Original Article

Comparison of Intraoperative Periarticular Injections Versus Liposomal Bupivacaine as Part of a Multimodal Approach to Pain Management in Total Knee Arthroplasty

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ABSTRACT

Background: Total knee arthroplasty (TKA) has been shown to restore mobility, return an individual to activities of daily living, and improve quality of life. Nearly 80% of patients undergoing TKA report moderate to severe pain in the first 2 weeks following surgery.

Methods: A retrospective study was conducted in 103 patients who underwent TKA between October 12, 2014 and May 30, 2015 by a single surgeon at a small community hospital. During this period, data were analyzed for differences in outcomes with a change from intraoperative periarticular (IOPA) injections containing an anesthetic/analgesic mixture of ropivacaine, epinephrine, ketorolac, and clonidine to liposomal bupivacaine. Patient records were reviewed to extract study data including postoperative opioid use, length of stay (LOS), opioid-associated adverse events, and non-opioid analgesic use.

Results: No statistical differences were determined between groups for mean postoperative opiate usage in morphine equivalences during any time frame or for total opiate usage (79.4 vs 89.2 mg; $P = .259$) during the first 72 postoperative hours. Patients who received a liposomal bupivacaine injection did have a statistically significant increase in hospital LOS (70.0 vs 75.5 hours; $P = .013$) when compared to patients who received an IOPA injection. The incidence of nausea or vomiting, pruritus, or oversedation did not differ between groups.

Conclusion: Pain control in TKA with a multimodal pain management protocol was not improved with the addition of liposomal bupivacaine compared to the IOPA injection at a community hospital.

Key Words—intraoperative periarticular injection, liposomal bupivacaine, narcotics, total knee arthroplasty

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Total knee arthroplasty (TKA) is performed with the goals to restore mobility, return an individual to activities of daily living, and improve quality of life.¹ However, a substantial number of patients experience severe pain following a TKA, and management of the pain represents a significant clinical problem.² Nearly 80% of patients undergoing surgery report moderate to extreme pain in the first 2 weeks following surgery.³ Inadequate management

of perioperative pain has been associated with poor functional recovery, including slower rehabilitation, delayed return to activities of daily living, increased financial costs, or progression to a persistent pain state.^{4,5} In contrast, good pain management contributes to improved healing, faster mobilization, fewer opioid-associated adverse effects, shortened hospital stays, reduced health care costs, and increased patient satisfaction.^{5,6}

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Standard methods of analgesia include administration of epidural anesthesia, peripheral nerve blocks, local anesthetics, parenteral and oral opioids, and non-opioid medications.^{5,7} Sole reliance on high doses of intravenous patient-controlled analgesia (PCA) or oral opioids may induce negative physiological or psychological effects and frequently cause adverse events that limit an individual's overall clinical improvement.⁴ In an effort to diminish postoperative pain while minimizing complications, a multimodal drug therapy approach combining 2 or more agents has become the standard of practice.⁶ When utilized, lower doses of various drugs that provide different mechanisms of action produce maximized pain control with minimized side effects.²

In October 2011, the US Food and Drug Administration (FDA) approved liposomal bupivacaine, a local anesthetic formulation, for single-dose infiltration to the surgical site for postsurgical analgesia.⁷ The product contains liposomes composed of a phospholipid bilayer that encapsulates the aqueous bupivacaine. The phospholipid bilayer is denatured by the body's heat, which leads to a gradual breakdown of the liposome allowing for a slow, controlled release of bupivacaine over 72 to 96 hours.^{2,6,8} Liposomal bupivacaine is administered as a periarticular injection and is promoted as having a benefit of longer-acting pain control in TKA.² As such, the drug product has the potential to reduce opioid consumption without the need for a nerve block or catheter placement.⁷

The first studies of liposomal bupivacaine in postoperative pain management occurred in bunionectomy and hemorrhoidectomy procedures.⁹ Golf et al¹⁰ studied 193 patients undergoing bunionectomy. Bupivacaine liposome injection produced a significant reduction in pain intensity compared with placebo for up to 24 hours. After 24 hours, no difference was observed in mean pain intensity. Gorfine et al¹¹ studied 189 patients undergoing excisional hemorrhoidectomy. Bupivacaine liposomal injection demonstrated a statistically significant reduction in pain through 72 hours, but also decreased opioid requirements, delayed time to first opioid use, and improved patient satisfaction compared with placebo. A recent study by Kenes et al¹² compared the analgesic efficacy of liposomal with continuous infusion bupivacaine in patients undergoing various surgeries. No differences in postoperative opioid use were found after adjusting for baseline differences in the patient groups.

At least 2 studies have been completed using liposomal bupivacaine compared to alternative methods

for postoperative pain control in TKA. Bagsby et al² compared the liposomal product to a typical periarticular injection in a retrospective cohort study of 150 patients. Although pain control was similar in the 2 groups for the first 24 postoperative hours, the subsequent average absolute as well as categorical pain scores were significantly worse in the liposomal bupivacaine group for the remaining hospital stay. Similar results of no benefit for liposomal bupivacaine compared to femoral nerve block on pain control, nausea and vomiting, and narcotic use was observed by Surdam et al¹³ in patients undergoing unilateral TKA, although earlier ambulation and a decreased length of hospital stay (LOS) was determined in the liposomal bupivacaine group. In a dose-ranging study in TKA patients, Bramlett et al⁵ also failed to find significant clinical benefit from liposomal bupivacaine in the recommended dosage.

The efficacy and safety of an intraoperative periarticular (IOPA) injection approach containing several different combinations of ropivacaine hydrochloride, ketorolac tromethamine, epinephrine, and clonidine has been established.¹⁻⁷ However, there is no single recommended protocol for periarticular injections, and the analgesics incorporated, doses used, and administration techniques are variable.³ The purpose of the present study was to compare the effectiveness and safety of liposomal bupivacaine with an IOPA injection following TKA. It was hypothesized that narcotic use and LOS would be decreased with the use of liposomal bupivacaine.

METHODS

A retrospective study was conducted to compare patients who received an IOPA injection with those who received liposomal bupivacaine as part of a multimodal approach to pain management after TKA between October 12, 2014 and May 30, 2015. The 2 patient groups were studied in a sequential fashion. Prior to January 2015, patients who underwent TKA received an IOPA injection containing ropivacaine hydrochloride 246.25 mg, epinephrine 0.5 mg, ketorolac tromethamine 30 mg, clonidine 0.08 mg, and 0.9% sodium chloride 48.45 mL diluted to a total volume of 100 mL and placed in two 50 mL syringes. Prior to surgical site closure, the contents of the 2 syringes were injected into several soft tissue areas surrounding the replaced knee joint using a moving-needle technique. The entire mixture was injected. Starting in January 2015, the surgeon replaced IOPA injections with liposomal bupivacaine injections.

Twenty mL of 1.3% liposomal bupivacaine (1 vial containing 266 mg) was diluted in 40 mL 0.9% sodium chloride for a total of 60 mL solution and injected into the periarticular tissue at the conclusion of the surgical procedure. During the 2 sequential study periods, the only modifications in the multimodal pain management program were the different periarticular injections; no confounding variables were detected during the time of the study.

Patients for the study were identified from medical records of a single orthopedic surgeon at a small community hospital with a general orthopedic surgery unit. Data were collected from all patients who underwent unilateral or bilateral TKA performed by the surgeon between October 12, 2014 and May 30, 2015. Patients were excluded from the study if other types of knee surgery were performed or if the TKA was a revision.

Patient demographic data included age, gender, length of surgery, and home narcotic use prior to surgery in order to assess equivalence of the IOPA and liposomal bupivacaine groups. Primary efficacy outcomes were postoperative opioid use and hospital LOS. Data were assessed from the end of surgery to 72 hours postoperatively or discharge. Opioid usage was standardized by converting the quantity of the various opioids to intravenous morphine sulfate equivalents based on a commonly used equipotency chart.¹⁴ Concomitant use of non-opioid analgesics for pain control was also assessed. The safety outcomes included opioid-associated adverse events recorded in the medical charts; those were implied by the use of anti-emetics, antipyretics, or opioid reversal agents.² Per the orthopedic unit standard of practice, all patients were encouraged to ambulate starting in the afternoon on the day of surgery. A standard rehabilitation protocol was followed for all patients. Patients were deemed ready for discharge when they were considered medically stable, met physical therapy requirements, and demonstrated adequate pain control. Postdischarge use of opioids was not tracked.

Descriptive statistics (eg, frequencies, percentages, means, medians, standard deviations, and interquartile range) were used to describe the 2 main drug modality groups, as well as subgroups composed of unilateral or bilateral TKA patients. Analyses were performed on the entire TKA groups and the subgroups. Further comparisons were made for all study patients divided into 4 age groups (less than 60 years, 60-69 years, 70-79 years, and 80 years and above). Comparisons were made using chi-square or

Fisher exact probability tests of association for nominal data and *t* tests for independent samples with unequal variance or Mann-Whitney *U* test depending on whether the data were normally distributed. Alpha was set a priori at $P = .05$ per test. Analyses were performed in Microsoft Excel 2010 and IBM SPSS Statistics version 22 (IBM, Inc., Armonk, NY).

RESULTS

A total of 103 patients underwent TKA between October 12, 2014 and May 30, 2015. Fifty-three patients were included in the IOPA injection group and 50 patients were in the liposomal bupivacaine group. The 2 primary study groups were comparable for the demographic parameters (Table 1). However, a significant difference was seen between groups for home narcotic use, with a greater percentage of patients in the liposomal bupivacaine group receiving home narcotics at time of admission ($P = .007$).

With respect to the efficacy outcome variables, there was no statistical difference between groups in mean postoperative opiate usage in morphine equivalences at any time frame or for total opiate usage (Table 2). However, the median hospital LOS was 5.5 hours less in the IOPA injection group, a difference which was statistically significant, with a median LOS of 70.0 hours compared to 75.5 hours in the liposomal bupivacaine group ($P = .013$). In regard to the safety analysis, the overall incidence of nausea or vomiting, pruritus, and oversedation was similar in both groups. Non-opioid analgesic use showed no difference between groups at any time frame postoperatively (Figure 1).

When the groups were divided to subgroups, unilateral TKA consisted of 74 patients, with 41 included in the IOPA injection group and 33 in the liposomal bupivacaine group. Distribution between the groups showed no significant effect. Gender, age, and length of surgery were comparable between groups. As was seen for the whole groups, home narcotic use prior to surgery was significantly more common in the liposomal bupivacaine subgroup, occurring in 13 (38.4%) compared to 6 patients (14.6%) in the IOPA subgroup ($P = .015$). No significant differences were noted between groups with regard to opiate usage at any time post TKA. As with the entire groups, hospital LOS revealed a statistically significant difference between the IOPA injection and liposomal bupivacaine subgroups with medians of 53 hours and 74 hours, respectively ($P = .005$). Non-opioid analgesic use or the adverse

Table 1. Demographics of intraoperative periarticular (IOPA) and liposomal bupivacaine total knee arthroplasty patient groups

	IOPA	Liposomal bupivacaine	P value
Total group	<i>n</i> =53	<i>n</i> =50	
Male gender	31 (58.5)	24 (48.0)	.286
Age, years	67.5 ($\pm$ 8.3)	67.4 ($\pm$ 10.7)	.962
Home narcotic use	7 (13.2)	18 (36.0)	.007
Unilateral subgroup	<i>n</i> =41	<i>n</i> =33	
Male gender	23 (56.1)	17 (51.5)	.694
Age, years	67.5 ($\pm$ 8.8)	68.9 ($\pm$ 10.8)	.551
Home narcotic use	6 (14.6)	13 (39.4)	.015
Bilateral subgroup	<i>n</i> =12	<i>n</i> =17	
Male gender	8 (66.7)	7 (41.2)	.176
Age, years	67.3 ($\pm$ 6.9)	64.4 ($\pm$ 10.3)	.367
Home narcotic use	1 (8.3)	5 (19.2)	.168

Note: Unless otherwise stated, values expressed as mean ($\pm$ SD) or number of patients (%).

Table 2. Efficacy and safety outcomes for intraoperative periarticular (IOPA) and liposomal bupivacaine patient groups

	IOPA	Liposomal bupivacaine	P value
Total group	<i>n</i> =53	<i>n</i> =50	
Length of surgery, minutes	67.4 ($\pm$ 19.8)	69.5 ($\pm$ 18.6)	.590
Length of stay, hours	70.0 (52-78) ^a	75.5 (70.8-79.3) ^a	.013
Opioid use ^b			
Day of surgery, $\leq$ 24 hours	38.6 ($\pm$ 16.6)	41.3 ($\pm$ 17.9)	.418
POD1, 24-48 hours	33.5 ($\pm$ 21.1)	32.5 ($\pm$ 17.9)	.801
POD2, 48-72 hours	25.4 ($\pm$ 18.7)	22.9 ($\pm$ 15.6)	.629
Total opioid use	79.4 ($\pm$ 46.3)	89.2 ($\pm$ 41.2)	.259
Adverse events			
Nausea/Vomiting	25 (47.2%)	25 (50.0%)	.774
Pruritus	3 (5.7%)	5 (10.0%)	.411
Overdose	0 (0%)	0 (0%)	—
Unilateral group	<i>n</i> =41	<i>n</i> =33	
Length of surgery, minutes	57 (52-64) ^a	56 (50-66.5) ^a	.794
Length of stay, hours	53 (51-75) ^a	74 (56-78.5) ^a	.005
Opioid use ^b			
Day of surgery, $\leq$ 24 hours	34.7 ($\pm$ 13.9)	40.0 ($\pm$ 18.6)	.184
POD1, 24-48 hours	31.1 ($\pm$ 19.9)	30.2 ($\pm$ 17.4)	.842
POD2, 48-72 hours	21.9 ($\pm$ 14.9)	20.3 ($\pm$ 15.4)	.819
Total opioid use	68.5 ($\pm$ 37.1)	82.8 ($\pm$ 41.3)	.124

(continued)

Table 2. Efficacy and safety outcomes for intraoperative periarticular (IOPA) and liposomal bupivacaine patient groups (CONT.)

	IOPA	Liposomal bupivacaine	P value
Adverse events			
Nausea/Vomiting	18 (43.9%)	13 (39.4%)	.696
Pruritus	2 (4.9%)	3 (9.1%)	.473
Overdose	0 (0%)	0 (0%)	—
Bilateral group	n=12	n=17	
Length of surgery, minutes	86.5 (79-103.5) ^a	83 (78.5-98) ^a	.616
Length of stay, hours	86.5 (75.3-103) ^a	79 (73-100) ^a	.679
Opioid use ^b			
Day of surgery, ≤24 hours	51.6 (±18.9)	43.9 (±16.7)	.273
POD1, 24-48 hours	40.6 (±22.8)	36.8 (±18.4)	.638
POD2, 48-72 hours	29.6 (±23.7)	27.2 (±15.1)	.766
Total opioid use	116.8 (±56.1)	101.5 (±39.2)	.426
Adverse events			
Nausea/Vomiting	7 (58.3%)	12 (70.6%)	.494
Pruritus	1 (8.3%)	2 (11.8%)	.765
Overdose	0 (0%)	0 (0%)	—

Note: Unless otherwise stated, values expressed as mean (±SD) or number of events (%). POD = postoperative day.

^aMedian (interquartile range Q1-Q3) Kruskal Wallis test of independent samples.

^bValues expressed as mean milligrams of IV morphine equivalents per patient (±SD).

Figure 1. Non-opioid analgesic use by group and length of time post total knee arthroplasty surgery. All values are expressed as percent of patients receiving a non-opioid analgesic for patients still in the hospital for that time period. APAP = acetaminophen; IOPA = intraoperative periarticular; NSAID = nonsteroidal anti-inflammatory drug.

effects of nausea or vomiting, pruritus, or oversedation showed no differences between groups.

Twenty-nine patients made up the subgroup of bilateral TKA, with 12 patients in the IOPA injection group and 17 patients in the liposomal bupivacaine

group. No significant differences were determined for any demographic variable or the primary efficacy outcomes, and non-opioid analgesic usage and safety outcomes were comparable between the subgroups.

The age groups analysis showed a statistically significant difference with regard to opiate usage in patients under 80 years old using on average a total of 91.0 mg of IV morphine equivalence compared to 32.0 mg in patients 80 years old or older ($P < .01$). Further breakdown of age groups showed mean total opioid use by patients younger than 60 years old (103.4 mg), 60-69 years old (90.2 mg), and 70-79 years old (81.7 mg) was significantly greater for each when compared with patients 80 years old and older (32.0 mg) ($P < .01$). A clinically significant increased LOS was noted for patients 80 years old and older, with the greatest being a 20-hour time difference when compared to patients in the 60 to 69 years of age group at 89.8 and 69.5 hours, respectively.

DISCUSSION

Pain after TKA is a major concern to both patients and health care personnel. In an effort to optimize pain control and reduce the side effects associated with opioid consumption, multimodal pain management protocols for TKA patients have been developed. A component of the multimodal approach is the use of a periarticular injection for local analgesia that has been shown to successfully reduce postoperative pain in TKA.^{2,15}

The present retrospective study was conducted to determine whether a periarticular injection of bupivacaine liposomal provided comparative, and possibly additional, benefits to a multimodal pain management approach as did IOPA injections of ropivacaine, epinephrine, ketorolac, and clonidine used in TKA patients in the immediate prior time period. Results demonstrated no statistically significant difference in opiate use or adverse effects between the 2 groups, showing that liposomal bupivacaine did not provide additional pain control or safety compared to the IOPA injection. Hospital LOS analysis did however produce a statistically significant difference, with the LOS being shorter by 5.5 hours in the IOPA injection group ($P = .013$). However, clinical and cost importance of this difference was not assessed. In the subgroup analysis, a significantly decreased LOS in the IOPA group was seen for unilateral TKA ($P = .005$) whereas bilateral TKA demonstrated no difference ($P = .679$).

When patients were grouped based on age, a statistically significant difference was noted in total morphine equivalence administered, with patients younger than 80 years old receiving an increased amount compared to patients 80 years old and older ($P < .001$). This could not be explained by greater

utilization of non-opioid analgesics in patients 80 years old and older. While not assessed in the study, pharmacokinetic differences in the metabolism and pharmacodynamic differences in the effects of opioids in the elderly could contribute to the findings. Although LOS was not statistically significantly longer in patients 80 years old and older, it likely was of clinical importance when considering hospital resources and costs. The greatest difference of 20 hours was noted between patients 60 to 69 years old and patients 80 years old and older. This could be due to the concomitant comorbidities that typically accompany increasing age. Also, a majority of patients 80 years old and older were discharged to skilled nursing facilities (SNF); more time is need to coordinate discharge for these patients compared to patients who are discharged home.

This study has limitations that were recognized and taken into consideration. First, the study has the inherent limitation of not being a randomized, prospective study, but rather a retrospective cohort study. While allowing correlations to be determined, causation of any effects cannot be proven. Second, pain scores were not assessed in this study, and it was assumed that similar pain management goals were achieved between the groups. The validity of this assumption is supported by short study duration and no changes in personnel most responsible for pain management in TKA patients. Moreover, great variances in self-reported pain scores routinely occur between patients despite education on rating pain scores, bringing into question the value of using aggregate scores. Third, the effect of periarticular injections may be technique dependent and could affect results. However, the injection was identical in both treatment groups and was carried out by the same surgeon, which minimized the potential for confounding effects on injection technique. With the limitations in mind, the methodology and validity of this study were strengthened by the use of sequentially aligned groups to avoid cross-contamination of results, as well as the standardized perioperative anesthesia, maintaining the same surgeon with identical technique, and multimodal pain management protocol to minimize bias through isolation of a single variable, periarticular injection composition, to assess its effect on outcome.

CONCLUSIONS

The results of this retrospective cohort study demonstrated that periarticular liposomal bupivacaine compared an IOPA injection in TKA patients is

not associated with significant improvements in postoperative pain management as assessed by medication use and adverse effects. Results suggested a possible negative effect on hospital LOS with the liposomal bupivacaine. Based on the results of this study, the authors conclude that pain control in TKA with a multimodal pain management protocol is not improved with the substitution of liposomal bupivacaine for an IOPA injection. Our findings could have cost implications in certain settings, although that aspect was not assessed in the study. Larger randomized controlled trials may provide greater clarity on the comparative efficacy of liposomal bupivacaine over traditional intraoperative periarticular injections.

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