

A prospective analysis describing the innovative use of liposomal bupivacaine in burn patients

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ABSTRACT

Burn patients frequently require autograft harvesting to facilitate wound healing, often resulting in significant pain. Liposomal bupivacaine is indicated for administration into a surgical site to produce postsurgical analgesia. The objective of this study was to evaluate efficacy, safety, and duration of postoperative analgesia with liposomal bupivacaine for donor site pain in burn patients. This was an observational, case–control study including adult patients with <20% total body surface area (TBSA) burned who received liposomal bupivacaine for postoperative pain management after autograft harvesting from lower extremity donor site(s). Patients from the case group were matched to historical control patients treated with traditional pain management. The primary outcome was the cumulative pain scores on postoperative day one measured by the area under the curve (AUC0–24). Secondary outcomes included AUC0–72, total milligram morphine equivalents (MME), length of stay, and adverse events. Data were collected in 36 patients who received liposomal bupivacaine, with 21 patients eligible for matching to historical controls. Patients included in the intervention and control groups were well-matched at baseline. Patients in the intervention group had a significantly lower median (IQR) AUC0–24 [578 (408,740) vs. 680 (544,803); $p = 0.05$] and shorter length of stay [4 days (1,9.5) vs. 6 days (318); $p = 0.01$]. No differences in adverse events related to the administration of liposomal bupivacaine or opioid-related adverse events were observed. Results indicate liposomal bupivacaine is safe and effective in burn patients. The results of this study add to the limited body of literature examining efficacy in this population.

Keywords: Liposomal bupivacaine; Burns; Autograft; Donor site; Pain management.

1. INTRODUCTION

Post-operative pain can be a significant issue for patients and caregivers. In fact, pain has been found to be one of the three most common causes of delayed discharge after ambulatory surgery. A study from 2003 found that approximately 80% of patients stated they experienced acute pain after surgery, despite being on pain management therapy. Post-operative pain can be associated with several negative outcomes such as tachycardia, hypertension, myocardial ischemia, decreased alveolar ventilation, and poor wound healing [1].

Current guideline recommendations are consistent in recommending a multimodal pain management approach, including non-opioid management whenever possible to reduce the risk of opioid-related adverse events [[2], [3], [4]]. The frequency of opioid-related adverse events is relatively common, with a published incidence ranging from 20% to 48%. These can include nausea/vomiting, constipation, confusion/agitation, drug dependence, respiratory depression, and itching/hives. These events can be problematic for patients and are associated with a significant clinical impact such as an increased length of hospital stay, increased hospital costs, and ultimately inadequate pain control [5].

Recently, opioid-related morbidity and mortality has reached epidemic levels in the United States. In 2015, there were over 33,000 deaths attributed to opioid overdose in the United States, an increase of nearly 5000 compared with the previous year. For the first time, drug overdose has surpassed firearms and motor vehicle trauma as the most common cause of accidental death among adults. The epidemic appears to have been fueled by the prescription of opioids. More stringent laws have been passed in some states in which prescribers are obligated to prescribe no more than seven days of opioids for a first prescription [6].

Liposomal bupivacaine is indicated by the FDA for administration into a surgical site to produce postsurgical analgesia. It utilizes a drug-delivery mechanism which allows bupivacaine to release slowly for up to 72 h. This unique formulation of bupivacaine contains a DepoFoam® technology that is composed of naturally occurring biodegradable and biocompatible lipids that are cleared by normal metabolic pathways. The dosage form encapsulates bupivacaine in a multivesicular liposomal drug delivery technology that

releases bupivacaine over time as lipid membranes reorganize. After bupivacaine has been released and is absorbed systemically, the distribution, metabolism, and excretion is expected to be the same as for any bupivacaine HCl solution formulation [7]. Liposomal bupivacaine has been shown to reduce opioid consumption post-operatively and improve patient outcomes in a variety of surgical procedures, including plastic surgery [[8], [9], [10], [11], [12], [13], [14]]. Its use in burn surgery patients has been extremely limited, to our knowledge. Case reports describing its use have been limited by small sample sizes and lacked clinical outcomes data due to not utilizing a control group for comparative efficacy [15,16]. Furthermore, these reports did not describe the use of a standardized institution-specific protocol. The objective of this study was to evaluate the efficacy, safety, and duration of post-operative analgesia with liposomal bupivacaine versus traditional management strategies of donor site pain in burn surgery patients utilizing a standardized protocol.

2. METHODS

2.1. PROTOCOL CREATION

This study was conducted at a 315-bed safety-net, academic medical center. The study institution is a Level I Trauma Center and American Burn Association (ABA) — verified Regional Burn Center with 15 inpatient beds within the Burn Center. In order to maximize patient safety with the use of liposomal bupivacaine, an institution-specific protocol for burn surgery patients was developed and implemented prior to study initiation. The protocol described the steps of the medication use process, including the indications for use, preparation, administration, and monitoring parameters for patients who received liposomal bupivacaine based on information provided in the package insert. Liposomal bupivacaine is currently available as a 266 mg/20 mL vial with a maximum dose of one vial per surgical site. It may then be diluted with 280 mL of Lactated Ringer's or 0.9% sodium chloride. A total of 30 mL of 0.5% or 60 mL of 0.25% bupivacaine HCl may also be added based on surgeon preference. The solution is instilled via a 25-gauge needle or tumescence cannula no sooner than 20 min after the administration of other local anesthetics. Formulations of bupivacaine other than liposomal bupivacaine should not be administered within 96 h following initial administration. The protocol also outlined routine

monitoring of vital signs and pain scores during the procedure and after the use of liposomal bupivacaine. One-on-one nursing and OR staff education emphasizing potential adverse events with the use of liposomal bupivacaine (e.g. nausea, vomiting, and neurological and cardiovascular adverse events) was conducted in real time for each patient [7].

2.2. STUDY DESIGN

This was a prospective, observational, case–control study approved by the local Institutional Review Board. After protocol implementation, data were collected prospectively in patients who received liposomal bupivacaine beginning on October 1, 2016 through January 6, 2018 and retrospectively in historical controls managed with traditional pain management strategies from January 1, 2015 through September 30, 2016. Patients were included who were at least 18 years of age, admitted to the Burn Center, had <20% total body surface area (TBSA) burned, and received an autograft utilizing a lower extremity donor site. Patients who were pregnant, incarcerated, had a history of opioid abuse, or who had chronic opioid use prior to admission were excluded from the analysis. Historical controls were matched based on age (± 10 years), %TBSA ($\pm 5\%$), donor site size (± 100 cm²) and depth of injury (superficial, partial, and/or full thickness).

2.3. DATA COLLECTION

Data collected from the electronic medical record included age, gender, race, weight, %TBSA, length of stay, serum creatinine on the date of procedure, depth of injury (superficial, partial, full thickness), size and location of donor site, dose of liposomal bupivacaine, amount and type of diluent utilized, other local anesthetics utilized, and administration technique. Pain scores were collected at 30 min and two hours post-operatively, and every four hours through 72 h post-procedure. Morphine milligram equivalents (MME) used over 24 and 72 h postoperatively were also assessed. Safety endpoints included opioid-induced (nausea/vomiting, constipation, pruritus, urinary retention), cardiovascular (bradycardia, hypotension, arrhythmias), and neurologic (respiratory depression, weakness, paresthesia, paralysis, local anesthetic systemic toxicity requiring lipid rescue) adverse effects.

2.4. OUTCOMES

The primary outcome was area under the pain score time curve on postoperative day one (AUC0–24). In the event of a missing pain score, one of three methods was utilized as described in a similar study by Dasta, et al. [7]. If the missing pain score was prior to the first non-missing pain score, the median score from other patients at the same time point was utilized. If the missing pain score was between two non-missing pain scores, linear interpolation was utilized. Finally, if the missing pain score was after the last non-missing pain score, the last observed pain score was carried forward.

Secondary endpoints assessed efficacy and safety. Efficacy outcomes included a composite endpoint of pain scores up to 72 h post-operatively measured by the AUC0–72, total MME opioid rescue medications on postoperative day one and postoperative days one through three, and the amount of liposomal bupivacaine instilled per cm² of donor site (area-normalized dose). Safety outcomes included adverse events (opioid-related, cardiovascular, and neurologic) and incidence of local anesthetic systemic toxicity requiring lipid rescue.

2.5. STATISTICAL ANALYSIS

Statistical tests were performed using Minitab® 16 statistical software (Minitab Inc., State College, PA). Normally distributed data were reported with mean (SD), whereas non-parametric data were reported with median [interquartile range (IQR)]. Normality was tested using the Anderson–Darling Normality Test. The Student’s paired t-test was used to detect differences between normally distributed, continuous data. For non-parametric, continuous data, a Wilcoxon Signed Rank test was used to detect potential differences. The Fisher’s Exact or χ^2 tests were used to detect differences in nominal data. The significance level (alpha) was predetermined to be less than or equal to 0.05. A sample size calculation was not performed a priori as a convenience sample of all eligible patients who received liposomal bupivacaine was utilized.

3. RESULTS

3.1. PATIENTS

A total of 41 patients received liposomal bupivacaine, 36 of which met inclusion criteria. Reasons for exclusion were history of chronic opioid use (n = 2), incarcerated (n = 1), and use of liposomal bupivacaine outside the institution-specific protocol (n = 2). Data were collected in all 36 patients who received liposomal bupivacaine (overall cohort). Of these patients, 21 had pain scores charted through at least 24 h postoperatively (intervention group) and were eligible to be matched to historical controls (control group).

Patient demographics are listed in Table 1. The included patients were middle-aged, white males with a small %TBSA. The overall cohort, intervention group, and control group were well-matched for age, gender, race, mechanism of injury (thermal vs. non-thermal), burn injury depth (superficial, partial, and/or full thickness), weight, serum creatinine on the day of surgery, and size of donor site with no statistically significant differences seen between groups. The only difference between the intervention group and the control group was that the intervention group had a significantly smaller median (IQR) %TBSA when compared to the control group [4% (2,7) vs. 5% (4,9); p = 0.04]. However, the overall difference in %TBSA was not regarded to be clinically significant by the authors and would have no effect on the overall management of these patients. Details regarding the dosing of liposomal bupivacaine in both the overall cohort and intervention group are listed in Table 2, including total dose, size of donor site, area-normalized dose of liposomal bupivacaine, and use of a diluent. Of note, no patients received additional bupivacaine and all patients received lidocaine prior to the administration of liposomal bupivacaine.

Table 1. Patient demographics.

Parameter	Overall (n = 36)	cohort Intervention (n = 21)	group Control (n = 21)	group p- value
Age, years (mean ± SD)	46 ± 17	45 ± 16	44 ± 18	0.42
Male, n (%)	22 (61)	18 (86)	14 (67)	0.28

Parameter	Overall (n = 36)	cohort Intervention (n = 21)	group Control (n = 21)	group p-value
Caucasian, n (%)	24 (67)	19 (90)	17 (81)	0.66
Thermal injury, n (%)	31 (86)	19 (90)	18 (86)	1.00
%TBSA [median (IQR)]	3 n = 31	(2,5) 4 n = 16	(2,7) 5 n = 16	(4,9) 0.04
Superficial thickness, n (%)	1 (3)	1 (5)	1 (5)	1.00
Partial thickness, n (%)	27 (75)	15 (71)	15 (71)	1.00
Full thickness, n (%)	9 (25)	4 (19)	4 (19)	1.00
Weight, kg [median (IQR)]	81.6 (69.1,101) n = 35	81.6 (68,105.5)	72.6 (67.1,91.8)	0.53
SCr, mg/dL (mean ± SD)	0.85 ± 0.22 n = 30	0.87 ± 0.23 n = 19	0.77 ± 0.13 n = 19	0.07
Size of donor site, cm ² [median (IQR)]	200 (100,438)	300 (200,650)	300 (200,700)	0.

Table 2. Liposomal bupivacaine dosing.

Parameter	Overall (n = 36)	cohort Intervention (n = 21)	group
Dose of liposomal bupivacaine, mg [median (IQR)]	151 (72,266)	266 (106,266)	
Size of donor site, cm ² [median (IQR)]	200 (100,438)	300 (200,650)	
Area-normalized dose of liposomal bupivacaine, mg/cm ² [median (IQR)]	0.50 (0.32,1.22)	0.38 (0.25,1.11)	
Use of diluted liposomal bupivacaine, n (%)	27 (75)	16 (76)	
Amount of diluent used, mL [median (IQR)]	280 (8280)	280 (15,280)	

3.2. PRIMARY OUTCOME: AUC_{0–24}

Fig. 1 displays results for AUC_{0–24} in the intervention and control groups. The median (IQR) AUC_{0–24} in the liposomal bupivacaine group was 577.5 (407.9,739.8) versus 680.3 (543.6,802.8) in the historical control group and this difference was found to be statistically significant ($p = 0.05$).

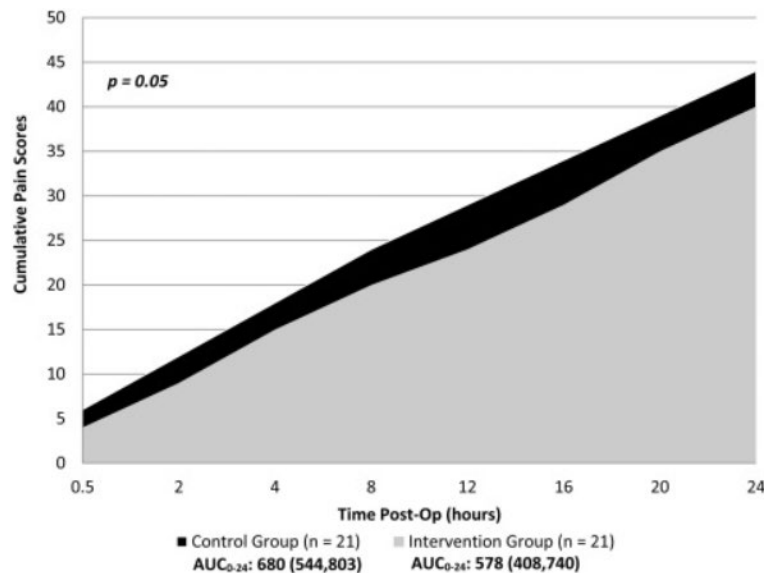


Fig. 1. Primary Outcome: AUC_{0–24} of matched intervention patients who received liposomal bupivacaine vs. AUC_{0–24} of historical control patients.

3.3. SECONDARY OUTCOMES

Secondary outcomes are reported in Table 3. In regard to the efficacy endpoints, there were no statistically significant differences in AUC_{0–72} or total MME administered over the first 24 or 72 h postoperatively. There was, however, significant decrease in median (IQR) hospital length of stay when comparing the intervention group vs. the control group [4 days (1,9.5) vs. 6 days (318); $p = 0.01$]. In regard to safety endpoints, significantly more patients had nausea/vomiting in the control group (95% vs. 67%; $p = 0.05$), and there were no statistically significant differences found in days to first bowel movement, documented pruritus, documented urinary retention, episodes of bradycardia or hypotension, or rates of arrhythmias. A bowel regimen was prescribed in greater than 95% of patients in both groups. No patients in either group experienced serious adverse events such as cardiac arrest, persistent anesthesia, paresthesia, weakness, paralysis,

respiratory depression requiring administration of naloxone, or local anesthetic toxicity requiring lipid rescue.

Table 3. Secondary outcomes.

Outcome	Intervention group (n = 21)	Control group (n = 21)	p-value
AUC₀₋₇₂ [median (IQR)]	3914 (34,824,984) n = 8	3138 (22,765,814) n = 8	1.00
Total MME over hours 0–24 [median (IQR)]	88.5 (33,110.5)	97.5 (63,137.3)	0.10
Total MME over hours 0–72 [median (IQR)]	246.3 (93,312.4) n = 8	137 (75,518) n = 8	0.62
Length of stay, days [median (IQR)]	4 (1,9.5)	6 (318)	0.01
Documented N/V, n (%)	14 (67)	20 (95)	0.05
Days to first bowel movement [median (IQR)]	1 (1,1.5) n = 9	2 (1,2.5) n = 9	0.10
Documented pruritus, n (%)	3 (14)	4 (19)	1.00
Documented urinary retention, n (%)	1 (5)	1 (5)	1.00
Episodes of bradycardia [median (IQR)]	0 (0,0)	0 (0,0)	0.68
Episodes of hypotension [median (IQR)]	0 (0,0)	0 (0,0)	1.00
Any arrhythmia, n (%)	0 (0)	1 (5)	1.00

MME = milligram morphine equivalents; N/V = nausea/vomiting.

4. DISCUSSION

Data from a study conducted by Apseloff, et al. showed time to onset of analgesia with liposomal bupivacaine and bupivacaine HCl to be similar. This was a Phase I, randomized, sequential-cohort, crossover study including 132 healthy volunteers randomized to four sequential cohorts to receive subcutaneous normal saline in one arm and either liposome bupivacaine 40 mg or bupivacaine HCl 7.5 mg in the other. At 30, 15, five, and two minutes after study drug administration for cohorts one through four

respectively, an incision was made in each arm and 18% acetic acid solution was applied to elicit pain. The primary outcome was a subject's assessment in pain intensity on a 100 mm visual analog scale. At two minutes post-dose, mean (SD) pain intensity scores were 26% lower with liposome bupivacaine versus placebo [47 (23) vs. 61 (19); $p < 0.0001$]. A greater than 30% reduction in mean pain scores was also observed for both liposome bupivacaine and bupivacaine HCl compared with saline placebo at five, 15, and 30 min after study drug administration, which was significant versus placebo at all three time points ($p < 0.0001$) [8,9].

Previously published studies have described the use of liposomal bupivacaine in a variety of non-burn surgical procedures [[9], [10], [11], [12], [13], [14]]. A meta-analysis by Dasta, et al. evaluated the comparative efficacy of liposomal bupivacaine versus bupivacaine HCl for post-surgical analgesia in over 900 patients. The analysis included nine double-blind, placebo, or active-controlled studies which evaluated the use of liposomal bupivacaine versus bupivacaine HCl, bupivacaine HCl plus epinephrine, or placebo. Surgical procedures included inguinal hernia repair, total knee arthroplasty, hemorrhoidectomy, breast augmentation, and bunionectomy. The results demonstrated patients who received liposomal bupivacaine had a significantly lower mean cumulative pain score (AUC) over 72 h post-operatively than patients who did not receive liposomal bupivacaine (283 vs. 329, respectively; $p = 0.039$). Additionally, patients who received liposomal bupivacaine had significantly less mean MME (12.2 vs. 19.0; $p < 0.001$), had a longer median time to opioid use (9.9 h vs. 2.7 h; $p < 0.001$), and had less patients with >1 opioid-related adverse event [101 (20.1%) vs. 147 (35.9%); $p < 0.001$] than patients who did not receive liposomal bupivacaine [10].

Liposomal bupivacaine has also been studied in a variety of plastic surgery procedures, which is relevant as data is often extrapolated from this patient population to the burn surgery population when such data is lacking. A systematic review by Vyas, et al. evaluated five studies reviewing the use of liposomal bupivacaine in abdominal wall reconstruction, augmentation mammoplasty, and mastectomy procedures. Overall, these studies demonstrated patients who received liposomal bupivacaine had lower pain scores, decreased opioid consumption in the first 72 h post-operatively, and a decreased

length of stay versus those who did not receive liposomal bupivacaine, similar to results described by Dasta, et al. [10,11].

Data are extremely limited describing the use of liposomal bupivacaine in burn surgery patients. Published data are limited to a case series from two institutions utilizing liposomal bupivacaine for donor site pain control in small burns (mean burn size 12% and 7% TBSA in each cohort). Our patient population included patients with similar burn size, suggesting smaller burn sizes (i.e. <10% TBSA) are most likely to see a benefit from the use of liposomal bupivacaine. These cohorts included small sample sizes of 20 patients and 5 patients. Both utilized liposomal bupivacaine into the donor site to assist with postoperative pain control, and found that pain scores appeared to be well-controlled with no donor site complications noted in either study [15]. While one cohort compared postsurgical medication use with the amount of opioids consumed the day before surgery, neither compared results to a control group to determine efficacy during the postoperative period. There was variation in these cohorts in the rates of addition of plain bupivacaine to the liposomal bupivacaine; however, in our study no patients received plain bupivacaine, which allowed us to control for this potential confounder. There was also an abstract presented at a recent American Burn Association meeting describing the use of liposomal bupivacaine for skin graft donor site analgesia. This abstract describes a retrospective review of 27 adult patients [median (IQR) burn size 4% (1–7)] who received full and split-thickness skin autografts utilizing liposomal bupivacaine for donor site pain management. Pain scores were reported postoperatively at 24 and 48 h and patients were asked to report pain from the donor site and the graft site separately. Results of this study include 90% of patients reported donor site pain as 3 or less 48 h after surgery and 80% of patients stated donor site pain was less than graft site pain (although differences in the scores were not reported). One patient experienced a donor site infection which was treated successfully with antibiotics and all donor sites had re-epithelialized by postoperative day 14. However, this study did not mention the use of a control group comparing donor site pain scores specifically and using the graft site as a comparator group is likely subject to additional variability (e.g., size of wound) outside of the use of liposomal bupivacaine. Donor sites also varied and included anterior thigh, posterior and anterior torso, and left arm. Dosing techniques in relation to liposomal bupivacaine were

not described in the abstract nor was there indication that a standardized protocol was utilized in terms of donor site location, medication administration techniques, or wound dressings. To our knowledge, this study has not been published to date [16]. Overall, these studies in burn surgery patients included small sample sizes limited to descriptive analyses, did not use control groups to determine efficacy in relation to concomitant pain medications in the postoperative period, and lacked clinical outcomes data or use of standardized protocols. Our study addresses these gaps in the literature in this patient population.

4.1. SUMMARY OF KEY FINDINGS

In our study, there was a statistically significant difference in the AUC_{0–24} and hospital length of stay in patients who received liposomal bupivacaine versus those who did not. This demonstrates the potential for liposomal bupivacaine to be used as part of a multimodal pain management pathway for donor site pain in burn patients. Although FDA-approved labeling states liposomal bupivacaine may produce postoperative analgesia for up to 72 h, the results from our study would indicate patients did not appear to see continued benefit past 24 h. This shorter duration of action was not surprising, as burn patients frequently require larger and more frequent dosing of medications due to the hypermetabolic state associated with burn injury. The onset and duration observed within our patient population are similar to those described in the study by Apseloff, et al. [8]. Additionally, the statistically significant difference found at AUC_{0–24} in combination with the decreased length of stay indicate patients were more likely to be discharged sooner in the intervention group, likely due to better post-operative pain control. In comparison to the meta-analysis conducted by Dasta, et al., our patients utilized significantly more opioids postoperatively than were used for other types of surgical procedures (which is to be expected in burn patients); however, they were still able to experience a statistically significant difference in pain control and length of stay [9]. While we did not observe a statistical difference in MME between groups, the difference in pain control and length of stay suggest these patients may be able to tolerate lower doses of opioid medications than traditionally utilized. In an effort to decrease overall opioid use, this practice could be addressed in the future through provider and nursing education. Finally, we saw a

significantly higher incidence of nausea/vomiting in the control group vs. the intervention group. We also observed a trend towards longer time to first bowel movement, increased pruritus, and increase in arrhythmias in the control group vs. the intervention group, but these differences were not statistically significant nor were we powered to detect these differences.

Our study reinforces the safety of the use of liposomal bupivacaine in this patient population as there were no major adverse effects noted. There appeared to be a trend of more opioid-related adverse effects in the control group, although we were not powered to detect this difference. To our knowledge, this is the largest study evaluating the use of liposomal bupivacaine in burn patients using a standardized protocol and the first to utilize a matched cohort for efficacy data evaluation.

4.2. STRENGTHS AND LIMITATIONS

Noted strengths of this study included its prospective study design using a matched cohort of patients using relevant factors, including standardization of using a lower extremity donor site in both groups and consistent wound dressings. We were able to describe a novel use of liposomal bupivacaine using a standardized protocol describing administration techniques to maximize patient safety, which can provide guidance for other Burn Centers nationally. Our study is the first of its kind, to our knowledge, to assess for efficacy and relevant clinical outcomes in this patient population using a matched cohort. Finally, we were able to use an opioid-sparing pain management strategy in burn patients during a national opioid crisis.

The major limitation of our study included that this was a single-center study, although this was a convenience sample which includes more patients than previous abstracts in burn surgery patients. The interpatient variability in the reporting of pain scores may have affected the results; however, this would be true for both groups. There were potentially charting inconsistencies between the historical controls and intervention groups as the health system utilized two different electronic health records during the study periods; however, methods described by Dasta, et al. were utilized to account for and standardize these differences. We did not collect data on the use of other non-opioid pain

management strategies such as acetaminophen, non-steroidal anti-inflammatory medications, or gabapentin due to the lack of ability to quantify the amount of these medications between the two groups, which is consistent with previous studies examining the use of liposomal bupivacaine.

Finally, we did not conduct a full economic analysis as part of this study, as this was beyond our scope. If the efficacy of liposomal bupivacaine in burn patients is supported by additional studies, economic analyses will be warranted, including evaluation of cost savings from decreased length of hospital stay versus cost of liposomal bupivacaine administration. Based on current average cost of inpatient hospital stay for our burn unit, which includes wound care and nursing time, each day costs approximately \$13,146, whereas one vial of liposomal bupivacaine costs \$315. Based on an estimated savings of \$26,292 from two fewer days admitted to the burn unit, and accounting for the expense of receiving one dose of liposomal bupivacaine, this translates into a potential overall cost savings of more than \$25,000 per patient.

5. CONCLUSIONS

Results from this study indicate liposomal bupivacaine is a safe, effective, and economical non-opioid pain management option for treating donor site pain for 24 h in smaller TBSA (<20%) burn patients after autograft harvesting. The patients in our study who received liposomal bupivacaine vs. traditional pain management strategies had statistically lower pain scores demonstrated by AUC0–24 and a significantly shorter length of hospital stay. Our protocol describing appropriate use of liposomal bupivacaine can be shared with other Burn Centers nationally with the potential for a multi-site study.

Conflicts of interest and source of funding

None declared.

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