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Original Article

Liposomal bupivacaine in total hip arthroplasty: Do the results justify the cost?

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ABSTRACT

Introduction: Liposomal bupivacaine has a paucity of data regarding narcotic requirements and hospital length of stay in comparison to other peri-articular injections, specifically in the total hip arthroplasty (THA) population.
Methods: 69 patients who underwent THA by a single surgeon were divided into two cohorts over a 3 year period in this retrospective study comparing narcotic requirements, hospital length of stay and cost. The study group (n = 29) received liposomal bupivacaine whereas a matched control group (n = 40) received a pharmacy-mixed cocktail in peri-articular structures. Statistical and clinical differences were reported in this unfunded study.
Results: No difference was found in hospital length of stay [2.9 days in the study group (range 1–14) versus 3.1 days (range 1–11) in the control group, p = 0.101], however, the study group required less narcotics per day [22.6 mg (range 5–53.3) versus 29 mg (range 6.7–80.8) in the control group, p = 0.045]. The clinical difference between cohorts averaged less than one pill per day of hospitalization. The cost per patient of the local injection was more than 11 times greater in the liposomal bupivacaine group.
Conclusion: Liposomal bupivacaine demonstrated a statistical improvement in narcotic requirements but not in hospital length of stay in comparison to a control group. The effects of liposomal bupivacaine on narcotic requirements and hospital length of stay may not justify its use in total hip arthroplasty patients given the substantial cost of these injections and the minimal clinical difference in outcomes compared to a more cost-effective injection.
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1. Introduction

Multimodal pain management in total joint arthroplasty is considered the standard of care in peri-operative pain control, with numerous studies showing improved outcomes and decreased complications.[1–5] It is well accepted that patients require adequate pain management following total joint arthroplasty to enable active participation in physical therapy and to mobilize sufficiently for safe discharge from the hospital. Opiates may be a potential hindrance to physical therapy, despite their utility as a pain modulator. Indeed the optimal pain modifier would provide peri-operative analgesia and avoid neuromuscular blockade as well as opiate-like side effects such as fatigue, constipation, nausea and dependence. Intraoperative injections of various formulations have been used for decades in an effort to decrease post-operative opiate use.

Parvataneni et al. conducted a prospective study in which they demonstrated the benefits of local peri-articular injection and its role in a multi-modal pain management strategy in total joint replacements.[6] In an effort to improve the delivery of injections administered by the surgeon at the time of the operation, a novel medication was developed using liposomal technology to allow time-released degradation of a given anesthetic. The use of this injectable time-released suspension in total hip arthroplasty (THA) is largely extrapolated from the literature on its use in total knee arthroplasty (TKA).[7,8] To our knowledge, there is only one controlled cohort study comparing standard peri-articular injections to liposomal bupivacaine in the THA population.

To add to the current body of evidence regarding peri-articular injections, we ask the following questions: (1) How does the average hospital length of stay compare between two cohorts of patients with the first receiving a pharmacy mixed peri-articular cocktail of multiple medications and the second receiving an

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injection of liposomal bupivacaine in the peri-articular tissues?; (2) What are the differences in narcotic requirements during the inpatient hospitalization between the same two groups?; (3) Is there any synergy with pre-operative epidural as part of a multimodal pain pathway within the two groups?; and (4) What is the cost difference between liposomal bupivacaine and the peri-articular injection cocktail?

2. Materials and methods

Following Institutional Review Board approval, the inpatient electronic medical records for all patients who underwent THA by a senior arthroplasty surgeon from July 2011 through August 2014 were queried. Out of 158 total hip replacements performed, the largest subgroup of patients having received a common prosthesis totaled 74. Five patients were excluded for having incomplete medical records required to answer our study questions, leaving 69 patients for inclusion in the data (Table 1). Exclusion criteria were subjects younger than 18 or older than 90 years of age, subjects who had surgery outside our study period, subjects who were undergoing revision THA, and subjects with incomplete medical records.

A peri-articular injection cocktail was used up until a discrete point in time in November 2013. After this transition point, the senior surgeon began using liposomal bupivacaine, Exparel® (Pacira Pharmaceuticals Parsippany, NJ) as a peri-articular injection prior to THA closure. Thus, 2 distinct cohorts of patients were generated for comparison. Cohort 1 is our control group consisting of those patients who received a peri-articular injection comprised of: 30 mg ketorolac, 10 mg morphine and 50cc of 0.5% marcaine without epinephrine. The injection was administered in 20cc aliquots targeting the anterior capsule, iliopsoas tendon and insertion site before reduction of the prosthesis. This was followed by injecting the abductors, fascia lata, gluteus maximus and its insertion, the posterior joint capsule, short external rotators and joint synovium after final reduction of the components. Cohort 2 is the study group consisting of those patients who received peri-articular injections of liposomal bupivacaine targeting the same anatomic structures as outlines above.

Approved by the Food and Drug Administration (FDA) in October 2011, liposomal bupivacaine has grown in popularity in the total joint community.[9] Exparel® is an injectable product in which bupivacaine is encapsulated in multivesicular lipid molecules.[10] These lipid molecules degrade and reorganize slowly allowing time-released bupivacaine in contrast to the rapid metabolism of raw bupivacaine delivered in bolus form. This injection was administered using the consensus technique guidance provided by the manufacturer and recently published in 2015 by Joshi et al.[11]

Data on length of stay (in days) and narcotic usage (in morphine equivalence) was obtained from the electronic medical record. All narcotic medications from the inpatient hospital stay were included in data collection and were comprised of: oxycodone immediate release 5 mg per tablet (recorded in milligrams), oxycodone continuous release 10 mg per tablet (recorded in milligrams), hydrocodone/acetaminophen 5/325 mg per tablet (recorded in tablets given), oxycodone/acetaminophen 5/325 mg per tablet (recorded in tablets given), fentanyl (recorded in micrograms per intravenous dose), morphine (recorded in milligrams per intravenous dose), and hydromorphone (recorded in milligrams per intravenous dose).

With all medication in dosage units, they were translated into morphine equivalence using equianalgesic dose ratios in accordance with our facility inpatient pharmacy as follows:

Fentanyl (IM/IV) – 0.1 mg
Hydromorphone (PO) – 7.5 mg
Hydromorphone (IM/IV) – 1.5 mg
Morphine (PO) – 30 mg
Morphine (IM/IV) – 10 mg
Oxycodone (PO) – 20 mg

In order to obtain the parenteral morphine equivalent, the total dose of each opioid given was divided by the equianalgesic dose for that opioid, which was then multiplied by the equianalgesic dose for the new opioid and route. Opioid per day of hospitalization was obtained by dividing the total narcotic used by the hospital length of stay (in days) resulting in an average use per day (parenteral morphine mg/day).

The cost of the peri-articular injection cocktail was obtained referencing the cost to the facility. This was compared to the contracted price of liposomal bupivacaine by our facility. Contracted prices for all medications were obtained from the pharmacy acquisitions department. All prices are in U.S. dollars and represent a single patient's dose.

Table 1
Demographic Variables.

	Cohort 1 (Control) n = 40	Cohort 2 (Exparel®) n = 29	P VALUE
Age (Avg in yrs)	57.2 Range 26–76 95% CI 53.6–60.8	57 Range 34–78 95% CI 52.8–61.2	0.932
Sex			
Male	29 (72.5%)	25 (86%)	0.727
Female	11 (27.5%)	4 (14%)	
Laterality			
Right	18 (45%)	16 (55%)	0.058
Left	22 (55%)	13 (45%)	
ASA Score			
I	1 (2.5%)	1 (3.4%)	N/A
II	25 (62.5%)	21 (72.4%)	
III	14 (35%)	7 (24.1%)	
GETA			
With Epidural	36 (90%)	20 (69%)	0.342
Without Epidural	4 (10%)	9 (31%)	

ASA: American Society of Anesthesiologists physical classification score as determined by anesthesia.
GETA: General Endotracheal Anesthesia.

2.1. Statistics

All statistical analysis was conducted using SPSS (version 12; SPSS, Chicago, Illinois). The Shapiro-Wilk test of normality was used on all continuous data. All continuous data, except for age, was found to be non-normally distributed. Analysis of Variance (ANOVA) was used to evaluate differences in age among our treatment groups. The Mann-Whitney test was used to evaluate all other differences in continuous data. Pearson chi-square and Fisher's exact tests were used to evaluate differences in proportions among categorical data. Statistical significance was defined as $p < 0.05$.

3. Results

The average length of stay was 3.1 days (range 1–11, 95% CI 2.48–3.72) in the control group versus 2.9 days (range 1–14, 95% CI 1.94–3.86) in the study group ($p = 0.101$). The average narcotic requirement for the hospitalization in the control group was 96.6 mg (range 17.5–390, 95% CI 69.0–124.2) compared to 64.7 mg (range 10–300, 95% CI 39.5–89.8) in the study group ($p = 0.036$). Additionally, the average narcotic requirement per day demonstrated statistical significance between the groups with the control group using 29.0 mg per day (range 6.7–80.8, 95% CI 24.4–33.6), while the study group used 22.6 mg (range 5–53.5, 95% CI 18.4–26.8) per day ($p = 0.045$). These data can be found in Table 2. The data on combined effects of epidural and local injection can be seen in Table 3. These data demonstrate the study group receiving both the liposomal bupivacaine injection and an epidural regional block used the least amount of narcotics (49.3 mg, [range 12.5–111.3, 95% CI 38.6–60.1]), while the sub-group who received neither liposomal bupivacaine nor an epidural used the most narcotics per hospitalization (103 mg [range 20–323.2, 95% CI −131.4 to 337.4]). The cost to the facility of our combined pre-mixed medication cocktail per dose given to a single patient in cohort 1 was $27. The purchase price to the hospital for a single patient's dose of Exparel® was $315.

Table 3
Average Narcotic Requirement for Hospitalization (in IV milligram morphine equivalent).

	Cohort 1 (Control)	Cohort 2 (Exparel)
With Epidural	95.9 Range 17.5–389.5 95% CI 68.8–123	49.3 Range 12.5–111.3 95% CI 38.6–60.1
Without Epidural	103 Range 20–323.2 95% CI −131.4 to 337.4	98.7 Range 10–300.2 95% CI 14–183.4

4. Discussion

Multiple studies support the concept of multi-modal pain management in patients undergoing total joint arthroplasty.[1–5] With more than 350,000 total hip replacements performed in the U.S. each year and an ever increasing emphasis on multi-modal pain pathways as part of the perioperative care of these patients, local injections at the time of surgery remain a powerful tool at the disposal of the surgeon and their use is only likely to increase in the future. In this study, we compared the hospital length of stay and narcotic requirements between our study population who received peri-articular liposomal bupivacaine (Exparel®) and a control group who received a less expensive pharmacy-mixed medication cocktail. Additionally, we sought to demonstrate any synergy between injections in the two cohorts and a pre-operative epidural as part of a multi-modal pain pathway. Finally, we demonstrated the institutional cost difference between these two options for local injection.

We found that in terms of hospital length of stay, there was no statistical difference between our control group and the study group with our study group leaving the hospital on average at post operation day 2.9 and the control group leaving on day 3.1. These findings differ from a previous study performed by Domb et al. in which the authors found a statistical improvement in hospital length of stay in the liposomal bupivacaine group in comparison to a control group.[12] To our knowledge, this is the only previously published controlled study evaluating the efficacy of liposomal bupivacaine specifically in total hip arthroplasty as it compares to a more generic peri-articular injection. Published in 2014, and funded by Pacira Pharmaceuticals Inc., the findings of Domb demonstrated a hospital length of stay of 1.93 days in the Exparel® group compared to 2.47 in their control group. Our study did not duplicate this finding.

Our results regarding the use of narcotics proved to be interesting. While the study group used an average of 64.7 mg of morphine equivalence per hospitalization, the control group used significantly more (96.6 mg). However, the clinical difference would be the equivalent of 21.3 mg of oxycodone, or just over four pills. The difference in narcotic usage averaged per day was also statistically significant with our study group using an average of 22.6 mg compared to 29.01 mg used per day in the control group. Again, while on the surface this does represent statistical significance, clinically this is the equivalent of 4.28 mg of oxycodone. This would amount to a difference of less than one pill per day. These findings of statistical difference are similar to previous studies on liposomal bupivacaine. Barrington et al., in their 2013 review on the literature supporting the use of liposomal bupivacaine as an adjunct in pain management, highlighted a randomized, multicenter, double blinded trial in which patients undergoing bunionectomy were found to have decreased opioid

Table 2
Hospital Length of stay and Narcotic Requirements.

	Cohort 1 (Control) n = 40	Cohort 2 (Exparel®) n = 29	P Value
Avg Length of Stay (Days)	3.1	2.9	0.101
Range	1–11	1–14	
95% Confidence Interval	2.48–3.72	1.94–3.86	
Narcotic Requirement Avg (in IV milligrams morphine equivalent)	96.6	64.7	0.036
Range	17.5–390	10–300	
95% Confidence Interval	69.1–124.2	39.5–89.8	
Avg per day	29.01	22.59	0.045
Range	6.7–80.8	5–53.3	
95% Confidence Interval	24.4–33.6	18.4–26.8	

use with nearly 7% of patients receiving Exparel® not requiring post-operative narcotics at 24 h following surgery.[13] The authors also noted 10 separate randomized, double blinded studies that demonstrated reduced opioid use and greater patient satisfaction with post-operative anesthesia. As previously mentioned, there is also literature to support the use of liposomal bupivacaine in total knee arthroplasty. Surdam et al. in 2014 performed a randomized prospective study in which liposomal bupivacaine provided similar pain relief to a femoral nerve block without the associated compromise in early rehabilitation that can often be associated with femoral nerve blocks.[14] Bramlett et al. also studied liposomal bupivacaine in total knee arthroplasty patients and noted statistically improved analgesia after surgery for patients receiving Exparel® over non-liposomal bupivacaine.[7]

Most recently, Yu et al. reported their findings of liposomal bupivacaine in the total hip population. In this study, the authors compared two cohorts of patients. The first received no Exparel®, whereas the second received the peri-articular liposomal bupivacaine. Both cohorts received peri-incisional injections of local analgesia. However, an important difference in the methods exists in that our study compares two patients groups both receiving peri-articular injections while the Yu study only had one of their groups receiving peri-articular medication. Yu et al. found liposomal bupivacaine provided improved pain relief and faster time to milestones in post-operative rehabilitation.[15] These findings would be expected as only the Exparel® group was given anesthetic in the peri-articular tissues. We feel our methods are a more relevant comparison in regards to methodology.

Our study also evaluated the synergistic relationship between our use of two different injections and a pre-operative epidural. As can be seen in Table 3, the patients in the control group who did not receive an epidural required the most narcotics during the hospitalization (103 mg). Conversely, the patients in the study group who also received an epidural required the least amount of narcotic (49.3 mg). This is a difference of 53.7 mg or the equivalent of 35.8 mg of oxycodone (over 7 pills). There does appear to be a graduated synergy with combined forms of analgesia which is what we would expect.

As a final point of consideration in the use of local injections, we determined the hospital price of the two forms of peri-articular injection as they compare between our cohorts. Our prices were contracted as part of one of the largest hospital acquisitions departments nation-wide and would likely prove to be externally valid to the majority of treatment centers in the United States. The Exparel® injection cost over 11 times that of the pharmacy mixed cocktail. The mark-up of these medications in the form of the price per injection as billed to the patient was not determined.

There are several limitations to our study. First, given its retrospective nature, we are unable to state definitively the efficacy of Exparel® in its use on peri-operative pain management. The numbers of patients in our study are smaller than the larger retrospective study performed by Yu et al.[15] However, we do feel that our methods provide a more powerful gauge in assessing the clinical effects of liposomal bupivacaine as it compares to other injections used in the same locations whereas in the Yu study, peri-articular liposomal bupivacaine was compared to a cohort which received no peri-articular injection whatsoever. This may not be as reliable a gauge in the efficacy of these injections. Our findings also represent those of a single surgeon and institution and may not be generalizable to all facilities. Despite this, we feel that by comparing two cohorts all operated on by a single surgeon we have decreased the variations in surgeon technique that may account for differences in the efficacy of the injection. There is also an intermittent use of visual analogue scores (VAS) as an assessment of the efficacy of liposomal bupivacaine in the literature. Some studies, including the previously mentioned industry sponsored study,[12] report VAS in their data. We found that the previous literature has not standardized the use of the VAS in terms of its use at rest or with activity, before or after physical therapy, etc. Additionally, we found that when analyzing our data retrospectively, the medical records were not consistent and standardized amongst our patient cohorts such that the VAS data could be used as an endpoint for our particular study. For these reasons we have not included the VAS in our findings. Prospective study design would better enable standardized measurements and recording of the VAS.

5. Conclusion

Our data indicate that while there was no statistical difference in hospital length of stay, there was a statistical difference in narcotic requirement and average narcotic requirement per day, with the study group requiring fewer narcotics. The clinical relevance of this statistical difference is questionable. Additionally, we found that the sub-group of patients given liposomal bupivacaine in conjunction with a pre-operative epidural required less total narcotics than did any other sub-group. Indeed, there appears to be a stratification of narcotic requirement whereby those patients who had neither epidural nor liposomal bupivacaine required more narcotics than the sub-groups who had one, the other or both. Finally, Exparel® costs over 11 times that of our generic cocktail and given the debatable clinical significance of its outcomes in our patient population, its role in peri-operative pain management should be scrutinized in our cost-conscious practices. Future prospective, randomized, blinded studies are necessary to truly show the statistical and clinical utility of this product in total hip arthroplasty patients, while taking into consideration the cost effectiveness.

Conflict of interest

The authors have none to declare.

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