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Original research

Periarticular injection of liposomal bupivacaine in total knee arthroplasty

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ABSTRACT

The purpose of this study was to determine whether the use of a periarticular injection using liposomal bupivacaine could decrease pain and improve outcomes after total knee arthroplasty. Fifty consecutive patients received no periarticular injections (group A). Another 50 consecutive patients received a periarticular injection of liposomal bupivacaine (group B). There were no differences in the groups with respect to gender, age, body mass index (BMI), or comorbidities. There was a significant reduction in the amount of narcotics used in the liposomal bupivacaine group (60.97-mg oral morphine equivalent vs 89.74 mg, $P = 0.009$). Patients in group B with a BMI <40 and a Charlson comorbidity index of 0-3 had decreased length of stay (2.64 vs 3.06 days, $P = .004$), narcotic use over 24-48 hours (110.66 vs 182.47 mg, $P = .013$), and narcotic use over 48-72 hours (49.61 vs. 112.65 mg, $P = .004$). In patients with a BMI <40 and comorbidity index of ≤3, periarticular injection using liposomal bupivacaine leads to earlier discharge along with decreased use of narcotics.

Introduction

The number of patients undergoing total knee arthroplasty (TKA) has increased substantially in the last two decades, and currently, TKA is one of the most common orthopaedic procedures performed in the United States [1]. For many patients, pain after TKA can be severe and can compromise postoperative management leading to poor outcomes. Using a multimodal pain management protocol has been shown to improve pain scores, increase patient satisfaction, and enhance early recovery [2]. Currently, there are many postoperative pain management protocols used by orthopaedic surgeons. Regional nerve blocks and local infiltrative analgesia are two techniques that have been shown to provide postoperative pain relief, lower narcotic usage, and improve patient satisfaction in the early postoperative period [3]. Liposomal bupivacaine, Exparel (Pacira Pharmaceuticals, Parsippany, NJ), is an extended-release local anesthetic that uses multivesicular liposomes to diffuse bupivacaine over a period of 72 hours after single injection at the operative site [4]. Postoperative pain reduction extended for a period of up to 72 hours would benefit the patient by allowing for a more accelerated rehabilitation protocol, which ultimately will lead to shorter length of hospital stay and improved outcomes. In other surgical procedures, liposomal bupivacaine has been shown to offer multiple clinical advantages over short-acting bupivacaine HCl. After hemorrhoidectomy, it demonstrated a longer duration of action, decreased opioid requirement, and fewer opioid-related adverse effects [5]. Extended-release bupivacaine has also been shown to provide extended pain relief and decreased opioid use after bunionectomy compared to a placebo-controlled group [6].

The purpose of this retrospective study was to understand the contribution to pain control and recovery after primary TKA that liposomal bupivacaine adds in the setting of a comprehensive pain protocol. Narcotic usage, length of hospital stay, and walking distance were the primary outcomes investigated. In addition, we aimed to stratify this patient cohort based on comorbidities and body mass index (BMI) to provide insight into which patient populations will benefit most from periarticular injection (PAI) using liposomal bupivacaine.

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Table 1
Equianalgesic conversion.

Drug	Administration	Dose (mg)	Conversion factor	PO morphine equivalent dose (mg)
Morphine	PO	10	1	10
	IV	10	3	30
Hydromorphone	PO	10	4	40
	IV	10	20	200
Hydrocodone	PO	10	1	10
Oxycodone	PO	10	1.5	15
Tramadol	PO	10	0.25	2.5

PO, oral; IV, intravenous.

Material and methods

Fifty consecutive patients who underwent primary TKA and received an intraoperative PAI using liposomal bupivacaine between April 2013 and August 2013 were retrospectively reviewed. A separate cohort of fifty consecutive patients who underwent primary TKA without PAI between June 2012 and August 2012 were retrospectively included as a control group. All procedures were performed by a single surgeon. This study was approved by our institutional review board and was Health Insurance Portability and Accountability Act compliant.

All patients received a single-shot femoral and sciatic nerve block performed by the anesthesia staff, and all patients received intravenous sedation unless general anesthesia was required for better airway control. A subvastus approach was the primary mode of exposure in both groups unless there was a contraindication. All cases were performed using a Stryker Triathlon TKA implant (Stryker, Mahwah, NJ). In the study group, the intraoperative PAI was performed after all components were implanted; the wound was irrigated with a dilute Betadine (Purdue Products LT, Stanford, CT 06901) irrigation and was then washed with normal saline from a pulse irrigator. The PAI was administered according to the liposomal bupivacaine manufacturer's instructions. The PAI consisted of 20 mL of 1.3% liposomal bupivacaine (1 vial; 266 mg) diluted with 40-mL normal saline to create a total injection volume of 60 mL. The control group did not receive any type of intraoperative PAI.

The postoperative pain control regimen was the same for both groups and included the use of oral acetaminophen, celecoxib, tramadol, patient-controlled analgesia, and oral narcotics. Patient-controlled analgesia was administered using morphine, unless contraindicated, at which point hydromorphone was substituted. All postoperative pain medications administered were tabulated and converted to a total oral morphine equivalent (mg) for use in the comparison of the two groups (Table 1) [7].

Table 2
Cohort characteristics.

Demographics	Liposomal bupivacaine PAI	No PAI	Chi square	df	*P* value
Male	16	18	0.18	1	0.67
Female	34	32			
			P value		
Age	64 (46-88)	64 (38-85)	0.837		
BMI	35 (21-58)	35 (20-63)	0.93		
CCI	3.34 (2-6)	3.58 (0-8)	0.366		
			Chi square	df	*P* value
Subvastus	33	39	1.79	1	0.18
Parapatellar	17	11			

df, degrees of freedom; PAI, periarticular injection.

Table 3
Outcomes in all patients.

Outcome & Narcotic Usage	Liposomal bupivacaine PAI	No PAI	P value
Length of stay (d)	2.94	3.26	0.092
Narcotic use 0-24 h (mg)	119.04	111.58	0.608
Narcotic use 24-48 h (mg)	114.74	132.18	0.217
Narcotic use 48-72 h (mg)	60.97	89.74	**0.009**
Walking distance POD 1 (ft)	61.32	44.5	0.067
Walking distance POD 2 (ft)	97.15	81.42	0.229
Walking distance POD 3 (ft)	101.93	123.07	0.246

POD, postoperative day; PAI, periarticular injection.

A standardized physical therapy protocol was initiated for each group on postoperative day 1. The physical therapy regimen consisted of 2 hours of continuous passive motion machine twice daily, assisted standing, and assisted walking. All patients were discharged when deemed medically stable, their pain was under control, and the physical therapy goals were met.

Standard statistical Student's *t* tests were used to evaluate the mean outcome of continuous variables between groups, and chi-square tests were used to evaluate categorical variables. Dedicated statistical software (SPSS 22; SPSS Inc., Chicago, IL) was used to perform the data analysis. The two groups were compared on the basis of length of hospital stay; amount of narcotic pain medication used over the first 24, 48, and 72 hours; and the distance walked on postoperative days 1, 2, and 3. Statistically significant difference was considered at $P \leq .05$ between groups.

Results

Fifty consecutive patients were identified in the study group, consisting of 34 female and 16 male patients, with an average age of 64 (range: 46-88) years and an average BMI of 35 (range: 21-58). This was compared to the control group of 50 consecutive patients, consisting of 32 female and 18 male patients, with an average age of 64 (range: 38-85) years and an average BMI of 35 (range: 20-63). The average Charlson comorbidity index (CCI) for the study group was 3.34 (range: 2-6), and for the control group, it was 3.58 (range: 0-8). There were no statistically significant differences between the groups with respect to gender, age, BMI, comorbidities, or surgical approach. The cohort characteristics are outlined in Table 2.

There was a statistically significant reduction in the amount of narcotics used over the 48-72-hour postoperative period in the liposomal bupivacaine group (60.97-mg oral morphine equivalent vs 89.74 mg, $P = .009$). There was no statistical difference between the two groups with respect to length of hospital stay, amount of narcotics used from 0-24 hours and 24-48 hours, or the postoperative walking distance (Table 3).

Table 4
Outcomes in patients with BMI <40, CCI 0-3.

Outcome & narcotic usage	Liposomal bupivacaine PAI	No PAI	*P* value
Length of stay (d)	2.64	3.06	**0.004**
Narcotic use 0-24 h (mg)	117.61	145.53	0.298
Narcotic use 24-48 h (mg)	110.66	182.47	**0.013**
Narcotic use 48-72 h (mg)	49.61	112.65	**0.004**
Walking distance POD 1 (ft)	73.29	59.07	0.456
Walking distance POD 2 (ft)	114.77	84.82	0.193
Walking distance POD 3 (ft)	137.27	119.38	0.545

POD, postoperative day; PAI, periarticular injection; BMI, body mass index; CCI, Charlson comorbidity index.

Table 5
Outcomes in patients with BMI <40, CCI >3.

Outcome & narcotic usage	Liposomal bupivacaine PAI	No PAI	*P* value
Length of stay (d)	3.07	3.55	0.252
Narcotic use 0-24 h (mg)	109.8	87.5	0.283
Narcotic use 24-48 h (mg)	108.93	92.23	0.228
Narcotic use 48-72 h (mg)	75.38	68.57	0.716
Walking distance POD 1 (ft)	61.43	40.95	0.08
Walking distance POD 2 (ft)	81.64	78.23	0.828
Walking distance POD 3 (ft)	82	122.1	0.176

POD, postoperative day; PAI, periarticular injection; BMI, body mass index; CCI, Charlson comorbidity index.

When a subset analysis was performed, the patients from the study group with a BMI <40 and a CCI of 0-3 were found to have a statistically significant difference with respect to length of stay (2.64 vs 3.06 days, $P = .004$), narcotic use over 24-48 hours (110.66 vs 182.47 mg, $P = .013$), and narcotic use over 48-72 hours (49.61 vs 112.65 mg, $P = .004$). There was a trend toward increased walking distance on postoperative day 2 (114.77 vs 84.82 ft, $P = .193$), but this was not statistically significant with the numbers available for study (Table 4). All other subsets reviewed did not show any statistically significant differences between the two groups with the numbers available for review (Tables 5-7).

Discussion

Periarticular injections after TKA have been widely used to alleviate postoperative pain to improve patient satisfaction and outcomes [8,9]. Many groups have used these injections as part of their multimodal pain control management plan after TKA. The use of liposomal bupivacaine as a PAI is a novel technique that can provide long-acting postoperative pain relief [10,11].

This retrospective study was undertaken to determine whether the addition of a PAI using liposomal bupivacaine compared to no PAI would enhance the postoperative pain relief of patients undergoing TKA. Based on our study, the use of a liposomal bupivacaine PAI led to a decrease in narcotic use in the immediate postoperative period in patients undergoing primary TKA. Patients receiving liposomal bupivacaine were able to be discharged from the hospital sooner and had a trend toward increased walking distance earlier in their postoperative course. The greatest benefit was seen for the healthier (CCI, ≤ 3) and nonmorbidly obese patients (BMI, <40). No statistically significant difference in length of stay, narcotic use, or walking distance was noted when comparing morbidly obese (BMI, >40) patients and those with multiple comorbidities (CCI, >3). Patients most likely to benefit from the addition of a PAI using liposomal bupivacaine in this study were those with a BMI <40 and a CCI ≤ 3.

There are limitations to this study, but despite being a retrospective review, this study was performed at a single institution using consecutive patients, without variation in surgical technique, anesthesia, or the postoperative protocol. The study cohort and control groups both consisted of a consecutive series of patients that underwent primary TKA during a similar time period of the year to best eliminate selection bias. There are several questions that arise from the results of this study, which need further exploration. There is an added cost to each case using liposomal bupivacaine as a PAI. In a study by Bagsby et al [12], they concluded that liposomal bupivacaine PAIs provided inferior pain control compared to the less-expensive traditional PAI using short-acting bupivacaine. However, this was also a retrospective study with two different surgeons, and the authors acknowledge that the results may be technique dependent. It is also important to note that this study compared PAI using liposomal bupivacaine versus short-acting bupivacaine, in comparison to our study, which compared liposomal bupivacaine to no PAI in the control group. A prospective, randomized study by Schroer et al [13] that comparing liposomal bupivacaine to standard bupivacaine did not show any significant benefit between the two periarticular injections in patients undergoing primary TKA. Long-acting pain relief with the use of PAIs appears to be an important part of a multimodal pain regimen that allows for earlier discharge and improved outcomes. There is increasing evidence that short-stay and outpatient TKA is feasible in the near future [14]. Long-acting pain relief through the use of PAI may allow for this to become a possibility. We demonstrated that healthier patients and those with a BMI <40 had a shorter hospital stay and used fewer narcotics with the use of liposomal bupivacaine. Patients who are morbidly obese and with multiple medical problems may have difficulty in earlier return to function because of their inherent comorbid conditions despite the use of PAIs. In addition, it is not clear whether there are any differences in absorption and release of these PAIs in the morbidly obese patients because of the excess adipose tissue. Additional studies are required to demonstrate the true benefits of liposomal bupivacaine with respect to cost effectiveness compared to a hospital pharmacy–prepared PAI, actual duration of pain relief, and its role in outpatient or short-stay hospitalization after TKA.

Table 6
Outcomes in patients with BMI >40, CCI 0-3.

Outcome & narcotic usage	Liposomal bupivacaine PAI	No PAI	P value
Length of stay (d)	3	3	1
Narcotic use 0-24 h (mg)	156.5	99.63	0.106
Narcotic use 24-48 h (mg)	155.39	126.75	0.38
Narcotic use 48-72 h (mg)	80	83.43	0.867
Walking distance POD 1 (ft)	45.56	31.43	0.482
Walking distance POD 2 (ft)	94.38	109.38	0.738
Walking distance POD 3 (ft)	96.67	156.67	0.214

POD, postoperative day; PAI, periarticular injection; BMI, body mass index; CCI, Charlson comorbidity index.

Table 7
Outcomes in patients with BMI >40, CCI > 3.

Outcome & narcotic usage	Liposomal bupivacaine PAI	No PAI	*P* value
Length of stay (d)	4	3	0.391
Narcotic use 0-24 h (mg)	77.25	119.67	0.618
Narcotic use 24-48 h (mg)	67.5	154.67	0.254
Narcotic use 48-72 h (mg)	30	125	0.237
Walking distance POD 1 (ft)	24.33	3	0.472
Walking distance POD 2 (ft)	47.67	11	0.28

POD, postoperative day; PAI, periarticular injection; BMI, body mass index; CCI, Charlson comorbidity index.

Conclusions

Periarticular TKA injection using liposomal bupivacaine in patients with a BMI of less than 40 kg/m2 and a comorbidity index of less than or equal to 3 leads to earlier hospital discharge and decreased narcotic usage.

References

1. Cram P, Lu X, Kates SL, et al. Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991-2010. JAMA 2012;308:1227.
2. Lamplot JD, Wagner ER, Manning DW. Multimodal pain management in total knee arthroplasty. J Arthroplasty 2014;29(2):329.

3. Moghtadaei M, Farahini H, Faiz SH, et al. Pain management for total knee arthroplasty: single-injection femoral nerve block versus local infiltration analgesia. Iran Red Crescent Med J 2014;16(1):e13247.
4. Pacira Pharmaceuticals, Inc. www.pacira.com; [accessed 4.11.2011].
5. Gorfine SR, Onel E, Patou G, et al. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2011;54(12):1552.
6. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv Ther 2011;28(9):776.
7. McPherson ML. Demystifying opioid conversion calculations: a guide for effective dosing. Bethesda, MD: American Society of Health-System Pharmacists, Inc.; 2009.
8. Essving P, Axelsson K, Kjellberg J, et al. Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty. Acta Orthop 2010;81(3):354.
9. Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty: a randomized trial. J Bone Joint Surg Am 2006;88:959.
10. Richard BM, Newton P, Ott LR, et al. The safety of EXPAREL® (bupivacaine liposome injectable suspension) administered by peripheral nerve block in rabbits and dogs. J Drug Deliv 2012;2012:962101.
11. 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(10):1609.
12. Bagsby DT, Ireland PH, Meneghini RM. Liposomal bupivacaine versus traditional periarticular injection for pain control after total knee arthroplasty. J Arthroplasty 2014;29(8):1687.
13. Schroer WC, Diesfeld PG, LeMarr AR, Morton DJ, Reedy ME. Does extended-release liposomal bupivacaine better control pain than bupivacaine after TKA? A prospective, randomized clinical trial. J Arthroplasty 2015;30(9):64.
14. Kolisek FR, McGrath MS, Jessup NM, et al. Comparison of outpatient versus inpatient total knee arthroplasty. Clin Orthop Relat Res 2009;467(6):1438.