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Research Paper

Ethnic Differences in Analgesic Efficacy and Safety of Liposomal Bupivacaine Among Asian and Caucasian Surgical Patients: A Retrospective Matched-Cohort Analysis

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Background: Extended-release local anesthetics allow for prolonged analgesia after a single administration. Although Asians demonstrate different pain thresholds than Caucasians, whether they have different postoperative local anesthetic analgesic effects has not been elucidated.
Objective: We aimed to compare the postoperative analgesic efficacy of liposomal bupivacaine on Asian and Caucasian adults, and the incidence of local anesthetic systemic toxicity (LAST) syndrome.
Methods: We conducted a retrospective, assessor-blinded cohort study of adult patients who received liposomal bupivacaine for surgery between 2012 and 2018. Asians and Caucasians were matched in a 1:1 ratio by clinical characteristics and surgery type. The primary outcome was pain management, defined as average pain score and opioid consumption during the initial 72 postoperative hours. The secondary outcome was the incidence of LAST syndrome. Reviewers were blinded to the ethnicity of the patient.
Results: After 1:1 propensity score matching, 130 Asians and 129 Caucasians were analyzed. All confounding variables were balanced, except for higher body mass index in the Asian group. Pain scores were lower (adjusted mean difference of -0.50 [97.5% CI, -0.98, -0.01]; superiority $P = 0.011$) and opioid consumption was not greater (geometric means ratio, 0.61 [97.5% CI, 0.36, 1.04]; non-inferiority $P < 0.001$) in Asian patients compared to Caucasian patients. Only one Caucasian patient was judged as having a potential case of LAST syndrome. The length of hospital stay and the incidence of additional complications were not different between the groups.
Conclusion: Asian adults receiving liposomal bupivacaine as part of multimodal perioperative analgesia demonstrated lower pain scores compared to matching Caucasians, despite not having greater opioid consumption.

Keywords: *ethnicity, postoperative pain, liposomal bupivacaine*

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Introduction

In the era of the opioid crisis and fast-track surgery, multimodal analgesia techniques including local wound infiltration and nerve blocks are often utilized.[1-3] Conventional local anesthetics have a short duration of action, generally limited to 8–12 hours. Effective long-lasting analgesia can be achieved by using catheters for continuous administration of local anesthetics. However, the use of these systems has been limited by cost and the resources needed to manage their use in the perioperative setting.

Extended-release formulations of local anesthetics have been available for clinical use in recent years, allowing for prolonged analgesia after a single administration. Bupivacaine liposome injectable suspension (Exparel®, Pacira Pharmaceuticals Inc., Parsippany, NJ, USA) was approved by the United States Food and Drug Administration (US-FDA) in 2011 for administration into surgical sites and was recently approved for brachial plexus nerve blocks.[4] It has been shown to decrease postoperative pain while reducing opioid consumption and side effects.[4-9] One common concern regarding longer-acting local anesthetics is the potential for increased toxicity. However, previous studies found that adverse events associated with the use of liposomal bupivacaine were comparable to conventional bupivacaine and were rare at clinically relevant doses.[10-12]

Pain sensitivity and threshold have been shown to differ among ethnic groups and races, as well as the response to analgesic medications and other prescribed treatments.[13-16] Several experimental studies have demonstrated a lower pain threshold and tolerance in Asian participants compared to Caucasians.[17-20] Although some of these differences can be attributed to psychological and environmental factors, emerging evidence suggests that genetic factors are related to clinical pain and experimental pain sensitivity.[21,22]

Asians account for 59.7% of the world's total population. Moreover, the Asian American population increased by 46% between 2000 and 2010 in the United States and is estimated to be the fastest-growing ethnic group over the next several years.[23] Whether Asians have different responses to the postoperative analgesic effects of local anesthetics has not been elucidated.

Our primary aim was, therefore, to compare the analgesic efficacy of liposomal bupivacaine in Asian and Caucasian adult surgical patients. Specifically, we tested the primary hypothesis that in Asian patients given liposomal bupivacaine, pain scores and opioid consumption during the initial 72 postoperative hours are not greater compared to Caucasian patients. Secondarily, we hypothesized that the incidence of local anesthetic systemic toxicity (LAST) syndrome after perioperative administration of liposomal bupivacaine is not higher in Asian compared to Caucasian adults. Finally, as an exploratory outcome, we compared the duration of hospitalization and the incidence of complications not qualifying as LAST syndrome between the two ethnic groups.

Methods

Study Design and Patient Population

With Institutional Review Board approval (Cleveland Clinic IRB #18-1019), we conducted a single-center, retrospective cohort analysis of patients receiving bupivacaine liposome injectable suspension (Exparel®) for perioperative analgesia. Asian adults having surgery in the Cleveland Clinic between January 2012 and July 2018 and receiving liposomal bupivacaine were directly matched by age, sex, and procedure type to Caucasian patients receiving liposomal bupivacaine in a 1:1 ratio. Patients with multiple surgeries during the same hospitalization were excluded if the repeat surgery occurred during the initial 96 postoperative hours; otherwise, only the first operation was considered.

Outcomes

The primary outcome was pain management, defined by both the average pain score and opioid consumption during the initial 72 postoperative hours. The secondary outcome was defined as the presence of 2 or more of the 13 complications described as part of LAST syndrome[24-26], as well as 6 other serious complications (Table 1). Complications related to the administration of local anesthetics were considered until 48 postoperative hours. A sensitivity analysis considered single signs or symptoms judged to be related to local anesthetic administration. The exploratory outcomes were the length of hospital stay and the incidence of any of the 19 postoperative complications, regardless of clinical association to the administration of local anesthetics. Patients' electronic medical and anesthesia records were manually reviewed. Each case was independently assessed by 2

Table 1. Signs and Symptoms Potentially Associated With LAST and Other Major Complications[24-26]

Secondary outcome (adverse event/complication)	Definition associated with LAST
Associated with LAST	
Dizziness	Patient experienced/documented/treatment received
Bradycardia requiring treatment	Documented event of bradycardia requiring treatment in the form of glycopyrrolate, atropine, epinephrine, pacing
Blurred vision	Patient experienced/documented
Tinnitus	Patient experienced/documented
Desaturation/hypoventilation	Requiring treatment with non-rebreather mask/BiPAP or CPAP/intubation and mechanical ventilation
Loss of consciousness	Patient experienced/documented/treatment received
Seizure	Patient experienced/documented/treatment received
Drowsiness	Patient experienced/documented
Dysarthria	Patient experienced/documented
Confusion	Patient experienced/documented
Malignant ventricular arrhythmias	Documented or requirement of advanced life support (e.g., epinephrine, cardioversion) VT/VF, asystole, ST changes, wide complex tachycardia
Hypotension	Documented event of hypotension, requiring treatment with fluids, vasopressors or cardioversion
Perioral numbness	Patient experienced/documented
Other major complications	
Agitation	Patient experienced/documented
Tachycardia requiring treatment	Patient experienced/documented/treatment received
New onset atrial arrhythmias	Patient experienced/documented/treatment received
Mortality	documented patient death
Cardiac arrest	diagnosis/chest compressions/epinephrine administration
Cardiopulmonary resuscitation	documented/chest compressions

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; LAST, local anesthetic systemic toxicity; VT/VF, ventricular tachycardia/fibrillation.

blinded adjudicators. Non-consensus and all positive cases were adjudicated by the senior investigator (Dr. Alparslan Turan).

Data Collection

Qualifying patients were identified from the Cleveland Clinic pharmacy database, Anesthesia Record Keeping System, Perioperative Health Documentation System, and the electronic medical record. Collected data included: (1) demographic and morphometric information; (2) surgical and anesthetic information; and (3) site, dose, dilution, and time of liposomal bupivacaine administration. In addition, all pain scores during the initial 72 postoperative hours (reported on a numerical rating scale [NRS] of 0 (no pain) to 10 (worst imaginable pain) at least once every 4 hours), postoperative opioid usage during the initial 72 postoperative hours (converted to intravenous [IV] morphine equivalents),[27] postoperative medications and interventions, adverse events or complications, and length of hospital stay were also collected.

Data Analysis

We used propensity score matching to adjust for potential confounding of the relationship between ethnicity (Asian vs. Caucasian) and outcomes. Specifically, we first fitted a logistic regression model predicting ethnic status (Asian = 1, Caucasian = 0) as a function of the available potential confounding variables, including age, gender, American Society of Anesthesiologists

physical status score, body mass index (BMI), duration of surgery, and major comorbidities. We matched each Asian patient to a Caucasian patient using a greedy distance matching algorithm without replacement, restricting successful matches to patients with the same type of surgery, and those whose estimated propensity score logits were within 0.2 of the standard deviation of the logit of the propensity score of one another.

After 1:1 matching, we reviewed charts and excluded non-qualifying cases which were identified by free text searching from surgical notes and pharmacy orders. Any imbalanced confounding variable after matching (absolute standardized difference [ASD] ≥ 0.20) would be adjusted for in the models.

For the primary outcome of pain management, we used a joint hypothesis testing method to assess whether Asian patients had lower average pain scores and less opioid consumption than Caucasian patients in the first 72 postoperative hours. We used the non-inferiority margin (delta, Δ) of 1-point in pain score and a relative 20% change in opioid consumption. For opioid consumption, we compared Asians and Caucasians on the log-transformed opioid dose using the same methods as above with a delta equal to the natural log of 1.2, corresponding to the noninferiority delta of 20% (i.e., a ratio of geometric means no more than 20% higher in Asian versus Caucasian patients). Since we required noninferiority on both pain score and opioid consumption to claim noninferiority and accept the primary hypothesis, no Bonferroni correction for multiple testing was needed (i.e., this is an intersection–union test). Both tests were conservatively conducted at the 0.025 significance level since they were 1-tailed. For each outcome, we also reported the confidence interval for the difference between Asians and Caucasians. If superiority was found for Asians versus Caucasians on either outcome (together with noninferiority on the other outcome), a conclusion of superiority could be made since that conclusion is on the rejection region for noninferiority.[28,29]

For the secondary outcome, we compared the propensity-matched groups using a 2-tailed chi-square test. The reason is that only 1 patient had two or more postoperative complications, OR (95% CI) can not be estimated. The length of hospital stay was a time-to-event variable defined as time to being discharged alive and was compared between the two groups using multivariable Cox proportional hazard models. The incidence of any single complication was compared between the two groups using multivariable logistic regression. SAS statistical software (version 9.4, Cary, NC, USA) was used for all analyses.

Results

From 2012 to 2018, 170 surgeries on 152 Asian patients and 13,349 surgeries on 11,876 Caucasian patients involving the administration of liposomal bupivacaine were identified. After 1:1 propensity score matching, we were able to include 164 Asians and 164 Caucasians in the analysis. The balance of demographic and surgical characteristics before and after matching is summarized in Table 2. After matching and excluding patients for which administration of liposomal bupivacaine was not verified according to manual review of their medical charts, 130 Asians and 129 Caucasians remained in the final analysis. All cofounding variables were balanced (i.e., ASD < 0.2), except for higher BMI in the Asian group (Table 2).

The dose of liposomal bupivacaine was higher in the Asian group than in the Caucasian group (mean ± SD, 262 ± 42 mg vs. 244 ± 68 mg; $P < 0.05$), respectively. But no difference was found on Exparel dosage per kg between the two groups (4.1 ± 1.1 mg/kg vs. 3.9 ± 1.3 mg/kg; $P = 0.13$) (Table 3).

Boxplots of pain score and total opioid consumption during the initial 72 postoperative hours are provided in Figure 1. We found that the pain score over the initial 72 postoperative hours was lower in Asian patients than in Caucasian patients, with an adjusted mean difference of -0.50 (97.5% CI, -0.98, -0.01; superiority test $P = 0.011$) (Table 4, Figure 2). Regarding opioid consumption, the estimated ratio of geometric means was 0.61 (97.5% CI, 0.36, 1.04) for the Asian group as compared to the Caucasian group, indicating that the Asians did not have a higher opioid consumption compared to Caucasian patients (noninferiority test $P < 0.001$) (Table 4, Figure 2).

Only 1 patient from the Caucasian group was found to have two or more postoperative complications clinically judged to be possibly related to the administration of local anesthetics (Table 1). No patient in the Asian group had the secondary outcome ($P > 0.99$). The single instance judged as a potential case of LAST syndrome was of a 49-year-old Caucasian old female who received 266 mg of liposomal bupivacaine diluted to 60 mL with normal saline administered by the surgeon during an abdominoplasty. Three hours after surgery, she became drowsy and unresponsive, with a blood pressure of 70/30 mmHg

Table 2. Patient Characteristics Before and After Matching, and in the Final Cohort[a]

Factor	Before matching			After matching			Final study population[b]		
	Asian (N = 170)	Caucasian (N = 13,349)	ASD[c]	Asian (N = 164)	Caucasian (N = 164)	ASD[c]	Asian (N = 130)	Caucasian (N = 129)	ASD[c]
Age, y	52 ± 16	55 ± 16	0.22	52 ± 16	54 ± 18	0.14	52 ± 16	55 ± 18	0.14
Weight, kg	67 ± 16	86 ± 26	0.85	67 ± 16	67 ± 16	0.00	66 ± 14	66 ± 14	0.01
BMI, kg/m^2	25 ± 6	30 ± 8	0.62	26 ± 6	25 ± 6	0.16	25 ± 5	24 ± 5	0.20
Duration of surgery, min	221 ± 145	234 ± 134	0.09	224 ± 147	220 ± 135	0.02	235 ± 156	217 ± 131	0.12
Female	115 (68)	8190 (61)	0.13	112 (68)	116 (71)	0.05	93 (72)	93 (72)	0.01
ASA status			0.39			0.03			0.05
1	12 (7)	467 (4)		10 (6)	17 (10)		10 (8)	8 (6)	
2	84 (49)	3791 (28)		82 (50)	63 (38)		62 (48)	55 (43)	
3	60 (35)	7922 (59)		59 (36)	79 (48)		48 (37)	61 (47)	
4	13 (8)	1162 (9)		12 (7)	5 (3)		9 (7)	5 (4)	
5	1 (1)	7 (0)		1 (1)	0 (0)		1 (1)	0 (0)	
Cardiac disease	56 (33)	6461 (48)	0.32	54 (33)	52 (32)	0.03	43 (33)	42 (33)	0.01
Liver dysfunction	5 (3)	791 (6)	0.15	5 (3)	5 (3)	0.00	4 (3)	4 (3)	0.00
Renal disease	9 (5)	1026 (8)	0.10	9 (6)	6 (4)	0.09	7 (5)	3 (2)	0.16
Epilepsy	1 (1)	176 (1)	0.08	1 (1)	2 (1)	0.06	0 (0)	2 (2)	0.18
Malnutrition	6 (4)	880 (7)	0.14	6 (4)	12 (7)	0.16	6 (5)	9 (7)	0.10
Neuromuscular disease	2 (1)	211 (2)	0.03	2 (1)	2 (1)	0.00	1 (1)	1 (1)	0.00

Abbreviations: ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; BMI, body mass index.
[a] The summary statistics are presented as mean ± standard deviation, or number (percent) of patients, as appropriate.
[b] Final study population–after excluding patients in which the administration of liposomal bupivacaine could not be positively verified after manual chart review.
[c] ASD defined as the absolute difference in means or proportions divided by the pooled standard deviation, with a criteria ASD ≥ 0. 2 considered as imbalanced.

Table 3. Dose, Dosage, Total Volume, and Administration Site for Liposomal Bupivacaine in Asians Versus Caucasians[a]

Factor	Asian (N = 130)	Caucasian (N = 129)	*P* value[b]
Exparel dose (mg)	262 ± 42	244 ± 68	0.03
Exparel dosage (mg/kg)	4.1 ± 1.1	3.9 ± 1.3	0.39
Total infiltration volume (mL)	54 ± 108	47 ± 36	0.54
Administration site			0.57
TAP block	27 (21)	32 (25)	
Abdomen	15 (12)	15 (12)	
Back	7 (5)	5 (4)	
Lower extremity	10 (8)	6 (5)	
Intra-articular	2 (2)	6 (5)	
Other[c]	69 (53)	65 (50)	

Abbreviation: TAP, transversus abdominis plane.
[a]The summary statistics are presented as mean ± standard deviation, or number (percent) of patients, as appropriate.
[b]*P* value from a t test for continuous variables and chi-square test for categorical variables.
[c]Most common sites in the "other" group include breast, peri-articular, and perineal injections.

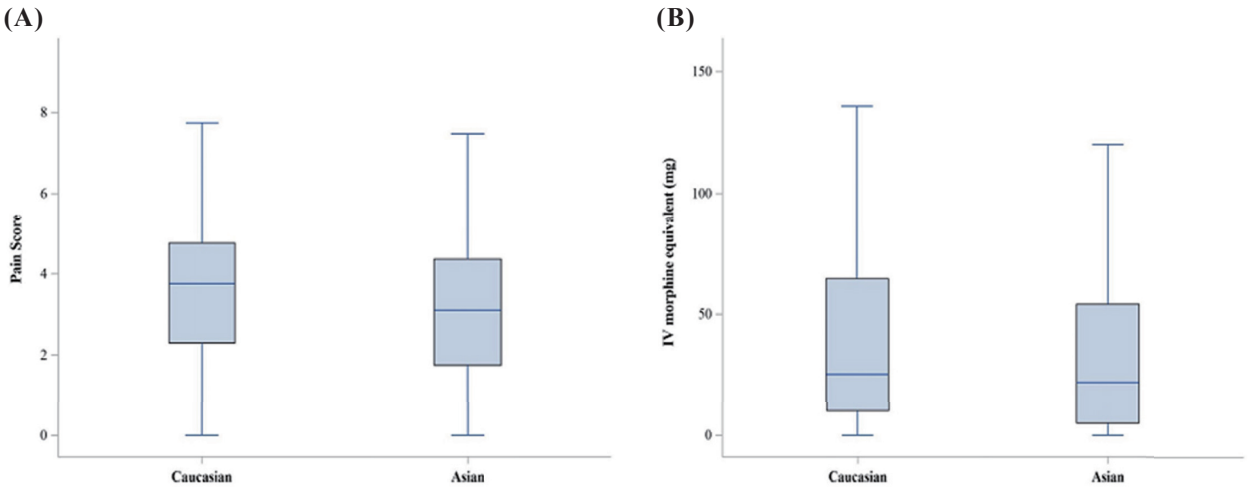

Figure 1. Boxplots of Pain Score and Total Opioid Consumption During the Initial 72 Postoperative Hours
Boxplots of time-weighted-average pain score (A, left panel) from 0 (no pain) to 10 (worse imaginable pain), and total opioid consumption (B, right panel) in intravenous (IV) morphine equivalents (mg) during the initial 72 postoperative hours between Asians (N = 130) and Caucasians (N = 129). The first quartile, median, and third quartile comprise the boxes; upper and lower whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively.

for about 10 minutes. She was treated with IV fluids and made a full recovery. She was discharged home 4 hours later with no other complications documented in her surgical follow-up. Although the caregivers never documented suspicion of LAST syndrome, the clinical adjudicators reviewing the case felt this could have potentially been related to local anesthetic systemic absorption. On the sensitivity analysis, 2 patients in the Asian group had dizziness judged as being possibly related to local anesthetic administration ($P = 0.16$).

The length of hospital stay was not different between the groups, with a median [Q1, Q3] of 2 [1, 4] vs. 2 [1, 4] days, and covariables-adjusted hazard ratio of 1.01 (95% CI, 0.80, 1.30; $P = 0.93$). The percentage of patients who presented any single complication (Table 5) was not different between the two groups (18% vs. 12%), with an estimated adjusted odds ratio of 0.59 (95% CI, 0.28, 1.24; $P = 0.98$).

Table 4. Comparison Between Asian and Caucasian Patients on Pain Score and Opioid Consumption During the Initial 72 Postoperative Hours Using the Joint Hypothesis Testing Framework[a,b]

Primary Outcomec	Asian (N = 130)	Caucasian (N = 129)	Test	α	δ	Difference in means (Asian – Caucasian)	*P* value[c]
Mean pain score	3.1 ± 1.7	3.5 ± 1.8	NI	0.025	1.0	-0.50 (-0.92, -0.07)	< 0.001[d]
			SUP	0.0125	0.0	-0.50 (-0.98, -0.01)	0.011[d]
						Ratio of geometric means (Asian / Caucasian)	
Opioid consumption IV morphine equivalents (mg)	22 [5, 54]	25 [10, 65]	NI	0.025	1.2	0.61 (0.36, 1.04)	< 0.001[d]
			SUP	0.0125	1.0	0.61 (0.33, 1.12)	0.034

Abbreviations: IV, intravenous; NI, noninferiority; SUP, superiority; α, significance level; δ, pre-defined non-inferiority delta.
[a]The summary statistics are presented as mean ± standard deviation or median [Q1, Q3] as appropriate.
[b]Using this framework, one group was deemed better than the other on pain management only if found noninferior on both opioid consumption and pain score and superior on at least one of the two.
[c]Pain score during the initial 72 hours after surgery was compared using a multivariable linear regression model. Total opioid consumption in IV morphine equivalents (mg) during the initial 72 hours after surgery was compared using a multivariable linear regression model after logarithm transformation. All analyses are adjusted for age, gender, duration of surgery, body mass index, American Society of Anesthesiologists status, and cardiac disease.
[d]Statistically significant.

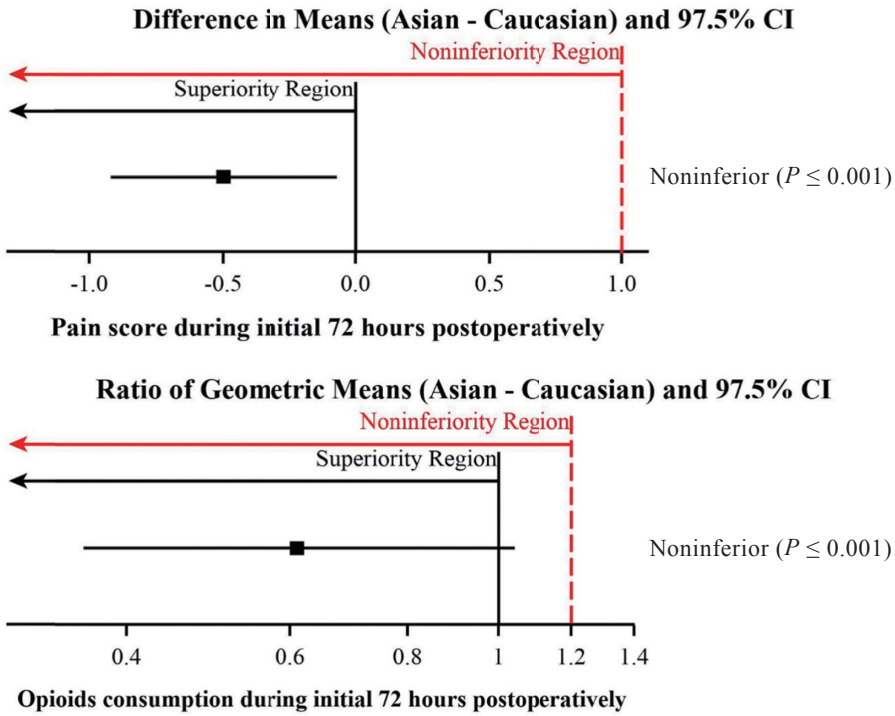

Figure 2. The Plot of Difference in Means of Pain Score (Upper Panel) and the Ratio of Geometric Means of Total Opioid Consumption (Lower Panel) During the Initial 72 Postoperative Hours

The difference in means of pain score and the ratio of geometric means of total opioid consumption were each estimated using a multivariable linear regression model. Both analyses were adjusted for age, gender, body mass index, American Society of Anesthesiologists score, duration of surgery, and cardiac disease. Asians were superior on pain score (superiority test $P = 0.011$) and noninferior on opioid consumption (noninferiority test $P < 0.001$) compared to Caucasians.

Table 5. Incidence of Postoperative Complications in Asians Versus Caucasians[a]

Factor	Asians (N = 130)	Caucasians (N = 129)	
Dizziness	13 (10)	5 (4)	
Bradycardia requiring treatment	2 (2)	2 (2)	
Blurred vision	0 (0)	0 (0)	
Tinnitus	0 (0)	0 (0)	
Desaturation hypoventilation	2 (2)	0 (0)	
Loss of consciousness	2 (2)	0 (0)	
Seizure	0 (0)	0 (0)	
Drowsiness	4 (3)	5 (4)	
Dysarthria	0 (0)	0 (0)	
Confusion	0 (0)	2 (2)	
Malignant ventricular arrhythmias	0 (0)	1 (1)	
Hypotension	8 (6)	4 (3)	
Perioral numbness	0 (0)	0 (0)	
Agitation	0 (0)	1 (1)	
Tachycardia requiring treatment	3 (2)	2 (2)	
New onset atrial arrhythmias	0 (0)	0 (0)	
Mortality	0 (0)	0 (0)	
Cardiac arrest	0 (0)	0 (0)	
Cardiopulmonary resuscitation	0 (0)	0 (0)	
Total number complications	34	22	
Number of patients with any complication[b]	24 (18)	15 (12)	0.59 (95% CI: 0.28, 1.24) $P = 0.98$

[a]Data expressed as number (%).
[b]Odds ratio (95% CI) and *P* value was from a multivariable logistic regression adjusted for age, gender, body mass index, American Society of Anesthesiologists score, duration of surgery, and cardiac disease.

Discussion

In this retrospective cohort analysis of patients receiving liposomal bupivacaine for perioperative analgesia, we found that Asians had lower pain scores and not higher opioid consumption over the first 72 postoperative hours compared to Caucasians. Only 1 Caucasian patient was detected as a potential case of LAST syndrome. Finally, the duration of hospitalization and the incidence of single complications were not different between the two groups.

To our knowledge, there are no previous studies comparing analgesic outcomes, the incidence of LAST syndrome, and duration of hospitalization when using liposomal bupivacaine in Asian versus Caucasian surgical patients. There are some previous experimental pain studies that addressed differences in pain sensitivity between ethnicities. They compared experimental pain sensitivity and tolerance between Asian and non-Hispanic white healthy young participants, and in those who suffer knee osteoarthritis. Most of these previous studies found that Asian participants have higher[17,18] or equal[19] pain sensitivity, a lower pain threshold, increased pain intensity, and greater pain unpleasantness, as well as lower tolerance when compared with non-Hispanic Caucasian participants.[20,30] Likewise, two systematic reviews found higher experimental pain sensitivity, lower pain tolerance, higher pain scores, and higher unpleasantness ratings in ethnic minorities (African-American, Hispanic, Asian) compared to non-Hispanic white patients.[15,21,31] Unlike those previous experimental studies, we analyzed data from a much larger cohort of real-life patients undergoing various surgeries, in which liposomal bupivacaine was part of a multimodal analgesic approach. In the clinical setting, Barrington et. al.[32,33] compared knee local infiltration with bupiva-

caine versus liposomal bupivacaine and evaluated the effect of patient's characteristics, including ethnicity, on postoperative pain after knee arthroplasty.[32,33] They found no effect of ethnicity on the postoperative pain scores. Conversely, Lavernia et al.[34,35] evaluated the influence of race and ethnicity on pain and function after total joint arthroplasty, and found African-Americans to have worse postoperative pain and function scores than Caucasian patients.

The underlying mechanisms of these differences in pain perception are not fully elucidated. However, emerging evidence suggests that genetic factors, like catechol-O-methyltransferase gene and mu-opioid receptor gene (OPRM1) influence pain sensitivity.[22] Furthermore, differences in pain responses between ethnic groups may be associated with allele polymorphisms of pain-related genes. For instance, the G-allele and the OPRM1 polymorphism of the 118 G are more common in Asians (40–50%) compared to other ethnic groups and they have been associated with increased pain sensitivity and differences in analgesic responses.[22] In addition, some of these differences in pain perception can be attributed to environmental factors, such as socioeconomic status and accessibility to specific healthcare resources or different socio-cultural factors (traditions, religion, prior experiences).[16] Several potential mechanisms can explain pharmacokinetic differences between races or ethnic groups, including differences in hepatic metabolism, renal excretion, and plasma protein binding,[13,36,37] but no data is available regarding differences in pharmacokinetics, pharmacodynamics, efficacy, or safety of local anesthetics between ethnicities.

Only one possible case of LAST syndrome was detected in our cohort, which is reasonable considering the reported rate of 1 to 2 cases per 1,000 patients receiving local anesthetics.[38,39] In addition, isolated dizziness judged as possibly related to liposomal bupivacaine administration was identified in 2 additional Asian patients. One possible explanation for the low incidence of the outcome in our cohort is that caregivers failed to detect or report complications as part of the clinical routine. This flaw is inherent to the retrospective nature of our study, but it is highly unlikely for the more severe complications. Another possible explanation is that we failed to recognize the relationship between the administration of liposomal bupivacaine and the reported complications. To address this, the assessors were specifically instructed to use a high index of suspicion and to specifically consider the unique pharmacokinetic profile of liposomal bupivacaine. Also, we conducted an exploratory analysis that ignored the perceived causality between the local anesthetic administration and the reported complications as judged by the adjudicators, and this analysis found similar results. The most reasonable explanation, though, is appropriate administration by experienced clinicians, combined with a good safety profile of the drug. We found no difference in the percentage of patients who presented any single complication. However, we report a relatively high incidence of complications that were judged as non-related to local anesthetic administration (34 and 22 in Asian and Caucasian patients, respectively) probably represents the comorbidity of the patient population having surgery in the Cleveland Clinic, the complexity of the surgical procedures, and the high index of suspicion used by adjudicators who manually reviewed each record.

Despite the significant difference in our primary outcome of pain management between the two study groups, this did not translate into a delay in discharge. Considering that the average pain score in both groups during the studied period was relatively low (below 4 NRS points), it is reasonable that other factors unrelated to pain management had a greater impact on the decision to discharge patients.

Our study has several limitations. First, as any retrospective analysis, residual unobserved confounding may introduce error. However, in our final cohort of 259 patients, the type of surgery and all baseline characteristics except BMI were well balanced between groups. Second, the reported baseline low incidence of LAST (0.1–0.2%)[38,39] limited the power of our analysis to detect differences in this complication. A significantly larger cohort is needed to make sound conclusions about safety, but unfortunately, such a cohort does not currently exist. Our manual review of all charts to specifically identify complications, even if not diagnosed as such by the caregivers, resulted in a relatively high incidence of mild complications, mostly not related to the administration of local anesthetics. The high index of suspicion intentionally used by the study team also resulted in the identification of a few cases of minor complications judged to be potentially related to drug toxicity. Finally, we used "self-declared" ethnicity from the medical records, potentially introducing significant heterogeneity to the Asian group, since patients from many different origins could consider themselves "Asians" (e.g.,

patients from India, the Middle East, etc.). However, self-identified ethnicity seems to be associated with differences in pain response.[40]

In conclusion, Asian adults receiving liposomal bupivacaine as part of multimodal perioperative analgesia demonstrated lower pain scores compared to matching Caucasians, despite not having greater opioid consumption. However, a difference of 0.5 points on pain score is not clinically important enough. Prospective clinical studies are required to further investigate the differences in pain sensitivity and local anesthetic effects in Asian versus Caucasian patients.

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Author Contributions

Eva Rivas, Barak Cohen: study design, data collection, data interpretation, and manuscript writing; Janet Adegboye, Ahmed Salih, David Chelnick, Yuwei Qiu, Remie Saab, Ilker Ince, Marianne Tanios, Tetsuya Shimada, Cecelia Hanline, Syed Raza, Mohamed Hassan, Hassan Hamadnalla, Hani Essber: data collection; Dongsheng Yang: data analysis and interpretation; and Alparslan Turan: study design, data interpretation, and manuscript writing.

Conflict of Interest

All authors report no conflicts of interest.

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