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

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BACKGROUND: In women undergoing cesarean delivery under spinal anesthesia with intrathecal morphine, transversus abdominis plane (TAP) block with bupivacaine hydrochloride (HCl) may not improve postsurgical analgesia. This lack of benefit could be related to the short duration of action of bupivacaine HCl. A retrospective study reported that TAP block with long-acting liposomal bupivacaine (LB) reduced opioid consumption and improved analgesia following cesarean delivery. Therefore, we performed a prospective multicenter, randomized, double-blind trial examining efficacy and safety of TAP block with LB plus bupivacaine HCl versus bupivacaine HCl alone.

METHODS: Women (n = 186) with term pregnancies undergoing elective cesarean delivery under spinal anesthesia were randomized (1:1) to TAP block with LB 266 mg plus bupivacaine HCl 50 mg or bupivacaine HCl 50 mg alone. Efficacy was evaluated in a protocol-compliant analysis (PCA) set that was defined a priori. The primary end point was total postsurgical opioid consumption (oral morphine equivalent dosing [MED]) through 72 hours. Pain intensity was measured using a visual analog scale. Adverse events (AEs) after treatment were recorded through day 14.

RESULTS: Total opioid consumption through 72 hours was reduced with LB plus bupivacaine HCl versus bupivacaine HCl alone (least squares mean [LSM] [standard error (SE)] MED, 15.5 mg [6.67 mg] vs 32.0 mg [6.25 mg]). This corresponded to an LSM treatment difference of -16.5 mg (95% confidence interval [CI], -30.8 to -2.2 mg; $P = .012$). The area under the curve of imputed pain intensity scores through 72 hours supported noninferiority of LB plus bupivacaine HCl versus bupivacaine HCl alone (LSM [SE], 147.9 [21.13] vs 178.5 [19.78]; LSM treatment difference, -30.6; 95% CI, -75.9 to 14.7), with a prespecified noninferiority margin of 36 ($P = .002$). In an analysis of all treated patients, including those not meeting criteria for inclusion in the PCA, there was no difference in postsurgical opioid consumption between groups. In the LB plus bupivacaine HCl group, 63.6% of patients experienced an AE after treatment versus 56.2% in the bupivacaine HCl-alone group. Serious AEs after treatment were rare ($\approx 3\%$ in both groups).

CONCLUSIONS: TAP block using LB plus bupivacaine HCl as part of a multimodal analgesia protocol incorporating intrathecal morphine resulted in reduced opioid consumption after cesarean delivery in the PCA set. Results suggest that with correct TAP block placement and adherence to a multimodal postsurgical analgesic regimen, there is an opioid-reducing benefit of adding LB to bupivacaine TAP blocks after cesarean delivery (ClinicalTrials.gov identifier: NCT03176459). (Anesth Analg 2020;131:1830-9)

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KEY POINTS

- **Question:** Does transversus abdominis plane (TAP) block with liposomal bupivacaine (LB) plus bupivacaine (BUPI) hydrochloride (HCl) compared with BUPI HCl alone as part of a multimodal analgesia protocol reduce opioid consumption after cesarean delivery?
- **Findings:** TAP block using LB plus BUPI HCl reduced opioid consumption by 51.6% through 72 hours compared with BUPI HCl alone.
- **Meaning:** LB plus BUPI HCl TAP block may be an important addition to multimodal analgesia protocols after cesarean delivery.

GLOSSARY

AE = adverse event; **ASA** = American Society of Anesthesiologists; **AUC** = area under the curve; **AUC₀₋₇₂** = area under the curve through 72 hours; **BUPI** = bupivacaine; **CI** = confidence interval; **HCl** = hydrochloride; **LAST** = local anesthetic systemic toxicity; **LB** = liposomal bupivacaine; **LSM** = least squares mean; **MED** = morphine equivalent dosing; **NSAID** = nonsteroidal anti-inflammatory drug; **OBAS** = overall benefit of analgesia score; **PCA** = protocol-compliant analysis; **SE** = standard error; **TAP** = transversus abdominis plane; **VAS** = visual analog scale

Cesarean delivery accounts for 32% of all births in the United States and ≈20% globally.^{1,2} In the United States, ≈1.2 million cesarean deliveries are performed each year, making it the most common surgery after cataract surgery.²⁻⁴ Inadequately controlled pain following cesarean delivery may interfere with infant bonding, delay recovery, and reduce breastfeeding success.⁵ Additionally, women who undergo cesarean delivery are at increased risk for long-term opioid use.⁶ Thus, an important goal following cesarean delivery is to improve analgesia while reducing opioid consumption.

Multimodal pain management approaches are recommended to improve analgesia, reduce opioid use, and decrease opioid-related adverse events (AEs) following cesarean delivery.^{7,8} Protocols include long-acting neuraxial opioids together with scheduled acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).^{9,10} However, most women still request opioids after cesarean delivery.¹¹ Local anesthetic techniques including wound infiltration and truncal blocks, such as transversus abdominis plane (TAP) block, may benefit women not receiving intrathecal morphine.^{9,10,12,13} However, benefit is limited when TAP block is used in women receiving intrathecal morphine.^{13,14} This is possibly related to the short duration of analgesia (≈5–8 hours) of standard local anesthetics, such as bupivacaine (BUPI) hydrochloride (HCl).¹⁵

Liposomal bupivacaine (LB) is a long-acting multivesicular liposome formulation that provides prolonged BUPI release.^{16,17} 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.^{16,17} LB is approved by the US Food and Drug Administration for postsurgical analgesia in adults via single-dose local infiltration or as interscalene brachial plexus nerve block.¹⁷ A retrospective study evaluated pain managed by a multimodal protocol with or without LB TAP block after

cesarean delivery.¹⁸ Pain management with LB TAP block significantly reduced mean postsurgical opioid consumption and pain scores by ≈50% compared with management without LB TAP block.

We performed a prospective, multicenter, randomized, double-blind trial comparing opioid consumption after TAP block with LB plus BUPI HCl versus TAP block with BUPI HCl alone as part of a multimodal analgesia protocol including intrathecal morphine in patients undergoing elective cesarean delivery with spinal anesthesia. We hypothesized that adding LB to TAP block with BUPI HCl would reduce opioid consumption through 72 hours compared with BUPI HCl alone.

METHODS**Trial Oversight**

Institutional review board approval compliant with the International Council for Harmonisation Good Clinical Practice and/or the US Food and Drug Administration Title 21 Code of Federal Regulations Part 56 was obtained at each study site. A list of sites is available in Supplemental Digital Content, Methods, <http://links.lww.com/AA/D142>. Written informed consent was obtained from each patient before study participation. The trial was registered at ClinicalTrials.gov (NCT03176459; principal investigator: S.S.N.; date of registration: June 5, 2017) and adheres to the Consolidated Standards of Reporting Trials guidelines.¹⁹

Trial Design and Patients

From August 3, 2017, through December 4, 2018, we conducted a multicenter, randomized, double-blind, active-controlled phase 4 study at 13 clinical sites in the United States. Women who were ≥18 years of age with term pregnancies of 37- to 42-week gestational age scheduled to undergo elective cesarean delivery under spinal anesthesia with an American Society

of Anesthesiologists physical status of II or III were enrolled. Inclusion and exclusion criteria are shown in Supplemental Digital Content, Table 1, <http://links.lww.com/AA/D142>. Because BUPI is regarded as compatible with breastfeeding, women who wished to breastfeed were included.²⁰

Eligible patients were randomized in a blinded 1:1 ratio to receive TAP infiltration with LB plus BUPI HCl or active BUPI HCl alone. Preoperatively, all patients received spinal or combined spinal epidural anesthesia with 1.4 to 1.6 mL of hyperbaric BUPI HCl 0.75% with 150 µg of morphine and 15 µg of fentanyl. Intraoperatively, ketamine and midazolam were permitted; dexamethasone for the prevention of nausea and vomiting was prohibited. Patients were excluded if the epidural component of the combined spinal epidural anesthetic was used. Within 90 minutes of surgery end, a bilateral, 2-point classic TAP block with LB 266 mg plus BUPI HCl 50 mg or BUPI HCl 50 mg alone (30 mL each side; 60 mL total for each) was performed under ultrasound guidance by experienced physicians, primarily staff anesthesiologists.²¹ Postoperatively, patients received acetaminophen and ibuprofen for up to 72 hours or until hospital discharge. Patients remained hospitalized for up to 72 hours after surgery. Follow-up calls to assess safety and pain were scheduled for all patients on postsurgical day 14. Further details on the protocol, methods of randomization, and blinding are included in Supplemental Digital Content, Methods, <http://links.lww.com/AA/D142>.

The original study protocol was amended 3 times. Amendment 1 was issued on April 12, 2017, before the screening of the first patient on August 3, 2017. This amendment clarified aspects of the protocol, including those related to spinal anesthesia, TAP block timing, multimodal regimen dosing, inclusion/exclusion criteria, and prohibited medications.

Initially, there was lack of clarity on the intended dosing of the TAP block such that the first 12 patients received a 20-mL TAP block volume, instead of the intended 30-mL TAP block volume, on each side. Patients dosed before the study amendment that clarified the intended TAP volume (amendment 2, issued on September 22, 2017) were excluded from the protocol-compliant analysis (PCA; see Statistical Analysis in the Methods). Subsequently, it became known that some sites were not adhering to the scheduled multimodal postsurgical analgesic regimen. An amendment clarifying the requirement for scheduled, not as-needed, multimodal postsurgical analgesic regimen (amendment 3) was issued on May 7, 2018, and all 39 patients who had been enrolled before that amendment were excluded from the PCA. Finally, 13 patients were excluded from the PCA because of incorrect TAP block placement, which occurred

throughout the study. Some patients excluded from the PCA belonged to ≥ 1 of the 3 noted categories. The statistical analysis plan signoff was on January 3, 2019; database lock was on January 5, 2019; and unblinding occurred on January 16, 2019.

End Points

The primary end point was total postsurgical opioid consumption through 72 hours. Secondary end points were 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 (AUC_{0-72}); the percentage of opioid-free patients through 72 hours; and 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 overall benefit of analgesia score (OBAS) of 0 for OBAS survey questions 2 through 6 (Supplemental Digital Content, Table 2, <http://links.lww.com/AA/D142>).²²

Tertiary efficacy end points included AUC of the VAS pain intensity scores at various time points. Additional tertiary end points are described in Supplemental Digital Content, Methods, <http://links.lww.com/AA/D142>. Safety end points were assessed by incidence of AEs from the time of study drug administration through day 14. Relationship of AEs to either drug injected was assessed by the blinded investigator.

Statistical Analysis

The safety analysis set included all patients who received TAP block with LB plus BUPI HCl or BUPI HCl alone. Safety analyses were based on actual treatment received. Efficacy was evaluated in a PCA set that was defined a priori and prespecified to include all randomized patients assessed for safety who underwent cesarean delivery and who also met the prespecified study criteria for correct TAP block placement, correct local anesthetic dosing, and adherence to a multimodal postsurgical analgesic regimen. Therefore, all patients enrolled before amendment 2 were excluded from the PCA because of incorrect local anesthetic dosing. Similarly, all patients enrolled before amendment 3 were excluded because of non-adherence to the protocol-specified multimodal postsurgical analgesic regimen. Patients who otherwise had protocol deviations beyond these prespecified criteria were included in the PCA. Efficacy was analyzed on the basis of randomized treatment regardless of the treatment received. 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. Following final data analysis, the authors reviewed the blinded TAP block images to validate the findings of the independent review committee. An additional post hoc efficacy analysis was performed in all patients who received TAP block with LB plus BUPI HCl or BUPI HCl alone. No multiplicity adjustments were made for efficacy. Details of the statistical methods used to analyze the study end points are included in Supplemental Digital Content, Methods, <http://links.lww.com/AA/D142>.

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.²³ The coefficient of variation in that study was $\approx 60\%$. Assuming a log-normal distribution for total opioid consumption with a 60% coefficient of variation, 5% α level, 1:1 randomization ratio, and 80% power, 72 patients per treatment arm would be sufficient to detect a 30% difference using a 2-sample *t* test. In estimating sample size, a 2-sample *t* test for the mean difference between groups in log-transformed total opioid consumption was considered; in analyzing between-group differences in opioid consumption, log transformation was not applied. Assuming 5% of the patients were not evaluable, a total sample size of ≈ 152 patients was needed to ensure 144 evaluable individuals.

RESULTS

Study Cohort

A total of 233 patients were screened for eligibility, with 186 (LB plus BUPI HCl, $n = 96$; BUPI HCl alone, $n = 90$) being randomized to study drugs (Figure 1). Of these, 136 patients (LB plus BUPI HCl, $n = 71$; BUPI HCl alone, $n = 65$) met criteria for inclusion in the PCA set. A total of 50 patients (LB plus BUPI HCl, $n = 26$; BUPI HCl alone, $n = 24$) were not included in the PCA set because they did not meet ≥ 1 criteria for correct TAP block placement ($n = 13$), correct local anesthetic dosing ($n = 12$), or adherence to a multimodal postsurgical analgesic regimen ($n = 39$). One patient was randomized to BUPI HCl alone but received LB 266 mg plus BUPI HCl; this patient was included in the LB plus BUPI HCl safety analysis set and the BUPI HCl-alone PCA set. Two patients in the BUPI HCl-alone group were mistakenly unblinded during the study; these patients were included in the safety analysis but not the PCA. Patient demographics and baseline characteristics were comparable across groups (Table 1) and between patients excluded from the PCA and those in the overall safety analysis set (Supplemental Digital Content, Table 3, <http://links.lww.com/AA/D142>).

A post hoc validation of the independent review committee adjudication of TAP block placement based on ultrasound images found that there was a lack of concordance between the independent review committee and the subsequent validation for 23 of 186 patients, indicating agreement in ultrasound review of 88%.

Primary Efficacy End Point

The primary end point of the study was met; total opioid consumption in MED through 72 hours was normally distributed and was reduced by 51.6% in the LB plus BUPI HCl group versus that in the BUPI HCl-alone group (least squares mean [LSM] [standard error {SE}], 15.5 mg [6.67 mg] vs 32.0 mg [6.25 mg]; Figure 2 and Supplemental Digital Content, Table 4, <http://links.lww.com/AA/D142>). This corresponded to an LSM treatment difference in MED of -16.5 mg (95% confidence interval [CI], -30.8 to -2.2 mg; $P = .012$).

The results for the primary end point were similar when patients were excluded because of incorrectly placed TAP blocks as determined by the subsequent post hoc validation of ultrasound images (LSM [SE] MED, 16.1 mg [7.00 mg] vs 31.7 mg [6.67 mg] in the LB plus BUPI HCl group versus the BUPI HCl-alone group). This corresponded to an LSM treatment difference in MED of -15.6 mg (95% CI, -30.8 to -0.3 mg; $P = .024$).

Secondary and Tertiary Efficacy End Points

In the LB plus BUPI HCl group versus the BUPI HCl-alone group, significant reductions in opioid consumption were observed at 48 hours (LSM [SE] MED, 9.1 mg [4.46 mg] vs 20.5 mg [4.18 mg]; $P = .010$) and 7 days (LSM [SE] MED, 23.3 mg [9.75 mg] vs 45.8 mg [9.13 mg]; $P = .018$). A nonsignificant reduction in opioid consumption was observed at 14 days (LSM [SE] MED, 28.2 mg [11.20 mg] vs 47.8 mg [10.49 mg]; $P = .054$).

The percentage of opioid-spared patients was 2.2 times higher in the LB plus BUPI HCl group versus that in the BUPI HCl-alone group at 72 hours (53.5% vs 24.7%; $P = .001$). The time to first opioid rescue ranged from 2.3 to 345.2 hours in the LB plus BUPI HCl group and from 2.5 to 345.7 hours in the BUPI HCl-alone group. The median time to first opioid rescue was longer in the LB plus BUPI HCl group (53.2 hours) than that in the BUPI HCl-alone group (41.1 hours); however, this difference was not statistically significant ($P = .754$). The percentage of opioid-free patients was not different in the LB plus BUPI HCl group versus that in the BUPI HCl-alone group at 24 hours (95.6% vs 93.7%; $P = .175$), 48 hours (58.4% vs 50.6%; $P = .196$), and 72 hours (51.9% vs 48.6%; $P = .361$).

The LSM (SE) AUC₀₋₇₂ of VAS pain intensity scores through 72 hours was 147.9 (21.13) in the LB plus BUPI

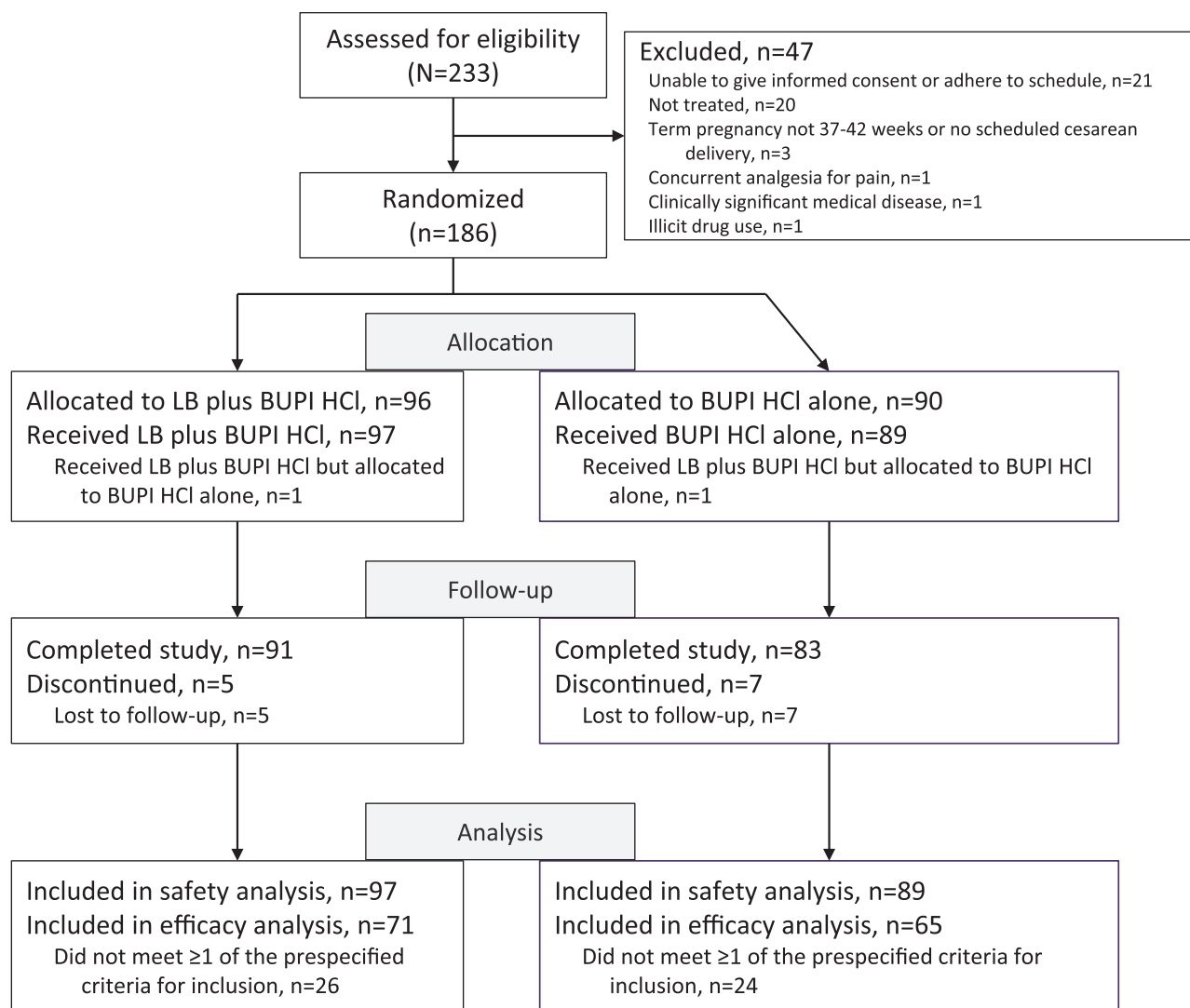


Figure 1. Patient disposition. Efficacy was evaluated in a prespecified protocol-compliant analysis set that included patients who underwent cesarean delivery and met the study criteria for correct transversus abdominis plane placement, correct local anesthetic dosing, and adherence to a multimodal postsurgical analgesic regimen. Those who did not meet ≥ 1 criteria for correct TAP block placement ($n = 13$), correct local anesthetic dosing ($n = 12$), or adherence to multimodal postsurgical analgesic regimen ($n = 39$) were excluded from the protocol-compliant analysis. Patients were considered “lost to follow-up” if the study team could not contact them after at least 3 attempts. BUPI indicates bupivacaine; HCl, hydrochloride; LB, liposomal bupivacaine; mITT, modified intent-to-treat.

HCl group versus 178.5 (19.78) in the BUPI HCl–alone group. The LSM treatment difference between the groups was -30.6 (95% CI, -75.9 to 14.7), with the upper limit meeting the prespecified noninferiority margin of 36 ($P = .002$) but not the superiority margin of 0. Reductions in AUC of the VAS pain intensity scores were observed in the LB plus BUPI HCl group at most time intervals examined from the 12-hour through the 72-hour period (eg, 12–24, 24–36, and 36–48 hours), with all meeting the criteria for noninferiority but not superiority (Supplemental Digital Content, Table 5, <http://links.lww.com/AA/D142>).

Results of additional tertiary end points are shown in Supplemental Digital Content, Table 6, <http://links.lww.com/AA/D142>. The summed pain intensity scores through 72 hours were lower in the LB plus

BUPI HCl group versus those in the BUPI HCl–alone group, meeting the criteria for noninferiority as prespecified. An analysis of the integrated rank assessment using sum of pain intensity scores at rest and MED of opioid rescue medications through 48 hours showed a statistically significant treatment difference ($P = .040$). No significant differences were observed between groups for other tertiary end points.

Analysis of All Treated Patients

In the post hoc efficacy analysis of the primary end point with all treated patients, which included those who were excluded from the PCA set because they did not meet criteria for correct TAP blocks, correct local anesthetic dosing, and adherence to a multimodal postsurgical analgesic regimen, there were

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 significant differences in LSM (SE) total opioid consumption (MED) through 72 hours in the LB plus BUPI HCl group (24.3 mg [6.03 mg]) and the BUPI HCl-alone group (27.5 mg [5.84 mg]; $P = .312$; Supplemental Digital Content, Table 7, <http://links.lww.com/AA/D142>). Similarly, there were no significant differences in the LSM (SE) AUC₀₋₇₂ of VAS pain intensity scores between the LB plus BUPI HCl group (158.8 [19.1]) and BUPI HCl-alone group (168.3 [18.4]; LSM treatment difference, -9.6 ; 95% CI, -49.2 to 30.0 ; Supplemental Digital Content, Table 8, <http://links.lww.com/AA/D142>).

In the 50 patients excluded from the PCA, LSM (SE) total opioid consumption through 72 hours was higher with LB plus BUPI HCl (MED, 52.1 mg [7.71 mg]) than BUPI HCl alone (MED, 10.5 mg [7.71 mg]; Supplemental Digital Content, Table 9, <http://links.lww.com/AA/D142>). The higher opioid consumption in the LB plus BUPI HCl group appeared to be largely due to the group of patients who were

excluded because of incorrect TAP block placement. Specifically, in the 13 patients excluded from the PCA because of incorrect TAP block placement, the LSM (SE) total opioid consumption through 72 hours was higher with LB plus BUPI HCl (MED, 70.7 mg [11.57 mg]) than that with BUPI HCl alone (MED, 9.7 mg [10.36 mg]; $P < .001$). Conversely, in patients who had correct TAP block placement but were excluded from the PCA for other reasons (incorrect local anesthetic dosing, nonadherence to a multimodal postsurgical analgesic regimen), the difference in LSM (SE) total opioid consumption through 72 hours between the LB plus BUPI HCl (MED, 32.2 mg [7.41 mg]) and BUPI HCl-alone groups (MED, 18.3 mg [8.34 mg]) was not statistically significant ($P = .11$). This was largely driven by 4 patients with incorrect TAP block placement in the LB plus BUPI HCl group whose total opioid consumption through 72 hours exceeded 80 MED mg compared with no patients in the BUPI HCl-alone group (Supplemental Digital Content, Table 10, <http://links.lww.com/AA/D142>).

Safety

The safety profile was comparable between groups, with 63.9% (62 of 97 patients) in the LB plus BUPI HCl group experiencing an AE after treatment versus 56.2% (50 of 89 patients) in the BUPI HCl-alone group (Table 2). Nausea and vomiting were reported more frequently in the LB plus BUPI HCl group (24.7% and 12.4%, respectively) than in the BUPI HCl-alone group (12.4% and 6.7%, respectively), while headache was more frequent in the BUPI HCl-alone group (11.2%) than in the LB plus BUPI HCl group (6.2%). Most AEs after treatment were mild or moderate in severity and were not considered by the investigator to be related to either drug injected. Six patients in the LB plus BUPI HCl group and 9 patients in the BUPI

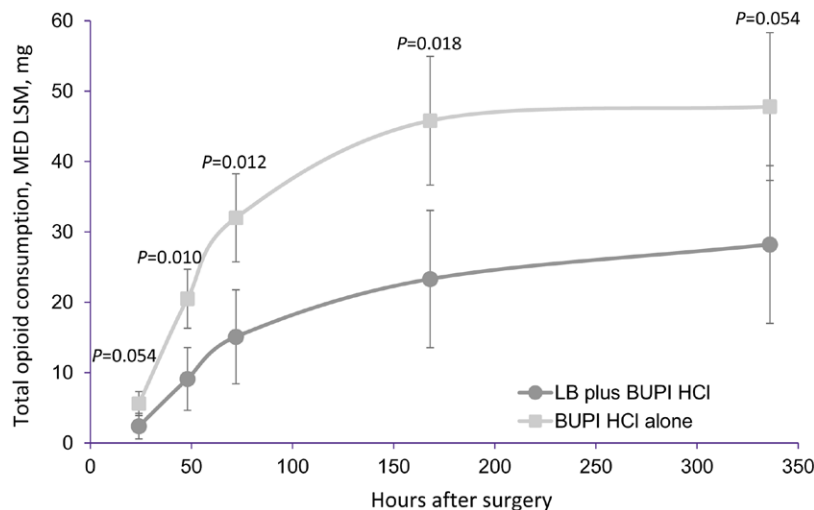


Figure 2. Total opioid consumption at 24, 48, and 72 h and at 7 and 14 d after surgery for cesarean delivery. The primary end point of the study was total opioid consumption through 72 h. Total opioid consumption through 24 and 48 h and 7 and 14 d were secondary end points. BUPI indicates bupivacaine; HCl, hydrochloride; LB, liposomal bupivacaine; LSM, least squares mean; MED, morphine equivalent dose.

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)

Values are the number (percentage). All AEs were recorded through day 14. AEs after treatment were recorded on or after the administration of study drug (which occurred after skin incision closure) through day 14.

Abbreviations: AE, adverse event; BUPI, bupivacaine; HCl, hydrochloride; LB, liposomal bupivacaine.

^aTreatment relatedness was determined by the investigator.

HCl-alone group experienced AEs that were considered to be related to either drug injected.

Of the 35 patients who experienced nausea, 27 (77%) first experienced nausea within 6 hours. Treatment-related nausea and vomiting each occurred in 3 patients in the LB plus BUPI HCl group. Serious AEs after treatment were reported in 3 patients in the LB plus BUPI HCl group (cardiomyopathy [occurred 9 days after start of treatment], abdominal wall hematoma [rectal sheath hematoma], and panic attack in 1 patient each). Similarly, in the BUPI HCl-alone group, 3 patients experienced serious AEs after treatment (retained placenta or membranes and urinary tract infection in 1 patient, postpartum pregnancy-induced hypertension in 1 patient, and postpartum hemorrhage in 1 patient). Investigators did not believe that any of the serious AEs after treatment were related to either drug injected, and all resolved with appropriate medical treatment. There were no treatment-related neurologic or cardiovascular AEs. No patients discontinued the study because of an AE, and there were no fatal AEs.

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. A greater number of patients in the LB plus BUPI HCl group versus BUPI HCl alone

were opioid spared. Additionally, 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, with pharmacokinetic measurements of plasma BUPI levels persisting for up to 120 hours following injection.^{16,17} 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.¹⁸ In that study, patients also had reduced discharge and postanesthesia care unit ready times, with decreased time to ambulation, which was not observed in our study.

Our study confirmed the importance of correct TAP block placement to achieve efficacy. 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. 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. The primary study findings were unchanged regardless of whether patients were excluded because of incorrectly placed TAP blocks as determined by either initial adjudication or subsequent validation.

Our prespecified PCA also required that patients adhered to a multimodal postsurgical analgesic regimen that included NSAIDs and acetaminophen given for up to 72 hours. While TAP blocks can help control somatic pain, nonopioid analgesics help control visceral pain, emphasizing the importance of adhering to a multimodal regimen.²⁴ Approximately 21% of patients did not meet the criterion for correct multimodal postsurgical analgesic regimen, and 12% did not meet the criterion for correct local anesthetic dosing. These protocol deviations were often due to institutional preferences (eg, not taking NSAIDs on a scheduled basis) conflicting with the study protocol. As Enhanced Recovery After Surgery guidelines for cesarean delivery become more widely adopted,^{25,26} it is anticipated that multimodal protocols will become standard. 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.

There were no unexpected adverse safety signals or cases of local anesthetic systemic toxicity (LAST) in this study. TAP block advantages should be considered against safety risks, such as LAST.^{27,28} TAP block requires the injection of large local anesthetic doses, which may increase LAST risk, especially in women who are pregnant.²⁹

There are several limitations to consider. 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. The results as reported from the PCA may be an overestimation of the true effects of LB in these patients, given that differences in efficacy between the 2 arms were not found in the analysis of all treated patients. 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. Furthermore, 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. The LB group received a higher total BUPI dose, and we cannot exclude if the analgesic benefit found was related to the higher dose in the LB group. However, the added benefit would likely be noted in the early time points only, given that BUPI HCl has a limited duration of action. Previously, no differences in outcomes following cesarean delivery were found in patients receiving a TAP block with 75 versus 150 mg BUPI HCl.³⁰ 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,³¹ but the minimum effective dose has not been determined. Additionally, a range of spinal anesthesia dosing with BUPI HCl was specified (1.4–1.6 mL). However, the expected duration of action for this amount of BUPI HCl is ≈2 hours.³² Any differences in dose would likely not have effects on outcomes beyond 24 hours. Finally, 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.

In conclusion, the results of 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. Along with 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. ■

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