Intra-operative Use of Liposomal Bupivacaine and its Effect on Post-operative Pain in Breast Augmentation

Steven A. Clark[1,2,*], John T. Lindsey[1], Sara A. Gaines[1], Dietric L. Hennings[1] and Karen D. Jordan[1]

[1]Tulane University School of Medicine, New Orleans, LA 70112, USA and [2]Clark Plastic & Hand Surgery, 6850 TPC Dr., Suite 116, McKinney, TX 75070, USA

Abstract: ***Introduction*:** Liposomal bupivacaine (Exparel©, Pacira Pharmaceuticals, Inc., Parsippany, NJ) is a local anesthetic, approved by the FDA for introduction into surgical sites for post-operative analgesia in October of 2011. Pharmaceutical advertisements claim that Exparel© relieves pain up to 72 hours, and that patients may require less pain medication during their recovery. Currently there is limited data with few non-industry funded, controlled studies concerning its efficacy.

***Methods*:** A single center, prospective open-label study was conducted over a year period comparing bupivacaine with epinephrine to liposomal bupivacaine, in regards to patient post-operative pain scores and narcotic usage on patients undergoing breast augmentation. All studied patients had breast augmentation with identical surgical technique. Studied patients had sub-muscularly placed saline implants performed by a single surgeon at one surgical facility.

***Results*:** Thirty-two patients of 40 successfully participated in the study (11 in the control group and 21 in the experimental group). Patients who received liposomal bupivacaine reported lower pain scores which was statistically significant at p=0.02, however patients who received liposomal bupivacaine required more narcotics at 72 hours than patients in the control group. Statistical analysis showed a trend that patients who received liposomal bupivacaine used less hydrocodone post-operatively (p=0.05).

***Conclusions*:** Patients who received liposomal bupivacaine reported improved pain scores compared to bupivacaine with epinephrine. The improved pain score was minimal, and did not translate into a significantly lower usage of narcotics post-operatively. Our data suggests that that liposomal bupivacaine only provides improved pain relief for 48 hours and not the advertised 72 hours.

Key Words: Post-operative pain, Pain score, Non-industry funded.

1. INTRODUCTION

A substantial amount of plastic surgery occurs in outpatient settings such that patients are discharged home the same day of the procedure [1]. Though the medical community is becoming more sensitive to patients' post-operative pain, some literature suggests that post-operative pain is still under-managed, with up to 85% of post-surgical patients experiencing moderate or severe pain during their recovery [2]. With the knowledge that effective post-surgical pain management leads to greater patient satisfaction, and that reduced opioid usage leads to fewer opioid-related side effects, surgeons who perform an abundance of outpatient procedures are always searching for a new product or method to improve their patients' post-operative pain [3,4].

Liposomal bupivacaine, Exparel©, a product of Pacira Pharmaceuticals, Inc. (Parsippany, NJ) is an aqueous suspension of multivesicular liposomes that contain bupivacaine. The encapsulated bupivacaine delivers the anesthetic in a time-released fashion, as the lipid membrane slowly dissipates [5]. It is a fairly new local anesthetic, as it was only approved by the FDA for introduction into surgical sites for post-operative analgesia in October of 2011. At this time, there is limited data with few non-industry funded, controlled studies concerning its efficacy. Pharmaceutical company advertisements claim the bupivacaine liposome can control pain up to 72 hours, and that patients may require less pain medication during their recovery [6]. Recent studies have shown that liposomal bupivacaine achieves longer lasting post-operative pain control for procedures such as bunionectomy and hemorrhoidectomy; however, these studies were compared to placebo [7,8]. Orthopedic literature comparing bupivacaine liposome to bupivacaine with epinephrine in regards to patients' post-operative pain scores has shown improved post-operative pain management with liposomal bupivacaine over a four-day period [9]. It has also been documented to decrease post-operative opioid use when compared to a patient controlled analgesia (PCA) pump in open abdominal colorectal surgeries [10].

There has been significant interest in liposomal bupivacaine's potential role in the cosmetic outpatient surgical setting. It has been the anecdotal experience

*Address correspondence to this author at Clark Plastic & Hand Surgery, 6850 TPC Dr., Suite 116, McKinney, TX 75070, USA; Tel: (214) 850-5624; E-mail: StevenClarkMD@ClarkPlastics.com

of the senior author (J.L.) that patients receiving intra-operative liposomal bupivacaine have improved post-operative pain control compared to patients who receive more traditional post-operative pain regimens.

In this study, we wish to objectively compare liposomal bupivacaine's post-operative pain control to 0.25% bupivacaine with epinephrine in patients undergoing breast augmentation. By examining patients' perceived pain and the amount of narcotics required by patients during the immediate post-operative period, we can objectively determine if the administration of liposomal bupivacaine significantly improves post-operative pain compared to 0.25% bupivacaine with epinephrine. It is our hypothesis that intra-operative administration of liposomal bupivacaine will reduce post-operative pain medication requirement and provide patients with superior pain control than standard 0.25% bupivacaine with epinephrine.

2. MATERIALS AND METHODS

We conducted a single center, prospective open-label study over a one-year period. All patients receiving breast augmentation from August of 2013 to August 2014 were selected for this study. Forty patients agreed to participate in the study; however, eight patients were excluded due to inadequate self-recording. Patients were informed of the claims made about the manufacturer of Exparel© (Pacira Pharmaceuticals, Inc., Parsippany, NJ), the current data, and the increased price of the product compared to 0.25% bupivacaine with epinephrine. After being educated by the senior author (J.L.), patients elected to be a part of the either control group (Group 1) which received bupivacaine with epinephrine or the experimental group (Group 2) which received liposomal bupivacaine.

Twenty-one patients received liposomal bupivacaine and 11 patients received 25% bupivacaine with epinephrine. All patients had breast augmentation with identical surgical technique with sub-muscularly placed saline implants performed by a single surgeon (J.L.) at one surgical facility. Both peri-areolar and infra-mammary fold incisions were used for implant placements. All patients in Group 1 (n=21) received the maximum dose (20 mg) of liposomal bupivacaine. This dosage was diluted to a total volume of 60 ml with normal saline. Patients in Group 2 (n=11) received 40 ml of 0.25% bupivacaine with epinephrine.

Prior to the start of surgery both groups received bilateral rib blocks (T2-T6). Rib blocks were performed in the mid-axillary line by infiltration of 2 ml of anesthetic under each rib using a 0.5 inch 25-gauge needle. Both groups also received infiltration of 10cc of the respective anesthetic solutions into the parenchyma of each breast mound. Patients in Group 2 had 10cc of the remaining dilute solution of liposomal bupivacaine placed into each dissected pocket prior to wound closure.

Post-operatively patients received intravenous Demerol for pain control in varying increments determined by the Post-Anesthesia Care Unit (PACU) nursing staff. Patients' post-operative pain was measured and recorded using a 10-point Visual Analog Pain Scale (VAS). Acceptable patient pain was defined as having a VAS score at less than or equal to four. The amount of narcotics required to keep patients comfortable was recorded, and all post-operative pain recordings were collected by a total of seven PACU nurses. Upon discharge from the surgical facility all patients were given a chart to monitor their use of pain medication. Patients were asked to record each time they required any medication to relieve post-operative pain. In addition to recording the time of administration, patients were also asked to record the dosage of the medication taken and their pre-administration pain level based on the VAS.

Post-operative pain was again evaluated at the patients' first office visit. Patients were seen five to seven days after their procedure. At this office visit, investigators collected patients' medication administration records.

Statistical significance was determined with an analysis of variance model (NOVA) using two factors without replication.

3. RESULTS

A total of 40 patients participated in the study. Eight patients were excluded from the study due to failure to adequately record data. Of the 32 patients who successfully recorded their data, 11 patients were in the control group and 21 patients were in the experimental (liposomal bupivacaine) group.

The average age and BMI in the control group was 30.4 years and 21.87, respectively. The average implant fill volume in the control group was 372.3 ml. One patient in the control group was identified as a smoker preoperatively. One other patient in the control group had a co-morbidity, diabetes mellitus, at the time of surgery. The average age and BMI in the experi-

mental group were 32.6 years and 22.6, respectively. The average implant fill volume in the experimental group was 364.2 ml. Two patients in the experimental group were identified as smokers preoperatively. Another patient had a co-morbidity, hypertension, at the time of surgery. Of note is that all patients identified as smokers preoperatively were required to stop smoking a minimum of 2 weeks before their surgery date. With respect to co-morbidities, patient age and implant fill volumes between the two groups, there were no statistically significant differences.

Patients' post-operative pain scores (PS) in the control group had average scores of 7.3, 6.6 and 5.7 for post-operative days 1, 2, and 3, respectively. Patients' post-operative pain scores (PS) in the experimental group had average scores of 6.5, 5.9 and 5.4 for post-operative days 1, 2, and 3, respectively. Statistical analysis determined that the lower PS reported by patients who received liposomal bupivacaine was statistically significant at p=0.02.

On average, patients in the control group required 49 mg of Demerol in the PACU. Patients in the liposomal bupivacaine group required an average of 17 mg of Demerol in the PACU. Appropriate statistical analysis could not be performed comparing Demerol dosage between the groups due to the small sample size and discrepancies with anesthesia operative narcotic administration.

Patients in the control group required 36.3 mg, 33.2 mg, and 19.9 mg of daily hydrocodone for post-operative days 1, 2, and 3, respectively. Patients in the experimental group required 28.2 mg, 26.8 mg, and 20.9 mg of daily hydrocodone for post-operative days 1, 2, and 3, respectively. Statistical analysis showed p=0.05, suggesting that there is a trend that patients who received liposomal bupivacaine used less hydrocodone post-operatively.

4. DISCUSSION

Liposomal bupivacaine (Exparel©) has become very popular in the surgical community in a very short time. A review of its efficacy is of interest due to the paucity of studies that were either absent pharmaceutical funding or which had a control group. Of interest was also whether each study included multiple procedures or multiple surgeons (Table **1**).

Morales *et al*. published a study in 2013 looking at liposomal bupivacaine use in abdominoplasty that was non-pharmaceutical industry supported. This study suggested that patients experienced reduced post-operative pain, required less postoperative narcotic medication, and resumed earlier ambulation with normal activity. This study failed, however, to have a true control group for comparison. This study also only included 10 patients who averaged seven different procedures performed in the study setting [11].

Smoot *et al*. published a study specifically looking at breast augmentation, which concluded that liposomal bupivacaine was associated with lower pain scores when compared with bupivacaine HCl [12]. This was a randomized, multicenter, double-blind study, where patients received either DepoFoam bupivacaine or bupivacaine HCl into the implant pockets at the conclusion of surgery. The primary efficacy measure was cumulative pain score with activity through 72 hours post-operatively. This study is very similar to our own research and has the advantage of being a randomized double-blinded study. Issues we had with this research is that the study was financially supported by Pacira and it was multi-centered therefore increasing the likelihood of non-standard surgical procedure or drug administration. This study also had authors who received financial support from Pacira.

Bergese *et al*. presented a meta-analysis including 1459 patients that noted that liposome bupivacaine appeared to be a potentially useful therapeutic option for prolonged reduction of postsurgical pain in soft tissue and orthopedic surgeries [13]. This analysis pooled nine studies to compare the efficacy of liposomal bupivacaine, bupivacaine HCl or placebo through 72 hours after surgery. Upon review of this study however, five different procedures: hernia repair, total knee arthroplasty, hemorrhoidectomy, breast augmentation, or bunionectomy were included with 10 different injection sites. Of those included procedures, patients in the breast augmentation group showed no statistical difference between liposomal bupivacaine and bupivacaine. This study had one author who received support from Pacira Pharmaceuticals Inc.

Our study is one of the few non-pharmaceutical company supported studies to objectively compare post-operative pain levels of patients who received liposomal bupivacaine versus standard bupivacaine (Table **1**).

Of note is that in only one of our three areas of interest, pain score as addressed by the VAS, did we find statistical significance. Looking more closely at the

Table 1: Study Comparisons

	Industry Funded/Paid Author	Controlled Study	Single Procedure	Single Surgeon
Current Study	**(-)**	**(+)**	**(+)**	**(+)**
Morales *et al.*	(-)	(-)	(-)	(-)
Smoot *et al.*	(+)	(+)	(+)	(-)
Cohen *et al.*	(+)	(+)	(+)	(+)
Bramlett *et al.*	(+)	(+)	(+)	(-)
Gorfine *et al.*	(+)	(-)	(+)	(-)
Apseloft *et al.*	(+)	(+)	(+)	(+)
Dasta *et al.*	(+)	(+)	(-)	(-)

differences in pain scores, it should be noted that each post-operative day the experimental group had less pain; however, this was only by a margin of 0.62 on the VAS (Figure **1**). When counseling patients pre-operatively and when determining if liposomal bupivacaine is indicated, surgeons should be aware that breast augmentation patients who received liposomal bupivacaine had reduced pain scores of less than a full point on the VAS. Patients should be educated by their physician and know of the cost-to-pain-relief ratio that liposomal bupivacaine has been shown to produce.

The amount of Demerol that patients required in the PACU could not be accurately analyzed. This was a design flaw with the study. In addition to having a low-powered study, there was too much variance between different anesthesiologists and their patterns of intra-operative pain management. Some anesthesiologists routinely gave patients large doses of Demerol before the completion of the procedure, which resulted in their patients requiring less narcotics in the PACU. Narcotic administration should have been standardized for all patients participating in the study towards the final minutes of the procedure to avoid this problem.

The manufacturers of Exparel© claim that it has improved pain relief for up to 3 days [6]. It is for this reason that our study measured the amount of narcotics used until post-operative day three.

Liposomal bupivacaine is chemically related to an amide local anesthetic as a homologue (mepivacaine) and is also related to lidocaine. Drug liposomes are suspended in a 0.9% sodium chloride solution with each vial containing bupivacaine at a concentration of 13.3 mg/ml. After bupivacaine, has been released from liposomal bupivacaine and is absorbed systemically, bupivacaine distribution is expected to be the same as for normal bupivacaine HCl solution.

It has recently come to the attention of the surgical community by the FDA that those claims of 72 hours of

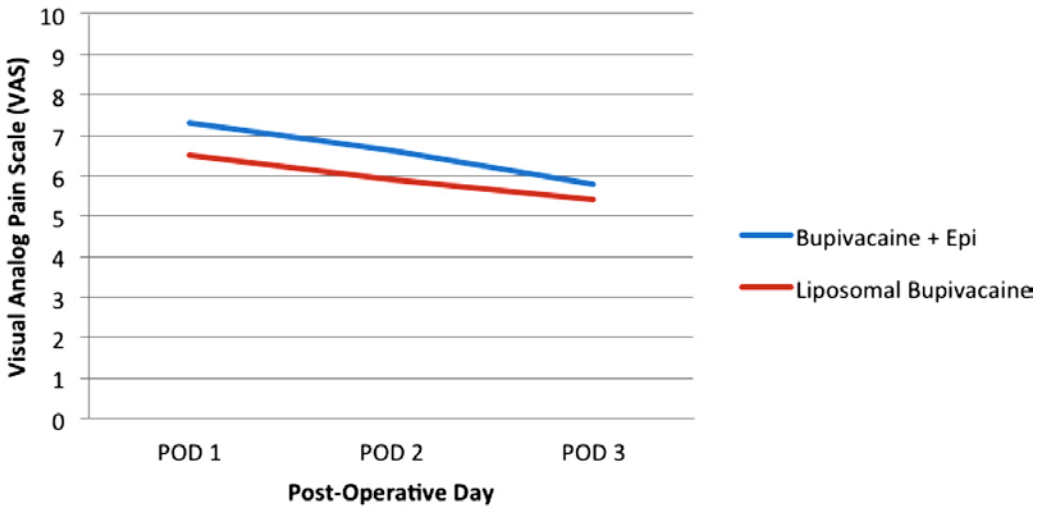

Figure 1: Post-operative pain levels based on visual analog score collected daily at home by the patients.

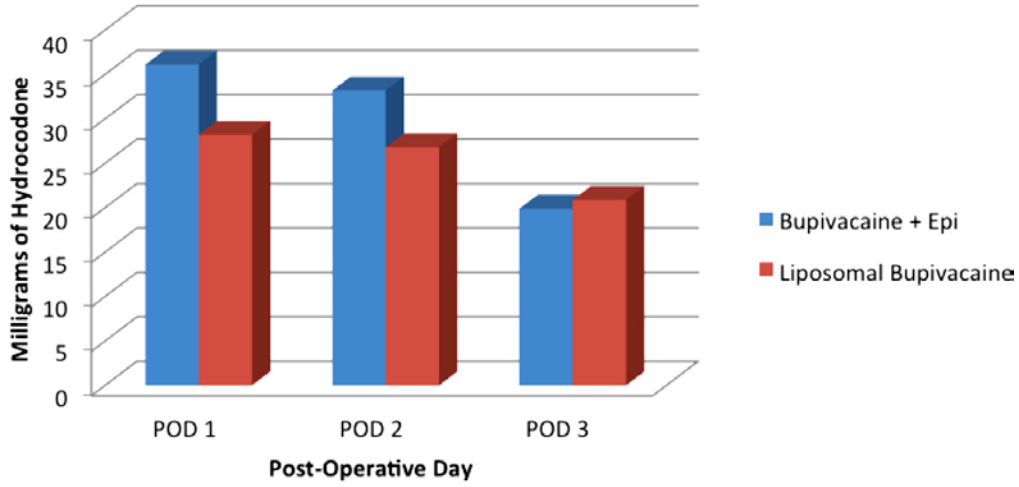

Figure 2: Average daily dosage of hydrocodone required for pain relief.

pain relief may be inflated as Pacira was forced to run full page correction ads in all journals in which Exparel© was advertised [14]. Our data supports the FDA's concerns. When comparing the amount of narcotics our patients required, both the control group and the group receiving liposomal bupivacaine had very similar narcotic usage (Figure **2**) with liposomal bupivacaine patients actually requiring slightly more post-operative narcotics than control patients at 72 hours.

5. CONCLUSION

Our data showed that patients who received liposomal bupivacaine reported improved VAS pain scores compared to bupivacaine with epinephrine. The improved VAS pain score was minimal, and did not translate into a significantly lower usage of narcotics post-operatively. In regards to breast augmentation, liposomal bupivacaine usage will make patients feel slightly better, but they will likely require the same amount of narcotics as if they had only received bupivacaine. The authors also agree with the FDA that Exparel© only provides improved pain relief for 48 hours and not the advertised 72 hours of relief, as our data showed that narcotic use increased on post-operative day 3 in Group 2. Ultimately it is the physician's choice as to which local anesthetic to use. It is important to have non-pharmaceutically funded studies to provide an unbiased assessment of each new drug. When considering the use of liposomal bupivacaine, physicians will now have more data to present to their patients concerning realistic post-operative pain expectations following breast augmentation.

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