Liposomal Bupivacaine and Periarticular Injection Are Not Superior to Single-Shot Intra-articular Injection for Pain Control in Total Knee Arthroplasty

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ABSTRACT

Background: Intraoperative injections can help reduce early postoperative pain in total knee arthroplasty. We proposed that liposomal bupivacaine would not be superior to more common and cheaper injections.

Methods: A single-blinded prospective randomized study with 207 consecutive patients was completed. Patients were randomized to treatment with periarticular liposomal bupivacaine injection, periarticular injection of bupivacaine/morphine, or intra-articular injection of bupivacaine/morphine at the conclusion of the procedure. Postoperative visual analog pain scores and narcotic consumption were recorded and analyzed.

Results: There was no significant difference in postoperative visual analog pain scores or narcotic consumption among the 3 study groups.

Conclusion: Intra-articular injection of bupivacaine and morphine is as effective for postoperative pain control in total knee arthroplasty as periarticular bupivacaine/morphine injection and liposomal bupivacaine. Use of liposomal bupivacaine in total knee arthroplasty is costly and not justified.

Total knee arthroplasty (TKA) is a widely performed orthopedic procedure that can provide long-term pain relief, restore function, and deliver patient satisfaction. During the acute postoperative period, patients’ rehabilitation can be hampered by severe pain, which not only slows recovery and is associated with increased complications but also can ultimately lead to inferior results. Previous studies have also demonstrated that uncontrolled pain can lead to increased hospital length of stay (LOS) and increased costs [1]. Adequate pain control is essential and is a field of ongoing investigation.

Although opiates are often regarded as the mainstay of treatment for postoperative pain management, multimodal analgesia has been shown to decrease the narcotic consumption while also preventing adverse side effects of medications [2]. Postoperative multimodal analgesia uses a combination of opioids with a variety of drugs of varying mechanisms of action. Some of these include the use of local anesthetics, clonidine, ketamine, nonsteroidal anti-inflammatory drugs, acetaminophen, and calcium channel blockers. Currently, multimodal analgesia is commonly used in the postoperative TKA setting in the form of a periarticular (PA) injection. This mode of postoperative pain control has been investigated and its efficacy has been established [3]. However, there are limited data demonstrating the superiority of a PA drug injection over a single intra-articular (IA) injection for TKA. Liposomal bupivacaine (Pacira Pharmaceuticals) combines a local anesthetic with a DepoFoam delivery system that can potentially provide pain relief for up to 72 hours postoperatively. However, no consensus currently exists on the use of liposomal bupivacaine after TKA. Liposomal bupivacaine has the potential to improve patients’ postoperative pain levels, decrease the need for opiates, mitigate dangerous side effects of narcotics, and perhaps even decrease hospital LOS. These theoretical benefits need to be investigated further and weighed against increased costs for the medication in the setting of postoperative TKA.
Therefore, the purpose of our study was to evaluate the effectiveness of liposomal bupivacaine in reducing postoperative visual analog scale (VAS) pain scores and narcotic consumption after TKA. We also sought to compare liposomal bupivacaine with a more commonly used PA injection of bupivacaine/morphine and our standard regimen of an IA injection of bupivacaine/morphine into the joint at the conclusion of TKA. Our hypothesis was that liposomal bupivacaine would be no more effective in reducing postoperative VAS for pain or narcotic consumption. We also hypothesized that pain scores and narcotic consumption would not be different between a single-shot IA injection of bupivacaine with morphine and a PA injection of bupivacaine with morphine.

Methods

A total of 207 consecutive patients were enrolled into a single-blinded prospective randomized single-center study. Patients recruited for this study were those who were scheduled to have a unilateral TKA at a high-volume arthroplasty center. The hospital is dedicated solely to hip and knee reconstruction, and patients follow total joint pathways that include standardized pain management, anesthesia, and physical therapy. All eligible patients were invited to join the study group. Data were collected from February 23, 2015, through April 23, 2015. We included patients undergoing unilateral TKA with a diagnosis of osteoarthritis, rheumatoid arthritis, or posttraumatic arthritis. Patients were excluded for any other diagnosis necessitating TKA, allergy to any of the medications used in the study, and for preoperative opiate use. We also excluded patients with renal impairment and women who were pregnant. Informed consent was obtained in the office before surgery. The study was approved by the hospital Institutional Review Board.

All patients were given a preoperative dose of 400-mg celecoxib unless they were found to have renal impairment. They were also given 10 or 20 mg of extended-release oxycodeone based on the patients’ age and weight. All surgeries were performed under tourniquet control by one of 5 fellowship-trained surgeons using either a posterior-stabilized or cruciate-retaining single-radius design prosthesis. Cruciate-retaining vs cruciate-substituting prostheses were chosen at the discretion of the surgeon. A midvastus approach was used and all patellae were resurfaced. Spinal anesthesia with sedation was used for all procedures as was tranexamic acid. No femoral nerve blocks were used. Postoperative pain control was achieved with 400-mg celecoxib per day, narcotics (oxycodeone, hydrocodone, or hydromorphone), and intravenous pantoprazole. All patients were given a preoperative dose of 400-mg celecoxib with 1:200,000 epinephrine and 10 mg of morphine at the conclusion of the knee arthroplasty directly into the joint space after the skin was closed but before removing the drapes. The patients in arm 2 received an injection of 30 mL of 0.25% bupivacaine with 1:200,000 epinephrine and 10 mg of morphine throughout the joint in a PA fashion, injecting the posterior capsule, lateral and medial subcutaneous tissues, medial and lateral collateral ligaments, quadriceps and patellar tendons, the medial retinaculum, and femoral periosteum. Patients in arm 3 received an injection of liposomal bupivacaine (Exparel; Pacira Pharmaceuticals) in the same PA fashion as described previously. The injections for arms 2 and 3 were completed after all bone cuts were made but just before implantation, and the remainder of the medication to be placed subcutaneously was completed after component implantation. The medications in each group were diluted with 0.9% normal saline to obtain a total volume of 60 mL for injection. Given that the manufacturer of liposomal bupivacaine recommends that the medication be delivered by a 25-gauge or larger bone needle, a 22-gauge needle was used for all injections [4].

Randomization to one of the 3 arms occurred in the operating room (OR) just before incision. Patients were randomized to one of the study groups by having the circulating nurse roll a standard die. There were no dropouts among these patients. After randomization, 82 patients were assigned to arm 1, 62 to arm 2, and 63 to arm 3. Enrollment in the study continued until all 3 groups had sufficient numbers of patients for statistical analysis, thus the difference in the number in each arm of the study. Demographics for patients in the 3 arms are shown in Table 1. All 3 arms were statistically similar when comparing mean age, mean body mass index, gender and race proportions, and mean hospital LOS.

In comparing postoperative average pain VAS, there were no differences in either mean overall or mean maximum postoperative pain scores among the 3 arms. In comparing mean morphine equivalents of opiate pain medications used per 24 hours postoperatively, there were also no statistically significant differences among the 3 arms (Table 2). When stratifying by gender or race, there again was no difference seen among the 3 arms of the study.
An analysis was also completed to evaluate total surgical time from skin incision to closure to determine whether there was any significant difference in the operative time between study arm groups. Only one of the 5 surgeons had a statistically significant increase in operative time when administering PA injections vs the IA injection (Table 3). The differences in surgical times seen between the difference surgeons were directly associated with time in practice and surgical experience. The 2 surgeons with the most experience had the shortest surgical times, whereas the longest surgical times were recorded by the most junior surgeon involved in the study.

In comparing the mean cost for pain control during the perioperative and postoperative periods combined, the cost for arm 3 (mean [standard deviation] = 402.09 [8.78] USD) was significantly higher than the cost for arm 1 (15.99 [5.01] USD) or arm 2 (23.21 [4.56] USD; P < .001).

### Discussion

The orthopedic literature is replete with examples of acceptable post-TKA pain reduction techniques. As noted previously, multimodal analgesia has allowed surgeons to mitigate patients’ pain after surgery and expedite patients’ recovery. This, in turn, has allowed patients to be safely discharged sooner and more frequently to their home vs a rehabilitation center. However, it has been difficult to compare perioperative pain management techniques given that many studies compare disparate treatment techniques. Some have compared femoral nerve block (FNB) with liposomal bupivacaine, whereas others have compared FNB with more commonly used PA injections. Other studies have examined the effect of PA injections vs a control group of no injections.

Outside of the field of orthopedics, liposomal bupivacaine has been studied in patients undergoing inguinal hernia repair, herniorrhoidectomy, breast augmentation, and prostatectomy. Given its excellent safety profile and effectiveness in providing postsurgical pain relief, investigators have been studying liposomal bupivacaine in the orthopedic arena [5]. Golf et al [6] demonstrated that the use of liposomal bupivacaine in bunionectomies resulted in lower pain scores and decreased narcotic usage. In a single-center matched cohort study, lower pain scores and shorter hospital stays have been demonstrated in TKA patients when using liposomal bupivacaine compared with FNB [7].

A more recent randomized prospective study comparing liposomal bupivacaine with FNB found no significant difference in postoperative pain scores or narcotic consumption, but the authors noted that there was no compromise in early rehabilitation in the liposomal bupivacaine group [8]. However, a power analysis was not provided in that study to indicate whether the study was sufficiently powered to find a difference between the 2 study groups. In both retrospective and prospective studies comparing liposomal bupivacaine with more common multimodal analgesia, no statistical difference in patients’ postoperative pain scores could be demonstrated [9].

Our results demonstrate that liposomal bupivacaine did not decrease mean or maximum painVAS after unilateral TKA when compared with either PA or IA bupivacaine/morphine injections. Furthermore, mean maximum pain VAS was not different when comparing the 3 arms in our study population. Schroer et al [10] recently demonstrated in their randomized prospective trial that liposomal bupivacaine mixed with 0.25% bupivacaine was not superior to 0.25% bupivacaine given in a PA fashion intraoperatively with regard to postoperative narcotic consumption and pain VAS. They also noted the increased costs associated with using liposomal bupivacaine. Our findings were similar; however, we incorporated a third group in which we simply used an IA injection of bupivacaine with morphine at the conclusion of the procedure, a standard performed for our patients for over a decade. It is commonly purported that IA injections do not provide the same effect as PA injections in TKA. To our knowledge, this is the first adequately powered randomized study that demonstrates that an IA injection of bupivacaine with morphine is as effective as a PA injection of the same medications. This is important for several reasons. Some surgeons note an increase in procedure times when administering a PA injection compared with an IA injection. This adds to the overall cost of TKA given the longer OR time and decreases the efficiency of high-volume centers without adding any proven benefit to the patient outcome. Interestingly, we did not find this to be the case. For 4 of the 5 surgeons, there was no significant difference in procedure times between the 3 arms in the study. It should be noted that a post hoc power analysis showed that our study was not powered to detect such a difference. In addition, there is lower risk with an IA injection compared with a PA injection. The PA injection typically includes not only the soft tissues about the knee but also the posterior capsule of the knee. Even with proper technique, there is a small risk of intravascular injection that is all but eliminated with IA injections.

With regard to cost, the liposomal bupivacaine group was the most expensive at approximately $400 USD when compared with the cost of either the PA injection (approximately $23 USD) or the IA injection (approximately $16 USD). With no demonstrable improvement in pain VAS or narcotic consumption, there is no

<table>
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<th>Arm 3</th>
<th>P Value</th>
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<tr>
<td>5</td>
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<td>67.7 (8.3)</td>
<td>68 (8.6)</td>
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### Table 1

Demographics.

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<td>.11 b</td>
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<tr>
<td>.62 b</td>
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<td>.09 a</td>
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BMI, body mass index; SD, standard deviation.

*a Using analysis of variance.

Table 2

Postoperative Outcomes.

<table>
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<tr>
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<td>.94 a</td>
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<tr>
<td>.97 a</td>
</tr>
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</table>

MME, mean morphine equivalents; SD, standard deviation.

*a Using analysis of variance.
justification for routine use of liposomal bupivacaine in TKA. In addition, the use of liposomal bupivacaine did not significantly change LOS of our patients (1.3 days for the IA group vs 1.4 days for the liposomal bupivacaine group). Therefore, there does not appear to be any true clinical benefit or cost savings when using liposomal bupivacaine.

There are some limitations to our study. First, 5 surgeons were involved in the data collection, which could bias the results seen. However, all 5 surgeons adhered to the same preoperative and postoperative regimen for pain management and physical therapy, and all data were collected from a single center. The nursing and physical therapy teams that cared for and assessed the patients postoperatively were also the same for all study patients. The protocols used for rapid recovery at our institution have been in place for years and were not altered in any way during the study period. In addition, all patients received the same preoperative and postoperative information and education, thereby minimizing differences among the patients. Second, although the patients and postoperative staff were blinded to the treatment arm, the surgeons and the OR team could not be blinded because the appearance of the various medications was different and the mode of administration differed as well, depending on the study arm (IA vs PA). However, to attempt to reduce bias as much as possible, the OR team and surgeons did not collect or analyze any of the data. Third, our LOS was short enough that it is possible that some of the positive effects of liposomal bupivacaine were missed. Several surgeons have noted that liposomal bupivacaine should be administered along with plain bupivacaine in the OR because of the delay in peak effectiveness of liposomal bupivacaine. They point out that plain bupivacaine gives pain relief locally for the 8-12 hours it may take for liposomal bupivacaine to take full effect. We chose not to add plain bupivacaine to the liposomal bupivacaine as the manufacturer advises against using other local anesthetics in the same location as liposomal bupivacaine at the time of surgery in their package insert. Furthermore, we wanted a true comparison of the effects of liposomal bupivacaine injection as recommended by the manufacturer vs PA and IA injections. Finally, if there were a bias against liposomal bupivacaine because of the short LOS of our patients and time for peak effectiveness, we would have expected it to impact the mean maximum pain scores noted, which it did not.

In the current era of medicine, value-based care is being sought out as the defining outcome of procedures, including one as common as TKA. Value is a combination of quality of care, including outcomes, and cost. To continue to improve outcomes while containing costs, treatment options must be critically evaluated with research that can discern what truly works and what does not. Our study demonstrates that the cost of liposomal bupivacaine is not warranted in routine unilateral TKA. Furthermore, a simple IA injection of bupivacaine with morphine is as effective as the potentially more time-consuming method of PA injection and is likely safer.

Acknowledgments

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References