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Liposomal Bupivacaine via Combined Sciatic and Saphenous Block After Lower Extremity Procedures: a Randomized, Double-blind, Phase 3 Trial

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OBJECTIVE

To evaluate combined sciatic and saphenous nerve block with liposomal bupivacaine with or without bupivacaine hydrochloride (HCl) versus bupivacaine HCl alone for foot and ankle procedures

CONCLUSIONS

1. In this phase 3 trial, although the primary endpoint was not met, pain intensity and opioid consumption were significantly reduced with liposomal bupivacaine ~36 to 96 and 24 to 96 hours after surgery, respectively, consistent with the mechanism of liposomal bupivacaine
2. In clinical practice, prolonged analgesia with liposomal bupivacaine can enhance the benefit of regional blocks for surgical anesthesia for optimized pain control with a reduced need for opioids

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ACKNOWLEDGMENTS: This study was sponsored by Pacira BioSciences, Inc. Assistance with poster preparation was provided under the authors' direction by Emma Hinkle, PhD, and David Boffa, ELS, of MedThink SciCom and funded by Pacira BioSciences, Inc.

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Presented at the Society for Ambulatory Anesthesia Annual Meeting; May 18-20, 2023; Phoenix, AZ

INTRODUCTION

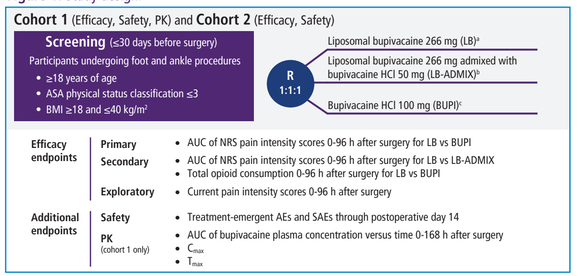
- Lower extremity surgical procedures often require postsurgical opioids for pain management[1]
- Use of peripheral nerve blocks for lower extremity procedures can reduce opioid consumption while shortening time in the hospital and reducing postsurgical complications[2]
  - Ankle blocks are recommended by clinical practice guidelines as a component of multimodal pain management after foot and ankle procedures, with opioids used only as a last resort[3,4]
  - Sciatic nerve blocks in the popliteal fossa are recommended for foot and ankle procedures where intense pain is expected and can be paired with a saphenous nerve block[3,5]
  - Lower extremity procedures such as bunionectomy can be performed using a combined saphenous and sciatic nerve block in the popliteal fossa; however, this has not been well investigated in a randomized controlled setting[4]
- Liposomal bupivacaine is a long-acting formulation of bupivacaine approved for postsurgical analgesia via wound infiltration in patients aged ≥6 years and as an interscalene brachial plexus nerve block in adults[6]
  - A previous phase 3 trial found that liposomal bupivacaine via wound infiltration reduced pain scores and total opioid consumption compared with placebo for bunionectomy[7]
  - A subsequent phase 3 trial found that liposomal bupivacaine via a sciatic nerve block in the popliteal fossa reduced pain and opioid consumption compared with bupivacaine HCl for bunionectomy[8]

METHODS

STUDY DESIGN

- This randomized, double-blind, active-controlled study enrolled 2 cohorts in parallel (NCT04518462; Figure 1)
  - Cohort 1 consisted of participants undergoing bunionectomy
  - Cohort 2 consisted of participants undergoing foot and ankle procedures
- Participants were randomized to receive liposomal bupivacaine 266 mg administered as 20 mL (266 mg) of liposomal bupivacaine mixed with 20 mL of saline (LB), liposomal bupivacaine 266 mg administered as 20 mL (266 mg) of liposomal bupivacaine admixed with 20 mL (50 mg) of bupivacaine HCl (LB-ADMIX), or bupivacaine HCl 100 mg administered as 40 mL (100 mg) of bupivacaine HCl (BUPI)

Figure 1. Study design.



[a]Liposomal bupivacaine 266 mg administered as 20 mL (266 mg) of liposomal bupivacaine mixed with 20 mL of saline. [b]Liposomal bupivacaine 266 mg administered as 20 mL (266 mg) of liposomal bupivacaine admixed with 20 mL (50 mg) of bupivacaine HCl. [c]Bupivacaine HCl 100 mg administered as 40 mL (100 mg) of bupivacaine HCl. AE, adverse event; ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; C_{max}, maximum plasma concentration; HCl, hydrochloride; PK, pharmacokinetics; NRS, numerical rating scale; T_{max}, time to maximum plasma concentration; SAE, serious adverse event.

TREATMENT ADMINISTRATION AND PERMITTED ANALGESIC MEDICATIONS

- The study drug was administered under ultrasound guidance 90 minutes (±30 minutes) before surgery in the popliteal fossa as a 20-mL sciatic nerve block and in the adductor canal as a 20-mL saphenous nerve block
- All participants received general anesthesia and were allowed medication for intraoperative nausea/vomiting prevention
- Participants were allowed medications as needed for breakthrough pain following a step-wise approach starting with acetaminophen or nonsteroidal anti-inflammatory drugs (not exceeding the maximum dose) and, if needed, escalating to an initial 5-mg dose of oxycodone, then to a 10-mg dose of oxycodone, and finally intravenous morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg)

STATISTICAL ANALYSES

- Statistical tests were conducted in hierarchical order with an analysis of covariance model with treatment as the main effect
- All tests were 2-sided with a significance level of 0.05

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- A total of 119 participants were randomized and treated in the study
  - 1 participant in the BUPI group withdrew because of pharmacokinetics blood draw refusal, and 1 participant in each of the liposomal bupivacaine groups was withdrawn by the investigator before receiving the study drug
  - Most participants (including all participants in cohort 1) underwent bunionectomy (n=110 [92.4%]); other lower extremity procedures included first metatarsophalangeal fusion (n=4 [3.4%]), specific forefoot procedures (n=2 [1.7%]), hindfoot fusion (n=2 [1.7%]), and total ankle arthroplasty (n=1 [0.8%])
- Participant demographics and baseline characteristics are shown in Table 1

Table 1. Demographics and Baseline Characteristics (Cohorts 1 and 2)[a]

	LB (n=39)	LB-ADMIX (n=41)	BUPI (n=39)
Age, median (range), y	51.0 (22-68)	49.0 (20-72)	45.0 (20-68)
Female, n (%)	35 (89.7)	37 (90.2)	26 (66.7)
Race, n (%)			
White	32 (82.1)	27 (65.9)	29 (74.4)
Black	7 (17.9)	14 (34.1)	10 (26.1)
ASA physical status classification, n (%)			
1	15 (38.5)	13 (31.7)	22 (56.4)
2	24 (61.5)	26 (63.4)	17 (43.6)
3	0	2 (5)	0
BMI, mean (SD), kg/m	28.2 (4.8)	30.2 (5.6)	27.7 (4.8)
Average pain intensity NRS, mean (SD)	2.3 (2.5)	3.3 (3.0)	2.1 (2.1)
Worst pain intensity NRS, mean (SD)	3.3 (2.6)	4.5 (3.1)	3.2 (2.7)
Pain Catastrophizing Scale total score, mean (SD)	11.7 (11.5)	13.2 (11.8)	11.1 (10.8)

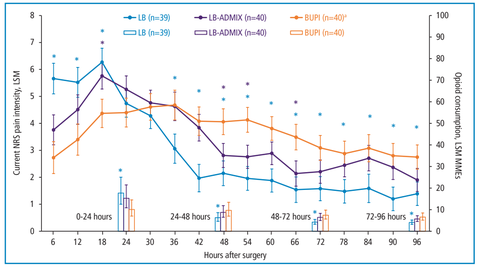
[a]Includes participants from both cohorts 1 and 2 from the safety analysis set (those who received the study drug). ASA, American Society of Anesthesiologists; BMI, body mass index; BUPI, bupivacaine hydrochloride 100 mg; LB, liposomal bupivacaine 266 mg; LB-ADMIX, liposomal bupivacaine 266 mg admixed with bupivacaine hydrochloride 50 mg; NRS, numerical rating scale; SD, standard deviation.

EFFICACY: PAIN INTENSITY AND OPIOID CONSUMPTION

From 0 to 96 hours after surgery, the primary endpoint of the least squares mean (LSM) area under the curve of the numerical rating scale (NRS) pain intensity score was nonsignificantly lower in the LB group versus the BUPI group (LSM [standard error], 286.9 [32.9] vs 348.6 [34.4]; LSM difference vs BUPI [95% confidence interval (CI)], −61.7 [−147.0, 23.6]; *P*=0.1564)

- Whereas mean current NRS pain intensity scores were significantly higher during the first 18 hours after surgery in the LB group compared with the BUPI group, they were significantly lower compared with BUPI at all timepoints examined from 36 to 96 hours (Figure 2)
- There were no significant differences for the LB versus BUPI groups in cumulative opioid consumption 0 to 96 hours after surgery (LSM [95% CI], 20.7 [13.5, 31.7] vs 19.8 [12.7, 31.0] milligram morphine equivalents; *P*=0.8857)
  - However, similar to pain scores, opioid consumption in those receiving LB was significantly higher from 0 to 24 hours and significantly lower from 24 to 96 hours compared with those receiving BUPI (Figure 2)

Figure 2. NRS pain intensity scores over time and opioid consumption over each 24-hour period from 0 to 96 hours after surgery for the LB, LB-ADMIX, and BUPI groups.

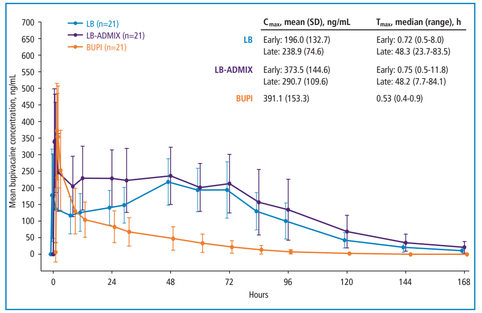


Lines represent NRS pain intensity scores over time (see values on left y-axis; error bars are standard error) and bars represent opioid consumption over each 24-hour period (see values on right y-axis; error bars are 95% confidence interval). [a]One participant from each treatment group withdrew from the study. *Significant difference compared with BUPI (*P*<0.05). BUPI, bupivacaine hydrochloride 100 mg; LB, liposomal bupivacaine 266 mg; LB-ADMIX, liposomal bupivacaine 266 mg admixed with bupivacaine hydrochloride 50 mg; LSM, least squares mean; MME, morphine milligram equivalent; NRS, numerical rating scale.

PHARMACOKINETICS

- The bupivacaine plasma concentration profile for the BUPI group exhibited 1 peak, after which plasma concentrations decreased; mean bupivacaine plasma concentrations after liposomal bupivacaine administration exhibited biphasic peak concentration profiles (Figure 3)
- The early maximum plasma concentration for the LB-ADMIX group was twice as high compared with the LB group because of the additional bupivacaine

Figure 3. Plasma bupivacaine concentration in the LB, LB-ADMIX, and BUPI groups from 0 to 168 hours after surgery.



BUPI, bupivacaine hydrochloride 100 mg; C_{max}, maximum plasma concentration; LB, liposomal bupivacaine 266 mg; LB-ADMIX, liposomal bupivacaine 266 mg admixed with bupivacaine hydrochloride 50 mg; T_{max}, time to maximum plasma concentration.

SAFETY

- Rates of adverse events (AEs) were similar between groups (Table 2)
  - The most commonly reported AEs were constipation, nausea, and headache
- The most frequently reported treatment-related AEs were hypoesthesia (18.8% in the liposomal bupivacaine groups combined vs 0.0% in the BUPI group) and paresthesia (10.0% in the liposomal bupivacaine groups combined vs 17.9% in the BUPI group)
- No participants died, had a serious AE, or discontinued from the study because of an AE

Table 2. Overview of Adverse Events

	LB (n=39)	LB-ADMIX[a] (n=41)	LB groups combined (n=80)	BUPI (n=39)
Any AE, n (%)	28 (71.8)	29 (70.7)	57 (71.3)	31 (79.5)
Mild	22 (56.4)	18 (43.9)	40 (50.0)	22 (56.4)
Moderate	6 (15.4)	11 (26.8)	17 (21.3)	8 (20.5)
Severe	0	0	0	1 (2.6)
≥1 treatment-related AE, n (%)	11 (28.2)	9 (22.0)	20 (25.0)	10 (25.6)
AEs by preferred term (≥10% in any group), n (%)				
Constipation	9 (23.1)	11 (26.8)	20 (25.0)	11 (28.2)
Nausea	8 (20.5)	12 (29.3)	20 (25.0)	7 (17.9)
Hypoesthesia	8 (20.5)	9 (22.0)	17 (21.3)	0
Headache	10 (25.6)	4 (9.8)	14 (17.5)	7 (17.9)
Paresthesia	5 (12.8)	3 (7.3)	8 (10.0)	11 (28.2)
Vomiting	1 (2.6)	6 (14.6)	7 (8.8)	2 (5.1)

[a]One participant randomized to the BUPI group received LB-ADMIX and was therefore included in the LB-ADMIX group for the safety analysis. AE, adverse event; BUPI, bupivacaine hydrochloride 100 mg; LB, liposomal bupivacaine 266 mg; LB-ADMIX, liposomal bupivacaine 266 mg admixed with bupivacaine hydrochloride 50 mg.

DISCUSSION

- Liposomal bupivacaine administered as a combined sciatic and saphenous nerve block for foot and ankle procedures resulted in significant reductions in current NRS pain intensity scores and opioid consumption with LB versus BUPI ~36 to 96 and 24 to 96 hours after surgery, respectively, with liposomal bupivacaine having a similar safety profile to bupivacaine alone
- In 2 recent subsequent studies designed to isolate the prolonged effects of nerve blocks alone, liposomal bupivacaine was administered as a sciatic nerve block in the popliteal fossa and a saphenous nerve block in the adductor canal for bunionectomy and total knee arthroplasty, respectively[8,9]
  - Each study included regional rather than general anesthesia, with opioids provided only for breakthrough pain[8,9]
  - Liposomal bupivacaine was associated with reduced pain and opioid consumption 0 to 96 hours after surgery compared with bupivacaine, with the most significant improvement after the first 30 hours in both studies[8,9]
- Consistent with the prolonged release of liposomal bupivacaine from multivesicular liposomes, this study demonstrates the efficacy of liposomal bupivacaine particularly after the first ~24 to 36 hours following surgery once the effect of immediate-release anesthetics has worn off