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Liposomal Bupivacaine via Adductor Canal Block After Total Knee Arthroplasty: a Randomized, Double-blind, Phase 3 Trial

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OBJECTIVE

To compare the postoperative analgesic effect of liposomal bupivacaine (LB) 133 mg admixed with bupivacaine hydrochloride (HCl) 50 mg (LB133-ADMIX group) versus bupivacaine HCl 50 mg (BUP50 group) when administered via adductor canal block (ACB) in participants undergoing primary unilateral total knee arthroplasty (TKA)

CONCLUSIONS

1. In this phase 3 study investigating ACBs with LB 133 mg vs bupivacaine HCl 50 mg, LB 133 mg resulted in significant reductions in both pain and opioid consumption from 0 to 96 hours after surgery
2. The concurrent reductions in pain and opioid consumption are notable because they are interdependent variables, and participants had lower pain scores without higher opioid consumption
3. This study was designed to isolate the effects of the ACB study intervention by use of a simplified pain management protocol
4. LB 133 mg was well tolerated, with a similar safety profile to bupivacaine HCl 50 mg

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REFERENCES: 1. Fillingham YA et al. *J Arthroplasty.* 2022;37(9):1691-1696. **2.** Fillingham YA et al. *J Arthroplasty.* 2022;37(10):1906-1921 e1902.

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BACKGROUND

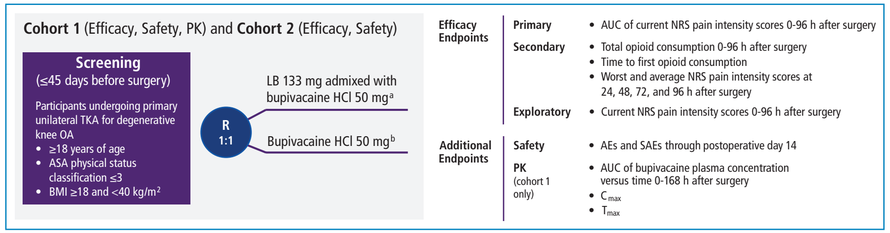
- Clinical practice guidelines recommend use of regional nerve blocks such as ACB for TKA[1]
  - ACBs can provide postoperative analgesia with reduced opioid consumption and contribute to improved recovery compared with femoral nerve blocks by preserving quadriceps strength after surgery[2]
- LB is a formulation of the local anesthetic bupivacaine that enables gradual release of bupivacaine for prolonged periods of analgesia
- More data are needed to determine the impact of LB admixed with bupivacaine HCl via ACB for TKA on pain intensity scores and opioid consumption

METHODS

STUDY DESIGN

- This phase 3, multicenter, randomized, double-blind, active-controlled study (NCT05139030) enrolled 2 cohorts (Figure 1)

Figure 1. Study design.



[a]LB 133 mg administered as 10 mL (133 mg) of LB admixed with 10 mL (50 mg) of bupivacaine HCl. [b]Bupivacaine HCl 50 mg administered as 10 mL (50 mg) of bupivacaine HCl admixed with 10 mL of normal saline. AE, adverse event; ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; C_{max} maximum plasma concentration; HCl, hydrochloride; LB, liposomal bupivacaine; NRS, numerical rating scale; OA, osteoarthritis; PK, pharmacokinetics; SAE, serious AE; TKA, total knee arthroplasty; T_{max}, time of maximum plasma concentration.

TREATMENT ADMINISTRATION AND PERMITTED ANALGESIC MEDICATIONS

- The study drug was administered as an ACB ~90 minutes before surgery
- Oral celecoxib 200 mg was administered within 4 hours before surgery, and spinal anesthesia with 0.5% bupivacaine HCl (≥15 mg) was administered immediately before surgery
- After study drug administration, all participants received local anesthetic containing 15 mL (37.5 mg) of 0.25% bupivacaine HCl for infiltration between the popliteal artery and capsule of the knee. Participants received two doses of 1000 mg intravenous (IV) acetaminophen: 1 dose at the time of surgical incision and 1 postoperative dose ~8 hours later
- Participants were not permitted to receive nonsteroidal anti-inflammatory drugs within 96 hours after surgery or opioids except oxycodone (up to a maximum of 10 mg) or IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) as needed for breakthrough pain

STATISTICAL ANALYSES

- Statistical tests were conducted in hierarchical order using an analysis of covariance model with treatment as the main effect
- All tests were 1-sided with a significance level of 0.025

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- A total of 166 participants were randomized and treated (cohort 1: n=45; cohort 2: n=121)
  - 6 participants discontinued from cohort 1 because of participant withdrawal (n=4), adverse event (AE; n=1), or failure to meet continuation criteria (n=1)
- Participant demographics and baseline characteristics are shown in Table 1

Table 1. Demographics and Baseline Characteristics

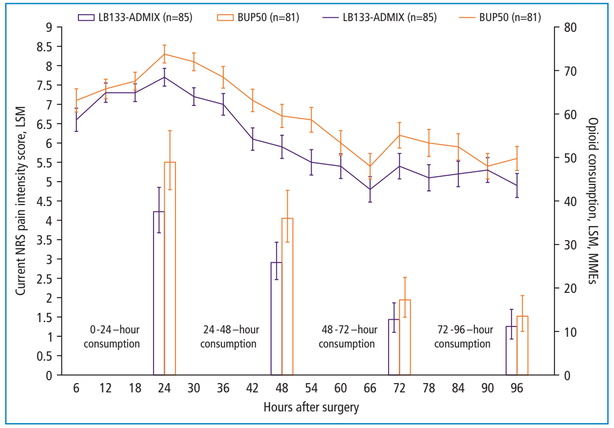
	Cohort 1		Cohorts 1 + 2		
	LB133-ADMIX (n=24)	BUP50 (n=21)	LB133-ADMIX (n=85)	BUP50 (n=81)	Total[a] (N=166)
Age, median (range), y	61.5 (51-75)	63 (45-80)	62 (44-75)	62 (37-83)	62 (37-83)
Female, n (%)	12 (50.0)	8 (38.1)	42 (49.4)	39 (48.1)	81 (48.8)
Not Hispanic or Latino, n (%)	16 (66.7)	17 (81.0)	64 (75.3)	66 (81.5)	130 (78.3)
Race, n (%)					
White	21 (87.5)	19 (90.5)	67 (78.8)	63 (77.8)	130 (78.3)
Black	2 (8.3)	2 (9.5)	14 (16.5)	15 (18.5)	29 (17.5)
Other	2 (8.4)	0	8 (9.4)	6 (7.4)	14 (8.4)
BMI, mean (SD), kg/m²	32.5 (5.0)	33.3 (4.8)	31.4 (4.8)	32.7 (5.0)	32.1 (4.9)
Worst pain intensity, median (min, max)	8.0 (3, 10)	8.0 (1, 10)	8.0 (2, 10)	8.0 (0, 10)	8.0 (0, 10)
Average pain intensity, median (min, max)	5.0 (0, 10)	5.0 (1, 8)	5.0 (0, 10)	5.0 (0, 10)	5.0 (0, 10)

[a]Including all participants in cohorts 1 + 2 pooled across treatment groups. BMI, body mass index; BUP50, bupivacaine hydrochloride 50 mg group; LB133-ADMIX, liposomal bupivacaine 133 mg admixed with bupivacaine hydrochloride 50 mg group; SD, standard deviation.

EFFICACY: PAIN INTENSITY AND OPIOID CONSUMPTION

- From 0 to 96 hours after surgery, the least squares mean (LSM) standard error (SE) area under the curve (AUC) of the numerical rating scale (NRS) pain intensity score (the primary endpoint) was 568.9 (20.1) in the LB133-ADMIX group and 634.7 (20.0) in the BUP50 group (LSM difference vs BUP50, −65.8 [95% confidence interval (CI), −118.7, −12.9]; *P*=0.0074)
- From 0 to 96 hours, total opioid consumption was significantly lower in the LB133-ADMIX group versus the BUP50 group (LSM, 101.8 [95% CI, 89.1, 116.3] vs 132.8 [95% CI, 116.3, 151.7] MMEs; LSM ratio compared with BUP50, 0.77 [95% CI, 0.64, 0.92]; *P*=0.0018)
  - Total opioid consumption was also consistently lower in the LB133-ADMIX group in 24-hour increments (Figure 2)
- Pain intensity scores were generally lower over time in the LB133-ADMIX group than the BUP50 group, particularly from 30 to 96 hours (Figure 2)

Figure 2. Current NRS pain intensity scores over time and opioid consumption over each 24-hour period from 0 to 96 hours after surgery in the LB133-ADMIX and BUP50 groups.



Lines: see values on left y-axis; error bars are the standard error. Bars: see values on right y-axis; error bars are the 95% confidence interval. BUP50, bupivacaine hydrochloride 50 mg group; LB133-ADMIX, liposomal bupivacaine 133 mg admixed with bupivacaine hydrochloride 50 mg group; LSM, least squares mean; MME, morphine milligram equivalent; NRS, numerical rating scale.

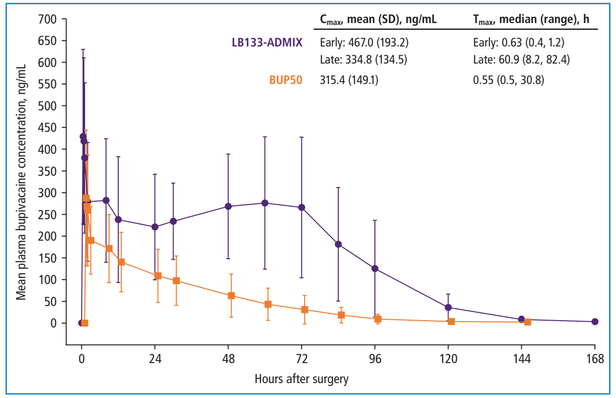
PHARMACOKINETICS

- The peak plasma concentration profile in the BUP50 group exhibited 1 peak, after which plasma concentrations decreased; the peak plasma concentration profile for the LB133-ADMIX group exhibited a biphasic peak (Figure 3)

SAFETY

- The frequency of AEs was similar between the LB133-ADMIX and BUP50 groups, with most AEs being mild to moderate in severity (Table 2)
  - 1 participant in the BUP50 group discontinued because of severe AEs (acute myocardial infarction and atrial fibrillation) considered unrelated to treatment
  - No deaths occurred during the study
- The rate of treatment-related AEs was low and similar between groups (LB133-ADMIX: 3.5%; BUP50: 2.5%)

Figure 3. Mean plasma bupivacaine concentration from 0 to 168 hours after surgery.



Error bars are the standard deviation. C_{max}, maximum plasma concentration; BUP50, bupivacaine hydrochloride 50 mg group; LB133-ADMIX, liposomal bupivacaine 133 mg admixed with bupivacaine hydrochloride 50 mg group; SD, standard deviation; T_{max}, time of maximum plasma concentration.

Table 2. AEs (Cohort 1 + 2)

	LB133-ADMIX, n (%)[a] (n=86)	BUP50, n (%)[a] (n=80)
Any AE	77 (89.5)	71 (88.8)
Mild AE	51 (59.3)	51 (63.8)
Moderate AE	24 (27.9)	19 (23.8)
Severe AE	2 (2.3)	1 (1.3)
AEs by preferred term (≥10% of Participants in Either Treatment Group)		
Nausea	34 (39.5)	30 (37.5)
Constipation	30 (34.9)	31 (38.8)
Muscle spasms	11 (12.8)	9 (11.3)
Insomnia	5 (5.8)	13 (16.3)
Headache	13 (15.1)	2 (2.5)
Hypotension	3 (3.5)	8 (10.0)

[a]One participant randomized to the BUP50 cohort received LB133-ADMIX and was therefore included in the LB133-ADMIX group for the safety analysis. AE, adverse event; BUP50, bupivacaine hydrochloride 50 mg group; LB133-ADMIX, liposomal bupivacaine 133 mg admixed with bupivacaine hydrochloride 50 mg group.