Liposomal Bupivacaine
A Comparative Study of More Than 1000 Total Joint Arthroplasty Cases

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KEYWORDS

• Liposomal bupivacaine • Knee arthroplasty • Hip arthroplasty • Pain control • Analgesia

KEY POINTS

- Pain after total joint arthroplasty (TJA) can be severe and difficult to control. A single-dose local analgesic has been introduced that delivers bupivacaine in a liposomal time-release platform.
- The study included 2248 consecutive hip and knee arthroplasty cases, in half of which (Pre) the subjects were treated using a well-established multimodal analgesia, including periarticular injection (PAI).
- In a matching number of procedures the PAI was substituted for a liposomal bupivacaine injection technique (Post).
- Visual analog scale pain scores were significantly lower for patients treated with liposomal bupivacaine for both hip (1.67 vs 2.30; $P<.0001$) and knee (2.21 vs 2.52; $P<.0001$) procedures.
- We found improvement in pain relief in a large series of patients who had TJA after the introduction of a liposomal bupivacaine as part of an established multimodal protocol.

INTRODUCTION

More than 1.1 million total joint arthroplasties (TJAs) are performed annually in the United States[1] and are widely considered highly successful in terms of improving the quality of life of patients with osteoarthritis.[2] Despite its success, pain after TJA can be severe and difficult to control.[3] Clinical studies and hospital record analysis have shown that severe postoperative pain can be associated with an increased risk of complications, including rehabilitation delay,[4] prolonged return to normal functioning,[5,6] progression to persistent pain states,[7,8] prolonged hospital stay,[9] and increased readmission rate,[10] all of which can lead to increased cost of care.[11–14]

Many complications after TJA may be associated with the pain management strategies. Opioid analgesics, including intravenous patient controlled and oral, have been a standard modality for postoperative pain management, but are associated with the risk of nausea, pruritus, vomiting, respiratory depression, prolonged ileus, and cognitive dysfunction.[15–17] Regional pain control techniques, such as femoral nerve blockade, may limit exposure to opioid related adverse events (ORAE), but may cause quadriceps weakness, neuropathy, and postoperative falls.[18,19] Periarticular injection (PAI) has been shown in case series and randomized controlled trials to decrease pain, increase function, and reduce ORAEs after TJA.[20–22] PAI has also been suggested to

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be cheaper and easier to perform than other regional modalities, such as femoral neck blocks.[3]

A single-dose local analgesic has recently been introduced that delivers bupivacaine in a liposomal time-release platform. To date, there is still little clinical evidence concerning the effect of the time-release mechanism on patient-reported pain among differing PAI modalities. This comparative study compared a large sample of procedures using a novel extended-release liposomal bupivacaine during PAI, to a control group of procedures previously conducted using PAI without liposomal bupivacaine, using pain control as the primary outcome measure. Because of the time-release mechanism incorporated in liposomal bupivacaine, we hypothesized that this group would have demonstrably lower visual analog scale (VAS) pain scores for the immediate postoperative period.

MATERIALS AND METHODS

In the period between December 2011 and October 2012, 1124 consecutive hip and knee arthroplasty procedures were performed using a well-established multimodal analgesia (including PAI with Marcaine, with or without ketorolac, and morphine) and therapy protocols (the Pre group). This sample included all procedures representative of a traditional hip and knee arthroplasty practice, including primary and revision hip and knee procedures, and unicompartmental knee arthroplasty procedures. Four surgeons in a dedicated arthroplasty practice provided cases for this study.

In the period that immediately followed (October 2012 to August 2013), a matching number of 1124 consecutive hip and knee arthroplasty procedures were performed with similar therapy protocols, but substituting the established PAI for an US Food and Drug Administration (FDA)–approved liposomal bupivacaine surgical site soft tissue injection (PAI) technique (EXPAREL, Pacira Pharmaceuticals, Parsippany, NJ) as part of their multimodal analgesia protocol (the Post group). The procedures covered during this period also represented the complete hip/knee arthroplasty practice and were performed by the same 4 surgeons. The sample size was chosen to maximize the number of patients who could be compared in a 1:1 fashion with a commensurate sample of patients receiving liposomal bupivacaine. Because more than 1000 patients were recruited for each group, this study has more than 90% power at an alpha level of 0.05 to detect an effect size of 0.20 in the average VAS pain score based on post-hoc power calculations.

The primary outcome measures were the average VAS pain score for each patient and the percentage of VAS pain scores during hospitalization that were 0, which is a result of patients answering that they had no pain. The average pain score was aggregated for each patient for the entire stay as well as for each individual day of stay. VAS pain data were collected by nursing personnel, who were blinded to the surgical analgesia treatment protocol, at every instance in which they had contact with the patient, which resulted in an average of 9 VAS scores taken for each day of hospital stay for each patient. The collection of VAS pain scores was implemented through a robust prospective data gathering system that is the result of a custom effort at the study site that occurred before the initiation of the current study protocol. VAS data and other relevant medical parameters are collected routinely on every case that passes through the study center.

Secondary outcome measures were analyzed for a subset of the patient sample (2000 patients) and included an analysis of the rate of mortality, infection, hemorrhage/hematoma, falls, deep venous thrombosis, major cardiopulmonary events (including pulmonary embolus), autologous transfusion, readmission, and missed therapy caused by nausea/vomiting. For this subgroup, which was selected based on direct data from hospital records, patient satisfaction and cost were also compared between groups. Overall patient-reported satisfaction was measured blind to the surgeon and hospital via the Press Ganey survey. The cost analysis included a comparison of total direct hospital costs for all supplies and pharmaceuticals for each treatment group, as reported by hospital administration. All patient information was deidentified, and this is an institutional review board–approved study via exemption. Statistical analysis was performed with SAS software (SAS Institute Inc, Cary, NC) version 9.4, comparing demographics, pain scores, complications, length of stay (LOS), and patient satisfaction. The study sample size was large enough that 2-sample Student *t*-tests were implemented to test for differences in the means between Pre and Post groups for age, body mass index (BMI), and LOS even though the variables were not normally distribution. For categorical variables, including gender, χ^2 tests were used. Differences in pain scores were tested using 2-sample *t*-tests to compare differences between group means. Furthermore, regression analyses were implemented to investigate associations between patient demographics, surgery, or treatment group with average pain scores overall and by day. Variables in the regression analysis included race, ethnicity, BMI, gender, hip/knee, LOS, surgeon, Pre/Post, and patient age at surgery. Satisfaction