applied to compare mean values for each pain reporting category (worst, least, average, and at survey time) at each time interval between the groups. Statistical significance was defined as p < 0.05.

RESULTS

All 34 of the patients were women. Thirty-one patients completed the study (three could not be reached for postoperative surveys despite multiple attempts and were withdrawn). The average age was 33 years (range 21-55 years). The average BMI was 21.9 kg/m² (range 15.3-32.3 kg/m²). Three pairs of saline implants were used, while the rest were silicone gel implants. The average gel implant size was 365.3 mL (range 250-550 mL). Other patient demographics are characterized in Table 1.

The average pain score for each category (worst, least, average, and at time of survey) was higher on the bupivacaine side than the liposomal bupivacaine side at every time point. The difference in pain scores ranged from 0.08 (the difference in the least pain category at 72 h postoperatively) to 0.98 (the difference in the worst pain category at 12 h postoperatively). Statistically significant differences in pain scores between the right and left breast were noted in the category of worst pain over the previous 12 h at 12, 24, 36, and 48 h, with average differences of 0.98, 0.58, 0.81, and 0.87, respectively, and corresponding p-values of 0.002, 0.061, 0.006, and 0.001, respectively. In the least pain category over the previous 12 h, statistically significant average differences were noted at 24, 36, 48, and 60 h, with average differences of 0.56, 0.61, 0.58, and 0.48, respectively, and corresponding p-values of 0.022, 0.013, 0.006, and 0.015, respectively. The rating of the average pain over the preceding 12 h was statistically significant at every time point, with average differences in time order of 0.53, 0.50, 0.73, 0.66, 0.50, and 0.39, and corresponding p-values of 0.025, 0.046, 0.005, 0.002, 0.007, and 0.026, respectively. In the final category, pain rating at the time of the survey, statistically significant average pain score differences occurred at 24, 48, and 72 h postoperatively, with the average differences being 0.58, 0.58, and 0.37, respectively, and corresponding p-values of 0.040, 0.011 and 0.008, respectively. The p-values and complete data are shown in Table 2. From these p-values, it can be said with 95% confidence that liposomal bupivacaine is more effective at relieving pain than bupivacaine for a period of 72 h.

Figures 1-4 demonstrate the pain assessment curves for the bupivacaine and liposomal bupivacaine for each of the categories of the brief pain inventory. In each category, the bupivacaine curve is above the liposomal bupivacaine curve, indicating a higher pain score at each time point. The lines are nearly parallel for each time point and in every category.

Additionally, at the completion of data analysis (May 2013), the senior author (Dr Vasko) called the patients and asked whether the benefit they received from the study drug (now unblinded) would be worth a $250 upcharge. Twenty-three of 34 (67.6%) patients were able to be reached. Of those who were reached, 16 (69.6%) said that the pain relief they received was not worth the additional cost to them.

All patients had satisfactory aesthetic outcomes according to surgeon assessments and patient verbalizations during routine follow-ups. Outcomes are routinely assessed by the senior surgeon (Dr Vasko) at each follow-up visit, beginning at 6 weeks (6 weeks, 3 months, 6 months, and 1 year). There were no revisions. There were no complications.

DISCUSSION

Our standard protocol is to instill bupivacaine in the implant pocket to assist with early postoperative pain control. We were hopeful that liposomal bupivacaine would provide a longer duration of local anesthesia, improving postoperative pain control. We chose to use patients as their own control to increase inter-patient reliability for pain scores. Given the

### Table 1. Patient Demographics (n = 34) and Implant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 (11.3)</td>
<td>21-55</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.9 (4)</td>
<td>15.3-32.3</td>
</tr>
<tr>
<td>Gel implant size (mL)</td>
<td>365.3 (77.15)</td>
<td>250-550</td>
</tr>
<tr>
<td>Saline fill volume (cc)</td>
<td>450</td>
<td>250-550</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>31 (91.2)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Implant type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicone</td>
<td>31 (91.2)</td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>3 (8.8)</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.
pharmacokinetics of liposomal bupivacaine, we predicted that the postoperative pain scores would be similar in the early time period and diverge at the 12-24 h point as the standard bupivacaine was metabolized, completing its duration of action, and the liposomal bupivacaine continued to act.

Table 2. Average Differences in Pain Scores for Each Category and Time Point and Their p-Values

<table>
<thead>
<tr>
<th>Postoperative Time (hours)</th>
<th>Worst</th>
<th>p-Value</th>
<th>Least</th>
<th>p-Value</th>
<th>Average</th>
<th>p-Value</th>
<th>At Time</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.98</td>
<td>0.002</td>
<td>0.21</td>
<td>0.221</td>
<td>0.53</td>
<td>0.025</td>
<td>0.48</td>
<td>0.077</td>
</tr>
<tr>
<td>24</td>
<td>0.58</td>
<td>0.061</td>
<td>0.56</td>
<td>0.022</td>
<td>0.50</td>
<td>0.046</td>
<td>0.58</td>
<td>0.040</td>
</tr>
<tr>
<td>36</td>
<td>0.81</td>
<td>0.006</td>
<td>0.61</td>
<td>0.013</td>
<td>0.73</td>
<td>0.005</td>
<td>0.39</td>
<td>0.076</td>
</tr>
<tr>
<td>48</td>
<td>0.87</td>
<td>0.001</td>
<td>0.58</td>
<td>0.006</td>
<td>0.66</td>
<td>0.002</td>
<td>0.58</td>
<td>0.011</td>
</tr>
<tr>
<td>60</td>
<td>0.50</td>
<td>0.020</td>
<td>0.48</td>
<td>0.015</td>
<td>0.50</td>
<td>0.007</td>
<td>0.08</td>
<td>0.367</td>
</tr>
<tr>
<td>72</td>
<td>0.34</td>
<td>0.075</td>
<td>0.08</td>
<td>0.310</td>
<td>0.39</td>
<td>0.026</td>
<td>0.37</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Figure 1. Patient-reported worst pain score over the previous 12 h of liposomal bupivacaine treated breast and bupivacaine treated breast for each survey time point.

Figure 2. Patient-reported least pain score over the previous 12 h of liposomal bupivacaine treated breast and bupivacaine treated breast for each survey time point.

Figure 3. Patient-reported average pain score over the previous 12 h of liposomal bupivacaine treated breast and bupivacaine treated breast for each survey time point.

Figure 4. Pain score of liposomal bupivacaine treated breast and bupivacaine treated breast at the time the survey was conducted for each survey time point.
Interestingly, each of the data points collected (least, most, and average pain over the previous 12 h) showed a lower pain score on the liposomal bupivacaine side that was maintained over the 72 h. The curves did not diverge as expected, and the difference in pain scores, although statistically significant, was small and likely clinically insignificant. Furthermore, with a consistent and maintained difference in pain scores, one wonders whether the dosing was truly equivalent. Alternatively, given the work of Pacik and Nelson, it is possible that the continued benefit from the long-acting liposomal bupivacaine contributed to a lower than expected pain score on the contralateral side. Pacik and Nelson found that, with the use of indwelling bupivacaine catheters, a unilateral bolus of local anesthetic lessened the pain in both breasts.

The vastly different pharmacokinetics of these products, as well as the relatively small experience with liposomal bupivacaine, are inherent limitations in this study. The chosen dosing for this study was based upon three components: previous study design comparing these medications, recommended dosing based upon the manufacturer’s guidelines, and practicality of maintaining equivalent volumes to conduct a blinded study, as well as likely usage patterns for liposomal bupivacaine given its packaging and short shelf life once opened. Equivalent dosing between bupivacaine and liposomal bupivacaine has not been well established in the literature and is a major limitation of this study.

Another potential limitation of our study is the use of the patient as their own control. While this limits differences in patient-to-patient variation in postoperative pain, it is imperfect in that patients may experience asymmetric breast pain after bilateral augmentation. Given that the breast treated with liposomal bupivacaine was chosen as the less painful side in every case, this limitation was likely of minor significance. The study is also limited by its small sample size.

It may be that the liposomal bupivacaine would be more effective if injected into the pectoralis major muscle and breast parenchyma. It is worth noting that bupivacaine instilled in the implant pocket showed significant pain reduction when compared to no drug in the implant pocket in previous publications, indicating that instillation rather than injection is a valid delivery method. Given the liposomal component of this new preparation, requiring metabolism for delivery, injection would be an interesting follow-up study as we begin to determine the appropriate uses and considerations for this new preparation of local anesthetic.

CONCLUSIONS

Given that the pain score was consistently lower on the liposomal bupivacaine side, it can be concluded that this drug did offer some benefit. However, it did not appear to offer appreciably more benefit beyond the usual duration of action of standard bupivacaine. After conducting this study, liposomal bupivacaine does not appear to provide additional benefit when compared to standard bupivacaine instilled in the implant pocket. However, there are several confounding factors that require further investigation, including establishing dosing equivalency for bupivacaine and liposomal bupivacaine as well as the possibility that the continued action of liposomal bupivacaine had a beneficial effect on the contralateral implant pocket. This study should be repeated with varying doses of both medications as well as with study arms that include patients receiving the same medication in both implant pockets to further elucidate the possible role of this costly medication in postoperative augmentation mammoplasty pain control.

Given the data presented here, and particularly the sentiments of the patients regarding cost, it is our assertion that the additional cost of liposomal bupivacaine is unjustified for this particular use. This is corroborated by 70% of our patients, who did not think the benefit they received justified the cost when polled at the conclusion of the study.

Disclosures

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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REFERENCES


