



Periarticular liposomal bupivacaine injection decreases length of stay, pain scores, and opioid usage after total knee arthroplasty when compared to femoral nerve block

Xander Parisky¹, Brian Gilmer², Jennifer Harkins¹, Michael Karch²

ABSTRACT

Purpose and Hypothesis: Evolving trends in total knee arthroplasty (TKA) have placed increased emphasis on shorter inpatient length of stay and minimizing opioid utilization while increasing patient satisfaction. Liposomal bupivacaine (LB) is a novel adjunct for post-operative pain management following TKA. Literature regarding the efficacy of LB versus other modalities has been conflicting. It appears the method of administration of LB may be linked to outcomes. We hypothesized a multimodal post-operative analgesia protocol including systematic infiltration of LB would lead to shorter duration of stay, decreased inpatient opioid utilization, and improved pain scores compared to a similar protocol employing femoral nerve block (FNB) after TKA.

Methods: We performed a retrospective review of data after initiation of a pain management protocol including LB and compared it to a similar control population using a multimodal analgesia protocol including FNB. LB administration was standardized with 60 mL infusion of 20 mL Exparel (Pacira Pharmaceuticals) expanded with 40 mL of a mixture including 0.25% bupivacaine, epinephrine, ketorolac, and normal saline divided into three steps of systematic infiltration. Primary outcome measures were length of stay (days), inpatient opiate usage (morphine equivalent dose [MED]), and day of discharge visual analog score (VAS) scores. Secondary outcome measures were 90 day readmission, complications (including infection and nerve dysfunction), and revision or secondary surgery. **Results:** The LB group consisted of 52 consecutive TKA patients while the FNB group consisted of 71 similar consecutive patients. LB group length of stay was significantly less in the LB group (1.1 days \pm 0.08) than in the FNB group (2.8 days \pm 0.18) ($P < 0.001$). Inpatient opioid usage MED was significantly less in the LB group (79.22 mg \pm 132.14) than in the FNB group (158.27 mg \pm 67.15) ($P < 0.001$). Mean day of discharge VAS scores was significantly decreased in the LB group (2.44 vs. 0.88) ($P < 0.001$). There were two infections in the LB group and none in the FNB group. **Conclusions:** We conclude the systematic application of LB is superior to FNB for post-operative analgesia after TKA and facilitates earlier discharge with less inpatient opioid utilization and improved patient comfort with no significant increase in complications or readmission.

KEY WORDS: Femoral nerve block, knee arthroplasty, liposomal bupivacaine, perioperative pain management

¹Department of Clinical Research, Mammoth Hospital, Mammoth Lakes, CA 93546, USA, ²Department of Orthopedics and Sports Medicine, Mammoth Orthopedic Institute, Mammoth Lakes, CA 93546, USA

Address for correspondence:

Brian Gilmer, Department of Orthopedics and Sports Medicine, Mammoth Orthopedic Institute, 85 Sierra Park Road Mammoth Lakes, CA 93546, USA. E-mail: bbgilmer@gmail.com

Received: December 14, 2016

Accepted: January 12, 2017

Published: March 01, 2017

INTRODUCTION

Recent trends in total knee arthroplasty (TKA) have emphasized improving patient-derived outcome measures and decreasing inpatient length of stay while diminishing reliance on opiates for post-operative pain control. The negative clinical and economic impacts of opioid analgesic programs have been well established [1]. Femoral nerve block (FNB) is a well-established post-operative treatment modality but carries risks and may prevent early rehabilitation due to lack of muscular control in the immediate post-operative period [2,3].

Liposomal bupivacaine (LB) is a novel treatment option for perioperative pain management after knee arthroplasty. The idea of encapsulating local anesthetics within carrier molecules to increase their residence time at the site of action has generated great interest in perioperative pain control. After successful reports from other fields, the orthopedic literature has been mixed regarding its efficacy compared to other common pain treatment modalities in patients undergoing TKA [4-11]. Some authors have suggested that efficacy of LB may be related to the technique of periarticular injection of LB [12].

We conducted a retrospective review of sequential patients undergoing TKA after initiation of a multimodal perioperative analgesia program utilizing intraoperative LB according to a specific injection protocol during TKA. We hypothesized the injection with LB would result in decreased length of stay inpatient opioid usage, and improved day of discharge visual analog scores (VAS) scores and compared to FNB. In addition, we describe a standardized and reproducible method for injecting LB during TKA.

MATERIALS AND METHODS

This study was examined and received institutional board approval for a retrospective review of records.

Pre-hoc power analysis was conducted and identified a sample size of 50 patients per group. Data were collected on all consecutive patients undergoing TKA between March 2014 and February 2015 by a single surgeon (MK) utilizing an experimental protocol including intraoperative administration of LB group. A corresponding control group of patients who underwent TKA between September 2011 and February 2014 utilizing a perioperative pain control protocol employing FNB group was evaluated for comparison.

Intraoperative Protocols

All patients were given a low dose spinal consisting of marcaine 0.75% (1.2 cc) ± 20 mcg fentanyl and a propofol infusion which was titrated to sedation.

Patients in the FNB group received a FNB utilizing 30 mL of 0.5% bupivacaine with epinephrine. FNB was administered preoperatively with of a nerve stimulator. A standardized inpatient post-operative pain regimen included toradol 30 mg intravenous (IV) every 6 h for 24 h, morphine sulfate IV 2-4 mg every 2 h as needed for breakthrough pain, oxycontin 10 mg post-operative every 12 h, and percocet 10/325 mg post-operative every 4 h as needed.

Patients in the LB protocol received the LB 266 mg in 20 mL (EXPAREL, Pacira Pharmaceuticals, Inc. San Diego, CA) in mixture according to manufacturer instructions with 25 mL of 0.25% bupivacaine, 1 mL of toradol 30 mg, 0.5 mL of epinephrine 1:1000, and 13.5 mL of preservative free NaCl for a total volume of 60 mL. Patients also received a standard inpatient post-operative pain regimen which included: Toradol 15 mg IV × 1 dose 6 h after surgery, celebrex 200 mg post-operative every day as an inpatient or ibuprofen 800 mg post-operative three times a day depending on insurance approval of celebrex, and norco 10/325 mg post-operative every 6 h as needed.

LB was systematically administered in accordance with the guidelines as described by the Best Infiltration Practices Working Group (Guideline Central - <http://eguideline.guidelinecentral.com/i/319830-hip-and-knee-arthroplasty-orthopedic-surgery>) utilizing a 22-gauge needle in three steps.

The volume of administration by site was 30 mL for the posterior capsule, cruciates, collateral ligaments, and extensor mechanism before component implantation (Step 1), followed by 15 mL for the deep dermal tissue planes emphasizing the distributions of the femoral, saphenous, and posterior tibial nerve distributions (Step 2) and 15 mL in the subcutaneous tissues and skin in preparation for closure (Step 3).

Data Collection

Retrospective chart review was then performed. Inclusion criteria were all consecutive primary TKA. Exclusion criteria were documented allergy to local anesthetics or opioids, active worker's compensation claim, conversion from spinal to general anesthetic, or failure to perform the described protocol.

Based on the above criteria two patients were excluded because of failure to perform a posterior capsular injection before placements of implants. Therefore, 123 patients were entered into final analysis.

The primary outcome measure was length of stay (days). Length of stay was defined as date of discharge based on review of records. Other primary outcome measures were opioid utilization as converted to morphine equivalent dose (MED) (mg) during inpatient stay (<http://globalrph.com/opioidonv.html>), and VAS on date of discharge.

Secondary outcome measures were complications including block-related complications (paresthesias or persistent motor blockade), falls, infection, 90-day readmission, and revision surgery.

Data Processing

Pre-hoc power analysis was performed for the primary outcome measure based on preliminary review and confirmed sample size of 50 patients per group. Statistical analysis was performed to compare both groups for demographic data, primary and secondary outcome measures using Microsoft Excel (Microsoft Corp., Bellevue, WA). Gender was compared by use of a Chi-square test. Age was compared by use of two-tailed *t*-test. Unpaired *t*-test was utilized to compare length of stay, opioid utilization, and VAS score.

RESULTS

Demographics

In the LB group 25/52 (48%) of patients were male versus 37/71 (52%) in the FNB group. Average age of patients in the LB group was 60.4 years versus 61.24 in the FNB group. Groups were statistically similar in regards to age and gender [Table 1].

Length of Stay

In regards to the primary outcome measure the mean (±SD [standard deviation]) length of stay was significantly

Table 1: Patient demographics are provided for each group

Patient variables	Standard protocol <i>n</i> =71 (%)	LB <i>n</i> =52 (%)
Age (years)	61.2±2.4	60.4±2.9
Gender		
Male	37 (52)	25 (48)
Female	34 (48)	27 (52)

LB: Liposomal bupivacaine

less in the LB group (1.1 days ± 0.08) than in the FNB group (2.8 days ± 0.18) (*P* < 0.001). Figure 1 maximum length of stay was 2 for the LB group and 6 for the FNB group. 1.6% of patients in the FNB group were discharged within 23 h compared to 86% of patients in the LB group.

Opioid Utilization

In regards to opioid utilization the mean (±SD) MED was significantly less in the LB group (79.22 mg ± 132.14) than in the FNB group (158.27 mg ± 67.15) (*P* < 0.001) [Figure 2].

Patient Reported Pain

In regards to patient reported pain scale (VAS) for FNB was 2.44 as recorded on the day of discharge. The average VAS for the LB group was 0.88 representing a statistically significant decrease in visual pain analog scales on the day of discharge between the two groups (*P* < 0.001).

No adverse affects or complications were seen as a result of using Exparel in the post-operative period. Two patients had persistent paresthesias after FNB which resolved at 2 week follow-up. There were 0 infections in the FNB group and 2 (2.2%) in the LB group. There were two reoperations in the LB group, one for removal of symptomatic cement fragment and one for removal of symptomatic suture, in the LB group and none in the FNB group. There were no readmissions in the 90 day period for either group.

Notably, one patient who underwent LB but who was excluded from the study due to failure to perform a posterior capsular injection before component implantation had a return to the emergency department within 24 h of discharge and was treated with a single dose of IV and an increase of oral outpatient opioids but was not admitted.

DISCUSSION

Presentation of unpublished data by Emerson and Barrington demonstrated highly favorable results for the use of LB in injection for TKA, which led to early enthusiasm for expanding its clinical use. The first published report by Broome and Burnikel also suggested that LB is safe and compares favorably to FNB after TKA [12]. However, all of these authors disclosed financial relationships with the manufacturer [8].

White *et al.* performed a retrospective cohort study and found no improvement between LB and controls for pain scores in the first 48 h after surgery but noted increased use of adjunctive

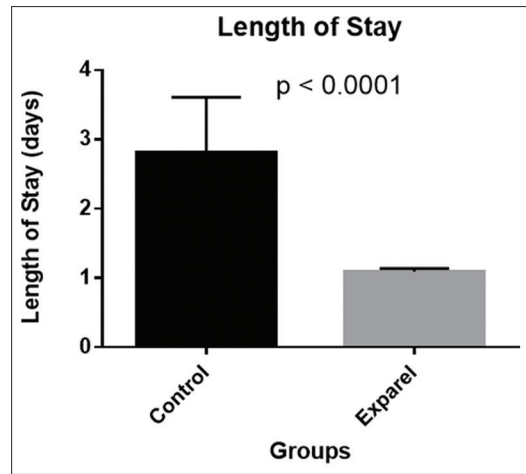


Figure 1: Length of stay. Inpatient length of stay is represented for both groups. Brackets represent standard deviation. *P*-value calculated by unpaired *t*-test

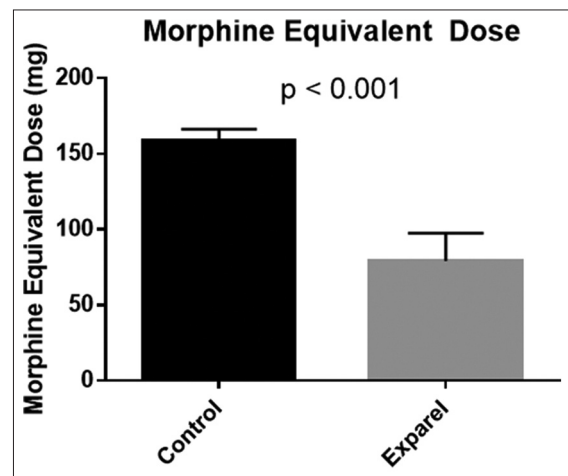


Figure 2: Inpatient opioid utilization. Inpatient opioid utilization is represented for both groups as morphine equivalent dose (mg). Brackets represent standard deviation. *P*-value calculated by unpaired *t*-test

analgesic requirements in the control group [13]. A study by Bagsby *et al.* concluded the LB was more expensive and no more efficacious than pericapsular injection with ropivacaine, and furthermore, raised concerns about a higher reoperation rate with LB [4]. In this study, injection was performed at the conclusion of the procedure and the specific details regarding the injection were not reported.

These inconsistencies in the literature have led to the hypothesis that the injection method or the specific cocktail of LB may be critical to obtaining optimal results [14,15].

We sought to determine the efficacy of LB based on a strict protocol for mixing and administration of LB.

Our primary finding was the inpatient length of stay, inpatient opioid utilization, and patient perceived pain scores on day of discharge were all significantly less after initiation of a

perioperative protocol utilizing LB without a significant increase in complications, reoperation, return to emergency department or 90-day readmission rate.

Interestingly, one patient who did not have posterior capsular injection in our series did require a return to the emergency department for uncontrolled pain. This highlights the importance of infiltrating all structures. It is possible, in the study by Bagsby *et al.*, the posterior capsule was not injected since administration was performed at the conclusion of the procedure after implantation of components [4].

There are several limitations to this study which include the retrospective nature and the fact that different protocols for injection procedure and dose were not examined.

Furthermore, there is concern the efficacy of LB may not extend beyond 24 has claimed by the drug manufacturer [4]. Our study does not address this concern because the time to discharge was short (1.1 days) and early discharge may hide increased pain at later time points. There are inherent difficulties in tracking outpatient opioid use such as outside prescribers and obtaining self-reported pain scores after discharge, which prevented further analysis. Nonetheless, there was no increase in return to the emergency department or 90 day readmission in the experimental group.

CONCLUSION

Perioperative utilization of a protocol involving systematic periarticular administration of LB is safe and effective in decreasing patient length of stay and inpatient opioid utilization when compared to a similar protocol using FNB.

ACKNOWLEDGMENTS

The authors would like to acknowledge Margy Klammer, Mammoth Hospital, Mammoth Lakes, CA for her assistance in acquisition of data.

REFERENCES

1. Kessler ER, Shah M, Gruschus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: Opioid-related adverse events and their impact on clinical and economic outcomes.

- Pharmacotherapy 2013;33:383-91.
2. Hebl JR, Dilger JA, Byer DE, Kopp SL, Stevens SR, Pagnano MW, *et al.* A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. *Reg Anesth Pain Med* 2008;33:510-7.
 3. Krych A, Arutyunyan G, Kuzma S, Levy B, Dahm D, Stuart M. Adverse effect of femoral nerve blockade on quadriceps strength and function after ACL reconstruction. *J Knee Surg* 2015;28:83-8.
 4. Bagsby DT, Ireland PH, Meneghini RM. Liposomal bupivacaine versus traditional periarticular injection for pain control after total knee arthroplasty. *J Arthroplasty* 2014;29:1687-90.
 5. Berend ME, Berend KR, Lombardi AV Jr. Advances in pain management: Game changers in knee arthroplasty. *Bone Joint J* 2014;96-B:7-9.
 6. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *J Pain Res* 2012;5:107-16.
 7. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of depof foam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. *Knee* 2012;19:530-6.
 8. Broome B. Periarticular injection with liposomal bupivacaine, is technique the key? *J Arthroplasty* 2014;29:2233.
 9. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. *Curr Med Res Opin* 2012;28:1609-15.
 10. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin Drug Investig* 2013;33:109-15.
 11. Tong YC, Kaye AD, Urman RD. Liposomal bupivacaine and clinical outcomes. *Best Pract Res Clin Anaesthesiol* 2014;28:15-27.
 12. Broome CB, Burnikel B. Novel strategies to improve early outcomes following total knee arthroplasty: A case control study of intra articular injection versus femoral nerve block. *Int Orthop* 2014;38:2087-9.
 13. White S, Vaughan C, Raiff D, Eward W, Bolognesi M. Impact of liposomal bupivacaine administration on postoperative pain in patients undergoing total knee replacement. *Pharmacotherapy* 2015;35:477-81.
 14. Barrington JW. Efficacy of periarticular injection with a long-acting local analgesic in joint arthroplasty. *Am J Orthop (Belle Mead NJ)* 2015;44:S13-6.
 15. Connelly JO, Edwards PK, Mears SC, Barnes CL. Technique for periarticular local infiltrative anesthesia delivery using liposomal bupivacaine in total knee arthroplasty. *J Surg Orthop Adv* 2015;24:263-6.

© **EJManager**. This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, noncommercial use, distribution and reproduction in any medium, provided the work is properly cited.

Source of Support: Nil, **Conflict of Interest:** None declared.