Journal club

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Obstetric Anesthesiology

ORIGINAL CLINICAL RESEARCH REPORT

Transversus Abdominis Plane Block With Liposomal Bupivacaine for Pain After Cesarean Delivery in a Multicenter, Randomized, Double-Blind, Controlled Trial

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Anesthesia-analgesia

December2020, Volume131, Number6

Background

- Cesarean delivery accounts for 32% of all births in the United States and 20% globally.
- Inadequately controlled pain following cesarean delivery may interfere with infant bonding, delay recovery, and reduce breastfeeding success.
- Multimodal pain management approaches are recommended to improve analgesia following cesarean delivery.

Background

- Protocols include long-acting neuraxial opioids together with scheduled acetaminophen and NSAIDs.
- Local anesthetic techniques including wound infiltration and truncal blocks, such as TAP block may be beneficial.
- However, standard local anesthetics, such as bupivacaine (BUPI) hydrochloride (HCl) provide short duration of analgesia (≈5–8 hours).

Background

- Liposomal bupivacaine (LB) is a long-acting multivesicular liposome formulation that provides prolonged BUPI release.
- Plasma BUPI levels persist for up to 120 hours following LB injection, indicating that BUPI remains at the target site for several days following an injection.

Background

- Hypothesis : Adding LB to TAP block with BUPI HCl would reduce opioid consumption through 72 hours compared with BUPI HCl alone.

Method

- Trial Design : Prospective, multicenter, randomized, double-blind trial

Primary outcome

- Total postsurgical opioid consumption through 72 hours.

Secondary outcome

- Total postsurgical opioid consumption through 24 hours, 48 hours, 1 week, and 2 weeks
- Time to first postsurgical opioid rescue medication
- Area under the curve (AUC) of visual analog scale (VAS) pain intensity scores through 72 hours (AUC0–72)
- The percentage of opioid-free patients through 72 hours
- The percentage of opioid-spared patients through 72 hours

Opioid free was defined as not receiving any opioid medication after surgery.
“Opioid spared” was defined a priori as taking ≤15 mg oral morphine equivalent dose (MED) after surgery with an over- all benefit of analgesia score (OBAS) of 0 for OBAS survey questions 2 through 6

Method : Inclusion criteria

- Women aged ≥ 18 years
- Term pregnancies of 37- to 42-weeks gestational age, scheduled to undergo elective cesarean delivery
- ASA physical status 2 or 3
- Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments

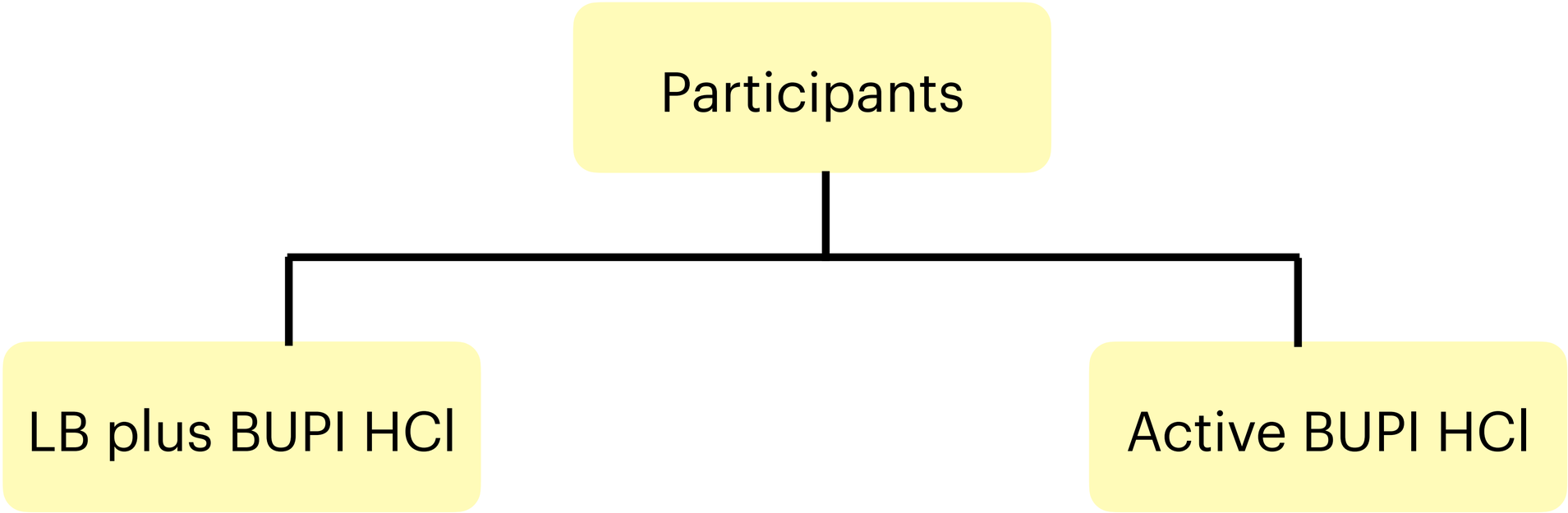
Method : Exclusion criteria

- Patients who, in the opinion of the study site principal investigator, have a high-risk pregnancy
- Patients with a pregnancy-induced medical condition
- Patients with ≥3 prior cesarean deliveries
- Pre-pregnancy BMI >50 kg/m2 or not anatomically appropriate for TAP block
- Allergy, hypersensitivity, or contraindication to any of the medications in the protocol
- Planned concurrent surgical procedure with the exception of salpingo-oophorectomy or tubal ligation

Method : Exclusion criteria

- Severely impaired renal or hepatic function
- Patients at an increased risk for bleeding or a coagulation disorder
- History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years
- Previous participation in a liposomal bupivacaine study
- Received the epidural component of CSE anesthesia

Method



- Randomized in a blinded 1:1 ratio

Method

- A centralized randomization system was used to generate treatment assignments.
- Patients and research personnel collecting data were blinded to allocation; only designated unblinded pharmacists responsible for preparing study drugs received the unblinded randomization assignments.
- The individuals administering treatments may have been able to identify the preparations containing LB because LB is a milky aqueous suspension.
- Those preparing or administering study drugs were not allowed to perform any of the study assessments or reveal the treatment to any other members of the study team.

Method

- The ultrasound images to assess for correct TAP block placement for each patient were adjudicated blindly by an independent review committee of expert anesthesiologists.
- Two independent reviewers were assigned to review each patient. If the reviewers disagreed, a third reviewer was assigned to make the final determination.

Sample size

- Sample size determination for this study was based on results of a previous retrospective study of TAP infiltration with LB plus BUPI in women undergoing cesarean delivery.
- 72 patients per treatment arm

  (80% power, $P < 0.05$)

Intraoperative

- Neuraxial anesthesia : spinal or combined spinal epidural
- C/S
- Skin closure : 15 mg of intravenous ketorolac and 1000 mg of intravenous acetaminophen
- LB 266 mg plus BUPI
- BUPI HCl 50 mg
- Confirmatory ultrasound images

Pain control management

- 6 hours after skin incision closure, oral acetaminophen and oral ibuprofen every 6 hours for up to 72 hours or until discharge

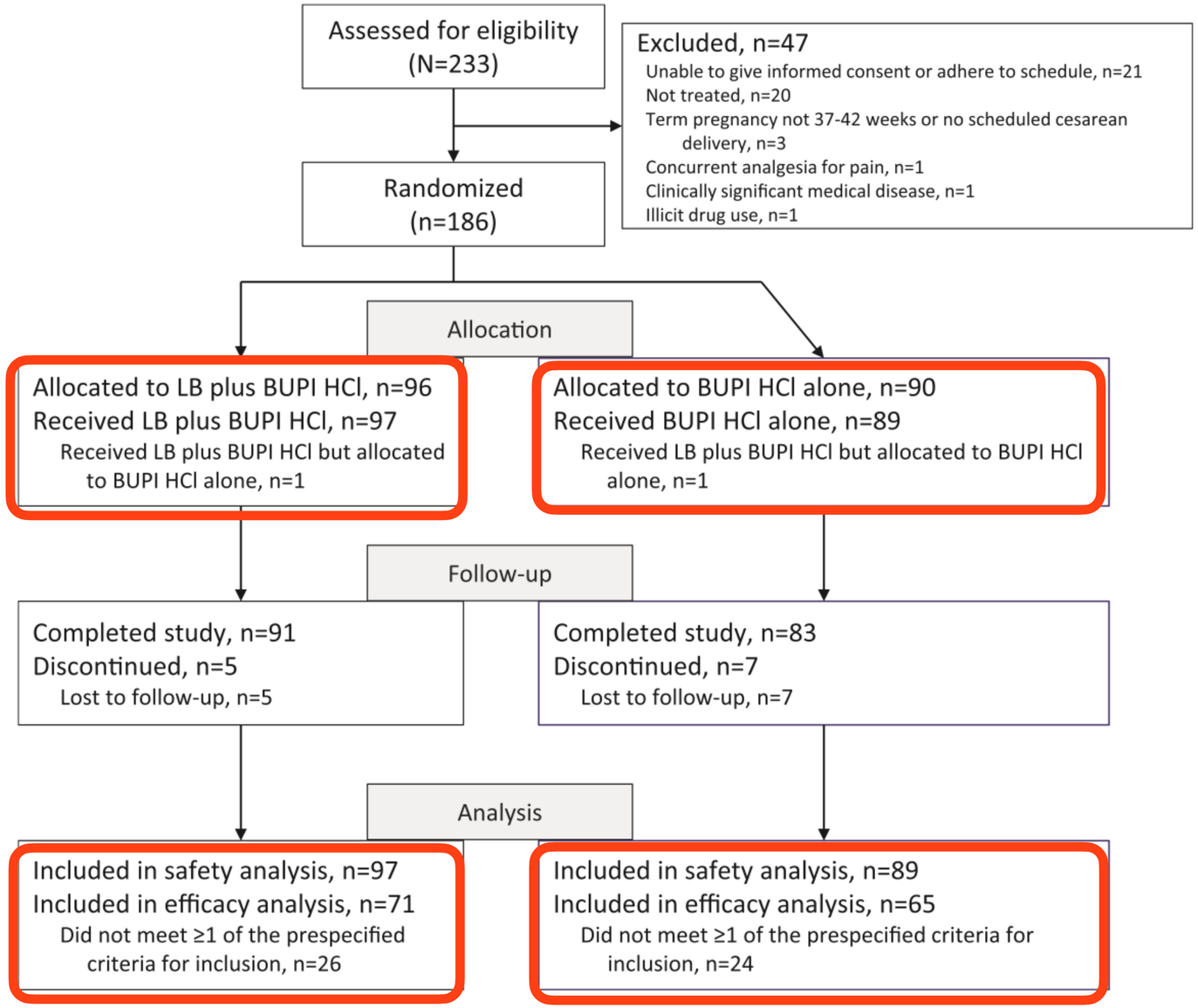
- Opioid pain medication if requested by the patient : immediate-release oxycodone initiated at 5–10 mg every 4 hours or as needed.

- If unable to tolerate: intravenous morphine initiated at 1–2 mg or hydromorphone initiated at 0.3–0.5 mg every 4 hours or as needed

Statically analysis

- Primary end point : an analysis of covariance (ANCOVA) model with treatment and site as the main effects and age and height as covariates.
- The percentage of opioid-spared and opioid-free patients : logistic regression model with treatment, site, age, and height as explanatory variables.
- Time to first opioid rescue: a Cox regression model with treatment and site as factors and age and height as covariates.

Result


Assessed for eligibility (N=233)
Excluded, n=47
Unable to give informed consent or adhere to schedule, n=21
Not treated, n=20
Term pregnancy not 37-42 weeks or no scheduled cesarean delivery, n=3
Concurrent analgesia for pain, n=1
Clinically significant medical disease, n=1
Illicit drug use, n=1
Randomized (n=186)
Allocation
Allocated to LB plus BUPI HCl, n=96
Received LB plus BUPI HCl, n=97
Received LB plus BUPI HCl but allocated to BUPI HCl alone, n=1
Allocated to BUPI HCl alone, n=90
Received BUPI HCl alone, n=89
Received LB plus BUPI HCl but allocated to BUPI HCl alone, n=1
Follow-up
Completed study, n=91
Discontinued, n=5
Lost to follow-up, n=5
Completed study, n=83
Discontinued, n=7
Lost to follow-up, n=7
Analysis
Included in safety analysis, n=97
Included in efficacy analysis, n=71
Did not meet ≥1 of the prespecified criteria for inclusion, n=26
Included in safety analysis, n=89
Included in efficacy analysis, n=65
Did not meet ≥1 of the prespecified criteria for inclusion, n=24

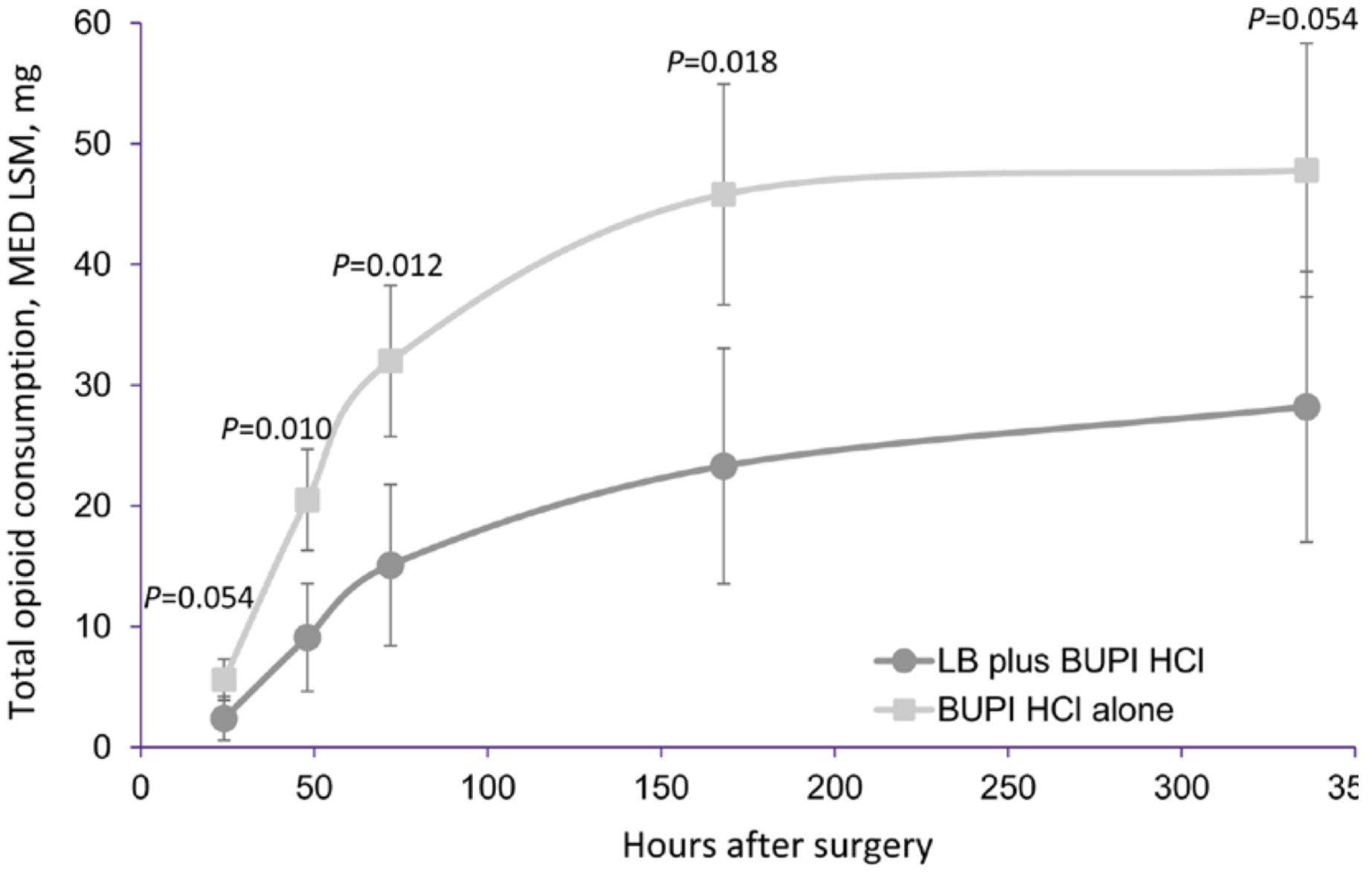
Result

Table 1. Patient Demographics and Baseline Characteristics (Safety Analysis Set)

	LB + BUPI HCl (n = 97)	BUPI HCl Alone (n = 89)
Age, median (range), y	34 (19–47)	33 (24–44)
Race, n (%)		
Caucasian	67 (69.1)	64 (71.9)
Black/African American	13 (13.4)	15 (16.9)
Asian	5 (5.2)	5 (5.6)
Other/multiple	12 (12.4)	5 (5.6)
Weight, mean (SD), kg	86.7 (17.8)	87.5 (17.5)
Height, mean (SD), cm	163.3 (6.6)	163.5 (7.8)
ASA classification, n (%)		
II	91 (93.8)	81 (91.0)
III	6 (6.2)	8 (9.0)
Prior cesarean delivery, n (%)		
0	34 (35.1)	35 (39.3)
1	50 (51.5)	41 (46.1)
2	13 (13.4)	13 (14.6)

Abbreviations: ASA, American Society of Anesthesiologists; BUPI, bupivacaine; HCl, hydrochloride; LB, liposomal bupivacaine; SD, standard deviation.

- No difference was observed


Total opioid consumption, MED LSM, mg
60
50
40
30
20
10
0
0
50
100
150
200
250
300
35
Hours after surgery
P=0.054
P=0.010
P=0.012
P=0.018
P=0.054
LB plus BUPI HCl
BUPI HCl alone

Supplemental Table 4. Total Opioid Consumption Through 72 hours (Primary End Point) and Other Time Points After Cesarean Delivery (PCA Set)

	LB plus BUPI HCl (n=71)	BUPI HCl alone (n=65)
Primary End Point		
MED through 72 hours, LSM (SE), MED mg	15.5 (6.67)	32.0 (6.25)
Treatment difference, LSM (SE)	−16.5 (7.28)	
95% CI of treatment difference	−30.8, −2.2	
P value	0.012	
Secondary End Points		
MED through 24 hours, LSM (SE), MED mg	2.4 (1.82)	5.6 (1.70)
Treatment difference, LSM (SE)	−3.2 (1.99)	
95% CI of treatment difference	−7.1, 0.7	
P value	0.054	
MED through 48 hours, LSM (SE), MED mg	9.1 (4.46)	20.5 (4.18)
Treatment difference, LSM (SE)	−11.4 (4.87)	
95% CI of treatment difference	−20.0, −1.9	
P value	0.010	
MED through Day 7, LSM (SE), MED mg	23.3 (9.75)	45.8 (9.13)
Treatment difference, LSM (SE)	−22.4 (10.65)	
95% CI of treatment difference	−43.3, −1.6	
P value	0.018	
Through Day 14, LSM (SE), MED mg	28.2 (11.20)	47.8 (10.49)
Treatment difference, LSM (SE)	−19.6 (12.23)	
95% CI of treatment difference	−43.6, 4.3	
P value	0.054	

BUPI, bupivacaine; CI, confidence interval; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; MED, morphine equivalent dose; PCA, protocol compliant analysis; SE, standard error.

Complication

Table 2. Adverse Events After Treatment (Overall and Treatment Related; Safety Analysis Set)

	LB + BUPI HCl (n = 97)	BUPI alone (n = 89)
Any AE after treatment	62 (63.9)	50 (56.2)
Any treatment-related AE after treatment	6 (6.2)	9 (10.1)
Serious AE after treatment	3 (3.1)	3 (3.4)
Fatal AE after treatment	0 (0.0)	0 (0.0)
AEs after treatment occurring in >5% of patients in either group		
Pruritus	27 (27.8)	28 (31.5)
Nausea	24 (24.7)	11 (12.4)
Vomiting	12 (12.4)	6 (6.7)
Headache	6 (6.2)	10 (11.2)
Dizziness	6 (6.2)	5 (5.6)
Constipation	6 (6.2)	4 (4.5)
Back pain	3 (3.1)	5 (5.6)
Rash	5 (5.2)	3 (3.4)
Treatment-related AEs after treatment occurring in patients in either group[a]		
Pruritus	2 (2.1)	8 (9.0)
Nausea	3 (3.1)	0 (0.0)
Vomiting	3 (3.1)	0 (0.0)
Dizziness	1 (1.0)	0 (0.0)
Back pain	0 (0.0)	1 (1.1)
Dysuria	0 (0.0)	1 (1.1)

Discussion

- TAP block using LB plus BUPI HCl as part of a multimodal analgesia protocol after cesarean delivery reduced total opioid consumption through the first 72 hours following surgery.
- Patients treated with LB plus BUPI HCl did not experience increased pain over the first 72 hours after surgery compared with patients who received BUPI HCl alone.
- The LB analgesic benefits are prolonged plasma BUPI levels persisting for up to 120 hours following injection.
- Our findings are consistent with a retrospective study of patients who received a multimodal regimen, where 47% reduction in mean postsurgical opioid consumption and 46% reduction in AUC pain scores were observed in those with LB TAP block versus without LB TAP block.

Discussion

- Multimodal regimen : TAP blocks can help control somatic pain, nonopioid analgesics help control visceral pain
- Our study confirmed the importance of correct TAP block placement to achieve efficacy.
- We conducted a post hoc validation of the adjudication of ultrasound images, which showed an 88% agreement between adjudication from the independent review committee and our subsequent validation.
- Approximately 6% of patients did not meet PCA inclusion criteria because of incorrect TAP block placement as determined by independent adjudication of ultrasound images, highlighting that TAP blocks may not always be effective in clinical practice because of inaccurate placement.

Discussion

- When data that encompassed all treated patients, including those not meeting criteria for correct TAP block placement, correct local anesthetic dosing, or adherence to a multimodal postsurgical analgesic regimen, were analyzed, there were no differences in postsurgical opioid consumption between the groups who received LB with BUPI HCl versus BUPI HCl alone.
- Post hoc analysis revealed that the lack of efficacy in the analysis of all treated patients may be mostly associated with incorrect TAP block placement, indicating that patients who receive an incorrectly placed TAP block may not fully benefit from addition of LB.

Limitation

- The participating centers had variations in their standard of care, which may have led to differences across sites in overall opioid consumption.
- As a result, in addition to incorrectly placed TAP blocks, this led to a substantial number of patients being excluded from the PCA.
- Additionally, the study did not include women at risk for increased postsurgical opioid use, such as those with concurrent painful physical conditions or illicit drug use.

Limitation

- The control group used a low dose of BUPI HCl (10 mL of 0.25% BUPI HCl vs 10 mL of LB 133 mg plus 10 mL of 0.25% BUPI HCl diluted with normal saline to a total volume of 30 mL per side), which may have provided limited analgesic benefit.
- A meta-analysis suggested that there might not be a difference in analgesic efficacy between high-dose (>50 mg BUPI) and low-dose (≤50 mg BUPI) TAP block, but the minimum effective dose has not been determined.
- The benefit of LB versus BUPI HCl needs to be considered in the context of higher costs of LB; studies investigating economic implications in this setting have not been conducted.

Conclusion

- This study show that a correctly placed TAP block using LB plus BUPI HCl as part of a multimodal analgesia protocol after cesarean delivery in women who received intrathecal morphine can reduce opioid consumption while managing pain versus TAP block with BUPI HCl alone.
- A multimodal analgesic regimen that includes NSAIDs and acetaminophen, as well as a correctly placed TAP block, the use of LB may bring patients closer to an opioid-free recovery.
- This management approach may be an important strategy in reducing overall postsurgical opioid consumption for the >1 million women undergoing cesarean delivery each year.

Critical appraisal : RCT

- Does this study address a clear question?

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Critical appraisal : RCT

- Are the results of this single trial valid?

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?			✓
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Critical appraisal : RCT

- Are the results of this single trial valid?

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes	Can't tell ✓	No
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

Critical appraisal : RCT

- What were the results?

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	• ?
10. How precise were the results? Were the results presented with confidence intervals?	• Yes

Critical appraisal : RCT

- Can I apply these valid, important results to my patients?

	Yes	Can't tell	No
11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?		✓	✓
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?	✓		

Thank you