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Liposomal Bupivacaine Associated with Cost Savings during Postoperative Pain Management in Fragility Intertrochanteric Hip Fractures

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Background: Intertrochanteric hip fractures are among the most common and most expensive diagnoses in the Medicare population. Liposomal bupivacaine is a novel preparation of a commonly used analgesic agent that, when used intraoperatively, decreases narcotic requirements and hospital length of stay and increases the likelihood of discharge to home. The purpose of this investigation was to determine whether there was an economic benefit to utilizing intraoperative liposomal bupivacaine in patients with fragility intertrochanteric hip fractures in comparison to a group of patients who did not receive liposomal bupivacaine.

Methods: This is a retrospective observational study performed at two academic medical centers. Fifty-six patients with intertrochanteric hip fractures treated with cephalomedullary nail implant who received standard hip fracture pain management protocol were compared to a cohort of 46 patients with intertrochanteric hip fractures who received additional intraoperative injections of liposomal bupivacaine. All other standards of care were identical. A cost analysis was completed including the cost of liposomal bupivacaine, operating room costs, and discharge destination. Statistical significance was set at $p < 0.05$.

Results: Although the length of hospital stay was similar between the two groups (3.2 days vs. 3.8 days, $p = 0.08$), patients receiving intraoperative liposomal bupivacaine had a lower likelihood of discharge to a skilled nursing facility (84.8% vs. 96.4%, $p = 0.002$) and a longer operative time (73.4 minutes vs 67.2 minutes, $p = 0.004$). The cost-benefit analysis indicated that for an investment of $334.18 in the administration of 266 mg of liposomal bupivacaine, there was a relative saving of $1,323.21 compared to the control group. The benefit-cost ratio was 3.95, indicating a $3.95 benefit for each $1 spent in liposomal bupivacaine.

Conclusions: Despite the increased initial cost, intraoperative use of liposomal bupivacaine was found to be a cost-effective intervention due to the higher likelihood of discharge to home during the postoperative management of patients with intertrochanteric hip fractures.

Keywords: *Hip fractures, Bupivacaine, Postoperative pain, Costs, Cost analysis, Bone nails, Intramedullary fracture fixation*

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Hip fractures are among the most common types of fragility fractures in the elderly population, with most fractures occurring in the intertrochanteric region.[1,2] The incidence is expected to increase with predictive models estimating the incidence of fragility hip fractures to be as high as 4.5 million globally by 2050. Intertrochanteric hip fractures are estimated to account for 42% of total hip fractures in the United States.[3] The cost of the initial hospitalization

is approximately $10,000 USD and the estimated 1-year healthcare and social costs are $43,000 USD.[4] The treatment and management of hip fractures are among the costliest diagnoses in the Medicare population accounting for over $5.96 billion in direct costs in the first year,[3,4] much of which can be attributed to complications secondary to postoperative pain.[5]

One of the most prevalent pharmacotherapies utilized in postoperative pain management is opioids. Albeit effective, these medications are associated with various medical side effects such as respiratory depression, postoperative ileus, hypotension, and significantly increased length of stays (LOSs) and hospitalization costs.[6] Orthopedic patients are more likely to develop an opioid-associated adverse event when compared to general surgery and obstetric patients.[6] These risk factors and the increased morbidity and mortality associated with opioid use have incentivized the use of multi-modal pain management following orthopedic procedures such as total hip arthroplasty (THA), rotator cuff repairs, and femur fractures.[5,7,8]

With healthcare transitions to a value-based payment model, it has become imperative that physicians focus on minimizing costs while optimizing outcomes and reducing the risk of complications.[9] The multivesicular liposomal formulation of bupivacaine allows for slower release compared to standard bupivacaine and prolonged period of pain relief of up to 72 hours.[10] With respect to intertrochanteric hip fractures, liposomal bupivacaine (LB) has been shown to improve functional outcomes and significantly reduce direct hospital costs per patient as a result of reduced LOS and increased discharge to home.[11] However, studies have yet to show if there is a cost benefit to using LB in the management of postoperative pain following fixation of intertrochanteric hip fractures. The purpose of this study was to evaluate the cost-effectiveness of LB as an adjunctive form of pain management in the postoperative care of intertrochanteric hip fractures. We hypothesized that using intraoperative LB would be more cost-beneficial than the current standard postoperative pain management when accounting for a greater likelihood of discharge to home.

METHODS

Patient Selection

Prior to the start of this investigation, approval was obtained from the Institutional Review Board of Pomona Valley Hospital Medical Center (IRB No. 2019-0306). A retrospective review was performed on prospectively collected patient data using the electronic medical records at two medical centers (Loma Linda University Medical Center and Pomona Valley Hospital Medical Center) from June 2016 to December 2017. International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) procedural codes and ICD, tenth revision, clinical modification (ICD-10-CM) procedural codes were used to identify patients with intertrochanteric hip fractures (820.21, S72.143A). This study included patients with intertrochanteric hip fractures treated with a cephalomedullary implant and intraoperative LB by the senior authors (NHA and HGB). Patients were excluded from this study if they presented with polytrauma, preexisting dementia or delirium, open reduction, pre- or postoperative anesthetic block administration, regional anesthesia, a chronic pain diagnosis, or fixation with a dynamic hip screw. All patients that were included in this study were treated across the two separate institutions. A control group was selected as consecutive patients treated during the same time but without LB that met identical inclusion and exclusion criteria. All patients who fit both the inclusion and exclusion criteria were included for analysis. Information regarding age, sex, American Society of Anesthesiologists (ASA) level, Charlson Comorbidity Index (CCI), time to surgery, fracture stability according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopedic Trauma Association classification,[12] cost of treatment, operating room (OR) costs, LOS, and place of discharge were collected (Tables 1 and 2).

Surgical Technique

After receiving perioperative clearance, patients were taken to the OR where they received general anesthesia as part of institutional protocol. Surgery was performed according to standard established practice.[13] Following reduction and fixation, 266 mg of LB in a 20 mL solution (Exparel; Pacira Pharmaceuticals, Parsippany, NJ, USA) was mixed with 80 mL of 0.9% normal saline and 20 mL of 0.5% bupivacaine. To provide immediate analgesia prior to liposomal degradation, standard bupivacaine was added to the LB. The total 120 mL volume distributed into six 20-mL syringes (18-gauge, 50.8-mm length) was injected into various locations. One syringe, 20 mL, was injected into the soft tissue and periosteum of the nail entry site, another 20 mL was injected into the superior and inferior nail bony entry sites, another 20 mL was injected anteriorly and posteriorly at the hip screw site into the periosteum, 10 mL was injected superior to the hip screw site into the periosteum, 30 mL into the fracture hematoma, and the last 20 mL into the distal interlock sites. Following the operation, patients received standardized postoperative pain

Table 1. Patient Demographics

Variable	Liposomal bupivacaine (n = 46)	Control (n = 56)	*p*-value
Age (yr)	76.3 ± 9.8	78.1 ± 10.5	-
Female : male	34 : 12	39 : 17	0.67
ASA level	3.4 ± 0.6	3.3 ± 0.5	0.20
CCI	1.7 ± 1.4	1.5 ± 1.3	0.10
Mean time to surgery (day)	1.2 ± 2.1	1.1 ± 2.4	0.57
Stable fracture	13.0	16.0	1.00
Unstable fracture	33.0	40.0	1.00

Values are presented as mean ± standard deviation.
ASA: American Society of Anesthesiologists, CCI: Charlson Comorbidity Index.

Table 2. Cost-Benefit Analysis

Variable	Liposomal bupivacaine	Control	Difference
Liposomal bupivacaine treatment cost ($)	334.18	0	334.18
Cost saving of likelihood of discharge home vs. SNF* ($)	–2,576.70	–687.12	–1,889.58
Operating room cost ($37.45/min[14]) ($)	2,748.83	2,516.64	232.19
Cost saving ($)			–1,323.21

SNF: skilled nursing facility.
*Determined by comparing total cost of hip fracture care for patient discharged with home health vs. SNF.

management in the post-anesthesia care unit (PACU).[15]

Pain Control, Discharge, and Rehabilitation Protocol

Rehabilitation, PACU care, pain management, and discharge protocols were standardized at both institutions.[14] The decision to discharge was a multifocal decision between pain control, physical therapy, and the functional status of the patient at the time. Postoperative pain management protocol was based upon visual analog scale for pain (VAS-pain). All patients without contraindications to the use of nonsteroidal anti-inflammatory drugs, such as history of gastrointestinal bleeding or diabetes mellitus, received 500 mg of Naproxen or 650 mg of acetaminophen every 6 hours around the clock. For patients reporting mild pain, defined as 0–3 on the VAS-pain scale, they received hydrocodone/paracetamol every 4 hours. If patients reported moderate pain (VAS-pain 4–7), they received oxycodone/acetaminophen every 4 hours. Patients reporting severe pain (VAS-pain 8–10) received 1–2 mg of morphine every 3 hours. Patients were discharged once they achieved adequate pain control and demonstrated that they were able to ambulate and return to a safe environment. Criteria for discharge home included the ability to obtain and self-administer medications, ability to perform self-care activities, ability to manage nutritional needs, and ability to engage follow-up care as needed. If the multidisciplinary evaluation demonstrated a failure to achieve all four of these criteria, the patient was discharged to a skilled nursing facility (SNF).

Cost Analysis

A cost-benefit analysis was conducted to determine the benefit-cost ratio (BCR; benefit divided by cost), and net benefit (benefit minus cost) of treatment with LB. This basic cost analysis was performed to assess the relative cost difference between the intervention and control groups. The added cost of LB, and direct and indirect cost savings associated with the differences in outcome measures were assessed. The cost savings associated with the likelihood of discharge home was calculated by subtracting the total cost of hip fracture care for a patient with home health from the total cost of a patient discharged to an SNF and multiplying this cost difference by the proportion of patients discharged home in each cohort. We also assumed that

the change in LOS would be incorporated into the savings from discharge home versus discharge to an SNF. These metrics were derived from patients undergoing hemiarthroplasty (diagnosis-related group 469), as these values were not readily available in the literature for extracapsular hip fractures.[16] The 90-day cost of SNFs and home health was $18,480 and $1,302, respectively.[3] OR costs were determined by the average operating time, as defined from incision to closure, and multiplying it by the average cost per minute using financial data from California's short-term general and specialty hospitals in fiscal year 2014.[17] Cost differences in mean morphine equivalent were not calculated as these would be dependent on the opioid formulation used and may be patient-dependent.

The investment cost of LB was $334.18 for 266 mg included in a single injection.[18] Benefits included direct hospital costs, encompassing differences attributable to the previously mentioned variables (OR time, disposition, and LOS). The basis of this analysis was not dependent upon the hospital costs incurred per day as there may be a multitude of factors other than pain that influence LOS. It is important to note that readiness to discharge is not equivalent to time to discharge from the hospital. However, the overall cost of the encounter was implemented into the cost analysis with discharge to home with home health aide versus discharge to an SNF accounting for the differences in cost. The costs for each patient were extrapolated for the global charge of going home versus discharge to a special nursing or rehabilitation facility.

Statistical Methods

The statistical analysis of this study was performed using Microsoft Excel (Microsoft, Seattle, WA, USA) and Stata ver. 13.0 (StataCorp., College Station, TX, USA). Descriptive analysis was completed of continuous variables and included means and standard deviations. Continuous variables were compared using unpaired two-tailed student *t*-tests, and categorical variables were compared with Fischer's exact and chi-square tests. Statistical significance was set at $p < 0.05$.

RESULTS

A retrospective chart review identified 46 patients who received intraoperative LB and 56 patients in the control group. There was no significant difference in demographic data including age, sex, CCI, and ASA level ($p > 0.05$) (Table 1). Both groups demonstrated similar LOS (3.2 days vs. 3.8 days, $p = 0.08$). However, the LB group demonstrated a greater likelihood of discharge home (15.2% vs. 3.6%, $p = 0.001$), a lower likelihood of discharge to an SNF (84.8% vs. 96.4%, $p = 0.002$), and a longer operative time (73.4 minutes vs. 67.2 minutes, $p = 0.004$).

The cost-benefit analysis (Table 2) indicated that an investment of $334.18 for the administration of LB resulted in a savings of $1,323.21 relative to the control group when factoring in the cost savings of likelihood of discharge home versus SNF and added OR time.[18] Compared to conventional treatment, the BCR was 3.95 (i.e., $3.95 in benefit per patient was realized for every $1 investment in LB), corresponding to a total net benefit (benefit minus cost) of $1,323.21 per patient.

Complications

During the initial hospital stay, 5 complications occurred in the intervention group and 7 complications in the control group ($p = 0.97$) (Table 3). There was no difference ($p = 0.51$) in the rate of readmission between the intervention group (n = 5, 10.8%) and the control group (n = 4, 7.14%). None of the observed study complications were consistent with documented adverse reactions from LB in adults, which include nausea, constipation, and vomiting.[18]

DISCUSSION

The results of this investigation demonstrate that although the use of LB during the fixation of an intertrochanteric hip fracture was associated with longer operative time (73.4 minutes vs. 67.2 minutes), likely due to the time for preparation and injection, LB proved to have a cost benefit when compared to the standard of care. LB treatment was associated with an average net benefit of $3.95 for every

Table 3. Complications

Complication	Intervention group	Control group
Delirium	5 (10.8)	3 (5.3)
Congestive heart failure	1 (2.1)	1 (1.8)
Anemia	1 (2.1)	0
Deep vein thrombosis	1 (2.1)	0
Urinary tract infection	1 (2.1)	1 (1.8)
Atrial fibrillation	0	1 (1.8)
Pneumonia	0	1 (1.8)
Shortness of breath	0	1 (1.8)
Stroke	0	1 (1.8)

Values are presented as number (%).

$1 spent on patients in the LB group. Accounting for this increased OR time, in this cohort, that translated to an average $1,323.21 saved per patient. A large part of this cost-benefit of LB was due to the fact that patients receiving LB had a greater likelihood of discharge to home than their counterparts, which can be attributed to better postoperative pain control leading to earlier mobilization and more intensive physical therapy, both of which have been shown to shorten hospital stay, improve physical function, and maintain ability to perform activities of daily living, giving the patients a better chance of fulfilling criteria for home discharge.[14] These cost savings are an important part of clinical decision-making as savings cumulatively impact the direct cost of care. These costs are becoming increasingly important in a society where the cost of healthcare has continued to steadily increase while reimbursements have decreased over the years.[3]

As one of the more common and most expensive diagnoses in the Medicare population, there is a targeted movement by healthcare administrators and researchers to make hip fracture management more cost-effective.[4] In 2014, the estimated annual economic burden of intertrochanteric fractures was $2.63 billion in direct costs.[3] The introduction of bundled payment initiatives has been shown to decrease the need for expensive post-acute care facility utilization after femur and hip fractures while optimizing patient outcomes.[19] In bundled payment structures, the hospital is reimbursed a single payment to cover an entire episode of a patient's stay from 72 hours before admission through 90 days after discharge.[19] Lott et al.[20] showed that bundled patients receiving THA had a significantly increased discharge to home as compared to non-bundled patients. In joint arthroplasty, it has been shown that discharge to SNFs is one of the strongest predictors of 30-day complications and readmission rates.[20] The two primary cost drivers during the 90-day after discharge period for intertrochanteric hip fractures are inpatient admission and discharge to SNFs.[3] According to Bentler et al.,[21] as many as 58% of patients with hip fractures are discharged to SNFs, contributing to 42% of the annual cost. It has been shown that discharge to home vs discharge to an SNF is associated with improved overall costs and better long-term outcomes, such as decreased morbidity, fewer unplanned readmissions, and fewer septic or urinary complications.[3,22] By minimizing post-acute hospitalization facility care and decreasing opioid requirements and associated complications, LB is another way to make hip fracture management more cost-effective for healthcare institutions. This study has demonstrated that LB is associated with a greater likelihood of discharge to home and is a valuable mechanism to improve the cost-effectiveness of hip fracture management.

Delivered in a bolus form, non-LB is a common method of analgesia with a low duration of efficacy.[23] LB is a novel preparation that utilizes encapsulating agents, which allow the anesthetic agent to be delivered in a sustained release manner resulting in prolonged analgesia. As the capsule composed of lipid layers decays in the body, the anesthetic is exposed from the aqueous sac, releasing a less concentrated burst of medication.[24] This formulation prolongs the anesthetic activity for up to several days with the most relief up to 72 hours.[10] In patients receiving LB during THA, Yu et al.[25] found that there was a statistical reduction in narcotic requirements when compared to other periarticular injections. In the management of intertrochanteric hip fractures, patients receiving LB required less morphine equivalents and reported improved postoperative pain scores during the first 24 hours.[11] These findings are also similar to other studies done in non-orthopedic patients such as colorectal and abdominal surgery.[26] In the postoperative pain management of the elderly, narcotics have long been the primary mainstay of treatment. However, narcotics are associated with a wide variety of 90-day complications, which often necessitate further management, for which hospitals and physicians would not be compensated.[6] In the search for non-opioid methods of managing of postoperative pain, LB is a valuable alternative for postoperative pain control without the associated medical complications of narcotics.

The findings of this study are similar to the findings of previous investigations that LB has a higher BCR compared to standard of care. Kirkness et al.[27] explored the use of LB in total knee arthroplasty and found that there was an investment cost to using LB. However, this cost was offset by a shorter LOS, which resulted in significantly shorter room and board costs. In regard to THA, Yu et al.[25] had similar findings with decreased LOS and increased discharge disposition to home in patients receiving LB. In addition to its use during arthroplasty, LB has been evaluated in the postoperative care of arthroscopic rotator cuff with similar findings.[9] Our study similarly found that although LB was associated with an investment increased OR times, the associated increased discharge to home made it a valuable cost-saving measure. To our knowledge, this is the first study that explores the BCR of using LB in the management of intertrochanteric hip fractures.

There are several limitations to our study. The primary limitation is that the control group did not receive standard bupivacaine as part of their pain management. Standard bupivacaine, a significantly cheaper alternative,

is likely to help alleviate postoperative pain, but for a lesser duration due to its formulation.[27] Research has shown the increased efficacy of LB versus standard bupivacaine, but including standard bupivacaine as part of the standardized pain management protocol for the control group would have strengthened the findings of this study.[28] A second limitation of this study is the smaller sample size (n = 102) when compared to other retrospective cohort studies. However, we are confident our study groups were sufficiently diverse and well generalizable to the U.S. population, while recognizing the limited generalizability across international healthcare systems due to differences in insurance coverage, post-discharge management, and regional cost differences. Larger follow-up studies and further economic analyses are necessary to fully prove the cost-effectiveness of this intervention. Additionally, our findings are based on data gathered from two orthopedic surgeons and their respective institutions, and therefore may not be accurately descriptive of all orthopedic practices in the United States. Another limitation is that we do not know the incidence of complications that may have occurred outside the hospital. The reported complications were during the initial hospitalization prior to discharge. Lastly, because this study relied on ICD-9 and ICD-10 codes, we could not account for potential confounding effects associated with miscoding or undercoding. However, the potential for missed adverse events or diagnoses was presumed to be equal between the treatment and intervention groups.

The use of LB as a means of managing postoperative pain is still relatively new and there are several aspects of its use that are yet to be explored. While LB has already been in widespread use off-label as an effective means of pain control, it was only recently approved by the Food and Drug Administration as a regional nerve block for shoulder surgery.[29] Long-term complications have not yet been studied. Another area of future study is to evaluate and compare the efficacy and cost-effectiveness of regional blocks vs intraoperative LB. This study excluded patients who received regional blocks before and after operative fixation; however, regional blocks have been found to be efficacious for management of postoperative pain in hip fractures and may reduce operative time when compared to intraoperative LB.[30]

Despite the increased initial cost, intraoperative use of LB was found to be a cost-effective intervention due to the higher likelihood of discharge to home during the postoperative management of patients with intertrochanteric hip fractures.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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