ORIGINAL CLINICAL RESEARCH REPORT

Comparison of Chloroprocaine Versus Lidocaine With Epinephrine, Sodium Bicarbonate, and Fentanyl for Epidural Extension Anesthesia in Elective Cesarean Delivery: A Randomized, Triple-Blind, Noninferiority Study

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BACKGROUND: For emergent intrapartum cesarean delivery (CD), the literature does not support the use of any particular local anesthetic solution to extend epidural analgesia to cesarean anesthesia. We hypothesized that 3% chloroprocaine (CP) would be noninferior to a mixture of 2% lidocaine, 150 µg of epinephrine, 2 mL of 8.4% bicarbonate, and 100 µg of fentanyl (LEBF) in terms of onset time to surgical anesthesia.

METHODS: In this single-center randomized noninferiority trial, adult healthy women undergoing CD were randomly assigned to epidural anesthesia with either CP or LEBF. Sensory blockade (pinprick) to T10 was established before operating room (OR) entry for elective CD. On arrival to the OR, participants received the epidural study medications in a standardized manner to simulate the conversion of "epidural labor analgesia to surgical anesthesia." The primary outcome was the time to loss of touch sensation at the T7 level. A noninferiority margin was set at 3 minutes. The secondary outcome was the need for intraoperative analgesia supplementation.

RESULTS: In total, 70 women were enrolled in the study. The mean onset time to achieve a bilateral sensory block to touch at the T7 dermatome level was 655 (standard deviation [SD] = 258) seconds for group CP and 558 (269) seconds for group LEBF, a difference in means of 97 seconds (90% confidence interval [CI], SD = −10.6 to 204; $P = .10$ for noninferiority). The upper limit of the 90% CI for the mean difference exceeded the prespecified 3-minute noninferiority margin. There was no meaningful difference in the requirement for intraoperative analgesia between the 2 groups.

CONCLUSION: Both anesthetic solutions have a rapid onset of anesthesia when used to extend low-dose epidural sensory block to surgical anesthesia. Data from the current study provide insufficient evidence to confirm that CP is noninferior to LEBF for rapid epidural extension anesthesia for CD, and further research is required to determine noninferiority. (Anesth Analg 2021;132:666–75)

GLOSSARY

APGAR = appearance, pulse, grimace, activity, and respiration; **BE** = base excess; **BMI** = body mass index; **BTL** = bilateral tubal ligation; **CD** = cesarean delivery; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials; **CP** = chloroprocaine; **CPD** = cephalopelvic disproportion; **CSE** = combined spinal-epidural; **CSF** = cerebrospinal fluid; **ITT** = intention to treat; **IV** = intravenous; **LA** = local anesthesia; **LAST** = local anesthetic systemic toxicity; **LEBF** = lidocaine, epinephrine, bicarbonate, and fentanyl; **LTCS** = low transverse cesarean section; **NRS** = numerical rating score; **OR** = operating room; **PDPH** = postdural puncture headache; **Q1** = first quartile; **Q3** = third quartile; **SD** = standard deviation

KEY POINTS

- **Question:** Is chloroprocaine (CP) noninferior to a mixture of lidocaine, epinephrine, bicarbonate, and fentanyl (LEBF) in terms of onset time to surgical anesthesia when used to convert epidural analgesia to epidural anesthesia for cesarean delivery (CD)?
- **Findings:** Onset time to surgical anesthesia was 655 seconds in the CP group compared to 558 seconds in the LEBF group.
- **Meaning:** Noninferiority of CP to LEBF could not be demonstrated, but both solutions provide rapid epidural extension anesthesia for CD.

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Approximately 71% of women in the United States used epidurals or another form of neuraxial analgesia during labor.[1] Intrapartum cesarean delivery (CD) anesthesia is commonly performed by the administration of a more potent local anesthetic solution through the epidural catheter. This is referred to as epidural extension anesthesia and, if successful, avoids the requirement for spinal or general anesthesia. Many studies have investigated various local anesthetics with and without additives to determine which mixture provides the most rapid onset of surgical anesthesia.

At our institution, 2 solutions are preferred for epidural extension anesthesia. The first solution, a mixture of 2% lidocaine, epinephrine, bicarbonate, and fentanyl (LEBF), provides high quality and rapid anesthesia, but requires mixing immediately before administration. The second solution, plain 3% chloroprocaine (CP), has the advantage of quick preparation and administration in emergencies, while minimizing the risk of drug errors.[2] In our practice, the LEBF solution is typically selected for urgent CDs and for anticipated emergencies in which there is time to prepare the solution, and plain CP is reserved for unanticipated emergencies.

A recent meta-analysis provides indirect evidence that lidocaine with sodium bicarbonate requires similar time to extend epidural analgesia to surgical anesthesia when compared with CP.[3] No study has directly compared LEBF with CP to verify that onset times are similar. Given the additional time needed to mix the LEBF solution,[4] we posited that CP would be an acceptable alternative to LEBF as long as the onset time to achieve a level suitable for surgery was within 3 minutes of the LEBF solution. Therefore, we conducted a randomized, noninferiority trial to compare epidural extension anesthesia with LEBF to CP.

METHODS

This randomized, triple-blind, noninferiority trial was approved by the institutional review board at the University of Arkansas for Medical Sciences, where this trial was conducted between February and November 2018. The principal investigator (Nadir Sharawi) prospectively registered the study at ClinicalTrials.gov (NCT03414359). This article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. Healthy women more than 17 years of age with a singleton pregnancy, at 36 weeks of gestation or more, were approached for recruitment on the day of elective CD. The exclusion criteria were nonelective CD, American Society of Anesthesiologists Physical Status III or greater, non-English speakers, contraindications to neuraxial anesthesia, severe fetal anomalies, weight >120 kg, <150 cm, and allergy to any study medications. Written informed consent was obtained from all patients. Participants were randomly allocated to 1 of 2 groups: (1) group CP received 20 mL of 3% CP with 4 mL of 0.9% sodium chloride; (2) group LEBF received 20 mL of 2% lidocaine combined with the following adjuncts: 0.15 mL of 0.1% epinephrine, 2 mL of 8.4% sodium bicarbonate, and 2 mL of 100 µg fentanyl. The total volume of solution in both groups was identical. A computer-generated randomization sequence was allocated in a 1:1 ratio in sealed opaque envelopes that were consecutively numbered 1–70 by an independent research assistant who was not involved in any other part of the study. Randomization assignments remained concealed until just before entry into the operating room (OR). Only the investigator preparing the study medication was aware of group allocation. This investigator was not involved in any other part of the study. The clinical team caring for the patient (surgeons, anesthesiologists, and nurses), outcome assessors, and study participants were blinded to randomization (triple blind).

The Clinical Model

Because it is logistically difficult to study the speed of onset of epidurally administered local anesthetic drugs in emergent CD, we designed a clinical model that would closely simulate the conversion of epidural analgesia to epidural anesthesia for intrapartum CD by enrolling women scheduled for elective CD and establishing preoperative epidural sensory blockade.

Approximately 1 hour before the scheduled time of CD, participants received a combined spinal-epidural (CSE) in the preoperative room on the labor and delivery ward in a standardized manner. Subjects received a 400 mL coload of lactated Ringer's solution and routine monitoring, including continuous cardiotocography. All subjects received the following preoperative medications: 975 mg of oral acetaminophen, 20 mg of intravenous (IV) famotidine, 10 mg of IV metoclopramide, and 30 mL of oral sodium citrate (0.3 M).

Women were placed in the sitting position, and the epidural space was identified by a loss of resistance to a saline technique using a 17-G Tuohy needle at the L3/4 or L4/5 interspace using anatomical landmarks and palpation. The dura was then punctured with a 27-G pencil point needle (Pencan; B Braun, Bethlehem, PA). Spontaneous return of cerebrospinal fluid (CSF) was confirmed, and 150 µg of preservative-free morphine diluted into 1 mL of normal saline was injected into the intrathecal space for postoperative analgesia. Intrathecal morphine was chosen instead of epidural morphine due to reports of reduced analgesic efficacy when epidural CP and morphine are administered in short succession.[5,6] A flexible 19-G spring-wound closed-tip catheter (Perfix, B Braun) was then

advanced 5 cm into the epidural space. The epidural catheter was secured with an occlusive dressing. A test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine was injected to exclude intravascular or intrathecal administration.

Five minutes after confirmation of a negative test dose, participants received 10 mL of 0.0625% bupivacaine with 2 μg/mL of fentanyl to establish a bilateral sensory level to pinprick at the T10 dermatome. Sensory block was evaluated according to the Hollmén criteria[7] (grade 0 = normal sensation to pinprick; grade 1 = pinprick sensation felt less sharp than the control stimulus applied to the upper arm immediately before testing; grade 2 = pinprick recognized as touch sensation; and grade 3 = no perception of touch), with Hollmén grade 1 at the T10 dermatome, defined as an adequate sensory level for randomization (Supplemental Digital Content, Table 1, http://links.lww.com/AA/D171). All measurements of pinprick were assessed using a Neurotip loaded onto a Neuropen (Owen Mumford, Oxford, UK). This noninvasive handheld device applies a consistent force of 40 g when pressed against the patient's skin and, therefore, provides a standardized "pinprick stimulus." If an adequate sensory level was not achieved 15 minutes after the loading dose, additional 5-mL aliquots were given every 10 minutes until the block height reached the T10 level, up to a maximum dose of 20 mL. Participants were excluded from the study if they did not develop a T10 block.

After a T10 block was confirmed, an investigator with no other involvement in the study opened the randomization envelope and prepared the assigned study drugs.

Meanwhile, bedside clinicians maintained the sensory level with a continuous epidural infusion (CADD-Solis; Smiths Medical, Dublin, OH) of 12 mL/h of 0.0625% bupivacaine with 2 μg/mL of fentanyl until OR entry. An investigator marked the T6 level at the midclavicular line bilaterally using the xiphoid process as a bony landmark in an effort to reduce inter-observer variability that has been previously reported.[24–26]

Routine monitoring was applied, and a coload of 500 mL of IV lactated Ringer's solution was given over 15 minutes. The motor block was assessed according to the Modified Bromage score:[8] (0) no motor block, able to raise extended leg and flex the knee and ankle; (1) inability to raise extended leg; able to move knees and feet; (2) unable to flex knee; and (3) unable to move lower limb. The sensory block was assessed, and all randomized study participants were confirmed to have at least a Hollmén grade 1 block to a T10 level.

Epidural extension was conducted in a standardized manner by a blinded anesthesiologist. After confirming negative aspiration of the epidural catheter, a test dose of 3 mL of study drug (CP or LEBF) was given, and the patient was monitored for 3 minutes for signs of accidental intrathecal injection. The remaining volume of blinded local anesthetic solution was then injected over 2 minutes. The start of injectate was defined as time 0 and the beginning of epidural extension.

Sensory testing was performed by the same 4 investigators. The Neuropen was pressed onto the skin at 1-minute intervals, moving from a caudal to cranial direction initially. The patient was asked "Tell me when you feel something touch your skin." As the block continued to ascend, the frequency of assessments increased, until the primary outcome of a Hollmén grade 2 block (loss of touch sensation) at the T7 dermatome level was achieved.

If a bilateral block to touch sensation was not achieved within 15 minutes after the start of epidural extension, then an additional 5 mL of study solution was administered. A final 5 mL of study solution was given if the block was still below the T7 level 10 minutes later. The patient was withdrawn from the study if the block had not achieved a T7 level 35 minutes after the start of epidural extension. Subsequent clinical management was at the discretion of the clinical team.

All participants received a 10-mL supplement of blinded "maintenance" solution at 40 minutes after the start of epidural extension. Subjects in group LEBF received 10 mL of saline placebo, and participants in group CP received 10 mL of 3% CP. A variable rate phenylephrine infusion was started at 25 μg/min, and the dose was titrated to maintain systolic blood pressure within 15% of baseline.

Intraoperatively, all patients received 2 g of IV cefazolin, 8 mg of dexamethasone, 4 mg of ondansetron, and 30 mg of ketorolac if there were no contraindications. After delivery of the infant, an oxytocin infusion was commenced according to institutional protocols.

To maintain blinding, the preoperative epidural infusion was restarted on admission to the postanesthesia care unit and continued until the discharge from the recovery room. The postoperative analgesic regimen consisted of 650 mg of oral acetaminophen every 6 hours and 600 mg of ibuprofen every 6 hours. Oral oxycodone was available every 4 hours for breakthrough pain as determined by the patient's pain score. For moderate pain (numerical rating score [NRS] 4–6), 5 mg of oxycodone was administered, and for severe pain (NRS 7–10), 10 mg of oxycodone was administered.

Outcomes

The primary outcome was the onset time to surgical anesthesia. This was defined as the start of epidural

extension anesthesia up until a bilateral block to the T7 dermatome was achieved to touch (first unblocked dermatome at T6). The sensory modality of touch and T7 dermatomal level were chosen as the most reliable marker for surgical readiness based on a review of the literature, and have been used in previous studies.[9–11]

The secondary outcome was the intraoperative analgesia supplementation rate. This was defined as the requirement for any rescue medications to control discomfort or pain during CD. The choice of medication, dose, and route of administration was at the clinical discretion of the anesthesiologist.

We also recorded the overall satisfaction score, opioid consumption in the first 24 hours, incidence of nausea, vomiting, itching, time from when the primary outcome was reached to the start of surgery, duration of surgery, maximum pain score during surgery, vasopressor requirements, and motor and sensory block (Hollmén grade 1) on arrival into the OR. Neonatal outcomes included the appearance, pulse, grimace, activity, and respiration (APGAR) score and the umbilical cord blood gases. Blinded researchers performed all clinical assessments and data collection. Data on adverse events were also collected, specifically local anesthetic systemic toxicity (LAST), postdural puncture headache (PDPH), and high spinal block (defined as upper limb weakness).

Statistical Analysis

Primary Analysis. The primary outcome of this noninferiority study is the time to loss of touch sensation bilaterally at the T7 dermatomal level. Welch's 1-sided, 2-sample *t* test was used to perform the noninferiority analysis by testing H_0: $\mu_{CP}-\mu_{LEBF} \geq 3$ minutes versus H_1: $\mu_{CP}-\mu_{LEBF} < 3$ minutes. An α-level of 5% was used to perform the hypothesis test. In addition, a 90% confidence interval (CI) around the difference in group means was calculated. Given the noninferiority design, a per-protocol analysis was conducted as the most conservative test of noninferiority. An intention-to-treat (ITT) analysis was also performed on all randomized participants who received the study drug,[12,13] including women with epidural block failure, for whom an onset time of 35 minutes was used.

Because there are no existing data in the literature that clearly define a clinically significant reduction in onset time of anesthesia,[14,15] the noninferiority margin of 3 minutes was defined a priori based on clinical reasoning. If LEBF demonstrated at most a 3-minute faster onset, given the additional time to prepare the LEBF solution,[4] then CP would remain as the preferred agent for unanticipated surgical emergencies, given the reduced complexity of drug preparation and presumed reduced risks of drug error and LAST.[16,17] Assuming that the true difference in onset times between CP and LEBF is 0, 62 mother–infant dyads (31 mother–infant dyads in each arm) will provide the noninferiority 90% power to exclude differences of 3 minutes or greater assuming a common standard deviation (SD) of 4 minutes[18,19] and a 1-sided significance level of 5%. In total, 70 female patients were recruited to account for any withdrawals.

Secondary Analyses. Wilcoxon rank-sum tests were used to compare the groups with respect to continuous or continuous-like outcomes. Pearson's χ^2 tests were used to compare the groups with respect to binary or categorical outcomes, except for outcomes with small expected cell counts (<5), for which Fisher exact tests were used. An α-level of 5% was used to interpret these tests, and no adjustments for multiple comparisons were made.

RESULTS

A total of 70 patients participated in the study. Table 1 presents the demographic, surgical indications, procedures, and preoperative epidural variables. No participants required an epidural loading dose of more than 20 mL of 0.0625% bupivacaine with 2 μg/mL

Table 1. Demographic and Clinical Characteristics

	CP (n = 33)	LEBF (n = 34)
Age (y)		
Median (Q1, Q3)	30 (24, 34.3)	27 (24, 32)
Mean ± SD	29.5 ± 5.8	28.2 ± 5.4
Weight (kg)		
Median (Q1, Q3)	86.6 (71.7, 101.6)	79.6 (73.6, 97.4)
Mean ± SD	86.9 ± 17.0	84.9 ± 15.6
BMI (kg/m^2)		
Median (Q1, Q3)	32.47 (28.7, 37.5)	31.40 (27.5, 36.9)
Mean ± SD	33.1 ± 6.3	32.4 ± 6.0
Ethnicity, n (%)		
African American	12 (36)	13 (38)
Others	21 (64)	21 (62)
Gestational age (d)		
Median (Q1, Q3)	273 (273, 275)	273 (267.5, 273)
Mean ± SD	271.4 ± 6.7	270.5 ± 5.3
Surgical indication, n (%)		
Breech	0 (0)	3 (8)
Maternal request	1 (3)	0 (0)
CPD	0 (0)	1 (3)
Gastroschisis	1 (3)	0 (0)
Malpresentation	1 (3)	0 (0)
Repeat LTCS	30 (91)	30 (89)
Surgical procedure, n (%)		
Primary LTCS	3 (9)	3 (9)
Repeat LTCS	16 (48)	14 (41)
Repeat LTCS + BTL	14 (42)	17 (50)
Epidural loading dose, n (%)		
10 mL	26 (79)	25 (74)
15 mL	2 (6)	7 (20)
20 mL	5 (15)	2 (6)
Epidural infusion duration (min)		
Median (Q1, Q3)	49.0 (36.0, 70.0)	48.0 (38.2, 72.5)
Mean ± SD	61.2 ± 40.6	59.7 ± 37.1

Abbreviations: BMI, body mass index; BTL, bilateral tubal ligation; CP, chloroprocaine; CPD, cephalopelvic disproportion; LEBF, lidocaine, epinephrine, bicarbonate, and fentanyl; LTCS, low transverse cesarean delivery; Q1, first quartile; Q3, third quartile; SD, standard deviation.

of fentanyl to achieve a bilateral sensory level to T10 preoperatively. The median duration of the epidural infusion was 49 and 48 minutes in the CP and LEBF groups, respectively.

In total, 33 patients from the CP group and 34 patients from the LEBF group completed the study protocol (Figure 1). Two patients in the CP group were excluded from the per-protocol analysis. One patient had a 1-sided block on entry to the OR and required replacement of the epidural (an onset time of 35 minutes used for ITT analysis of the primary outcome). The other patient did not receive the preoperative epidural loading dose or the maintenance infusion, but did receive the investigational medications. One patient in the LEBF group was excluded from the per-protocol analysis due to a sensory level lower than T10 on OR entry, but did receive the investigational medications. There were no other deviations from the study protocol.

Three patients in the CP group and 2 patients in the LEBF group required 5 mL of supplemental study solution because the primary end point was not reached within 15 minutes. One patient in the CP group and 1 patient in the LEBF group required 10 mL of supplemental study solution because the primary end point was not reached within 25 minutes. All patients who received the study medications achieved a T7 block within 35 minutes.

Primary Outcome: Onset Time to T7 Sensory Block

Per-protocol analysis of the primary outcome, the mean onset time to achieve a bilateral sensory block to touch at the T7 dermatome level, was 655 seconds (SD = 258, median = 620) for group CP and 558 seconds (SD = 269; median = 500) for group LEBF (Table 2). The mean difference in the onset time of sensory blockade between group CP and group LEBF was 97 seconds (90% CI,

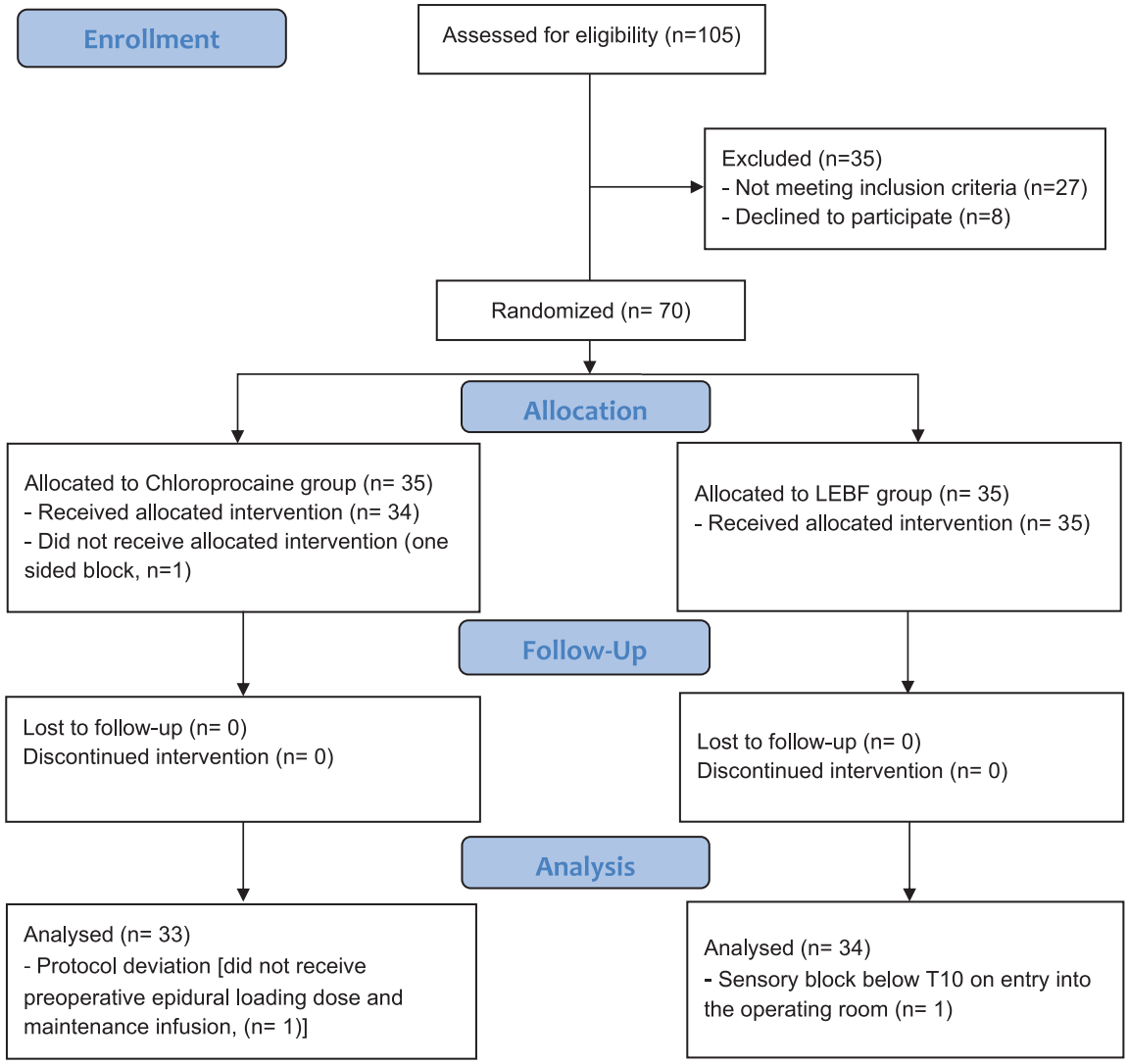

Figure 1. Consolidated Standards of Reporting Trials statement flow diagram. LEBF indicates lidocaine, epinephrine, bicarbonate, and fentanyl.

–10.6 to 204; $P = 0.10$ for noninferiority). The upper limit of the 90% CI for the mean difference was 204, which exceeded the prespecified noninferiority margin of 180 seconds (Figure 2). Therefore, the study did not provide evidence for the noninferiority of CP compared with LEBF regarding onset time to surgical anesthesia. ITT analysis of the mean onset time to achieve a bilateral sensory block to touch at the T7 dermatome level between the CP (666 ± 263 seconds) and LEBF groups (560 ± 266) produced comparable results: 106 seconds (90% CI, 0.2 –212.5; $P = 0.13$ for noninferiority). The time to onset of sensory blockade at T7 was assessed using the Kaplan-Meier survival analysis (Figure 3).

Secondary Outcome: Requirement for Intraoperative Analgesia Supplementation

Table 2 presents the intraoperative data. Seven subjects in the CP group and 4 in the LEBF group complained of pain during surgery and required intraoperative supplementation (21% vs 12%; $P = .30$). Supplemental analgesia was most commonly provided by the administration of additional epidural local anesthesia or IV fentanyl. No patient in either group required conversion to general anesthesia.

Exploratory Outcomes

There were no significant differences in the sensory block levels to pinprick or motor block before the administration of the study medications (Table 2). There were also no significant differences in the time of induction of anesthesia to the start of surgery, duration of surgery, cumulative dose of vasopressors, and incidence of side effects (Table 2). Patient satisfaction scores and median oxycodone consumption in the first 24 hours were not statistically significant in either group (Table 3). No evidence for a difference was

Table 2. Intraoperative Data and Side Effects

	CP (n = 33)	LEBF (n = 34)	*P*
Sensory block (pinprick)[a] on entry into the operating room, n (%)			
T6 or T7	1 (3)	5 (15)	.296[b]
T8	7 (21)	5 (15)	
T9	7 (21)	4 (12)	
T10	18 (55)	20 (59)	
Modified Bromage score on entry into the operating room, n (%)			
0	23 (70)	22 (65)	.725[b]
1	7 (21)	10 (29)	
≥2	3 (9)	2 (6)	
Onset time to T7 block (touch)[a]			
Median (Q1, Q3)	620 (550, 690)	500 (432, 599)	.003[c]
Mean ± SD	655 ± 258	558 ± 269	
Induction to surgery start (min)			
Median (Q1, Q3)	22 (18, 25)	20 (18, 22)	.094[c]
Mean ± SD	22.0 ± 5.2	20.7 ± 5.6	
Surgery duration (min)			
Median (Q1, Q3)	70 (50, 86)	56.5 (50.2, 66.2)	.158[c]
Mean ± SD	70.7 ± 25.6	61.1 ± 16.7	
Phenylephrine (μg)			
Median (Q1, Q3)	1800 (1445, 2295)	1840 (1278, 2766)	.843[c]
Mean ± SD	2336 ± 2004	2112 ± 1269	
Ephedrine use, n (%)	4 (12)	5 (15)	.756[b]
Intraoperative pain[d], n (%)	11 (33)	7 (21)	
Mild (1–3)	3 (9)	4 (12)	
Moderate (4–7)	6 (18)	2 (6)	
Severe (8–10)	2 (6)	1 (3)	
Intraoperative pain treatment, n (%)	7 (21)	4 (12)	.297[b]
Fentanyl (IV)	5 (15)	1 (3)	
Epidural LA	4 (12)	3 (9)	
Nitrous oxide	0	1 (3)	
Combination therapy	2 (6)	1 (3)	
Side effects, n (%)			
Nausea	15 (45)	13 (38)	.549[e]
Vomiting	2 (6)	7 (20)	.081[b]
Pruritus	7 (21)	11 (32)	.341[e]
Shivering	8 (24)	10 (29)	.633[e]

Abbreviations: CP, chloroprocaine; IV, intravenous; LA, local anesthetic; LEBF, lidocaine, epinephrine, bicarbonate, and fentanyl; Q1, first quartile; Q3, third quartile; SD, standard deviation.

[a]Upper sensory level measured using different sensory modalities (Hollmén grade 1 preoperatively and Hollmén grade 2 to assess primary outcome).

[b]Fisher exact test.

[c]Wilcoxon rank-sum test.

[d]Intraoperative pain scale from 0 (no pain) to 10 (worst pain).

[e]Pearson's χ^2 test.

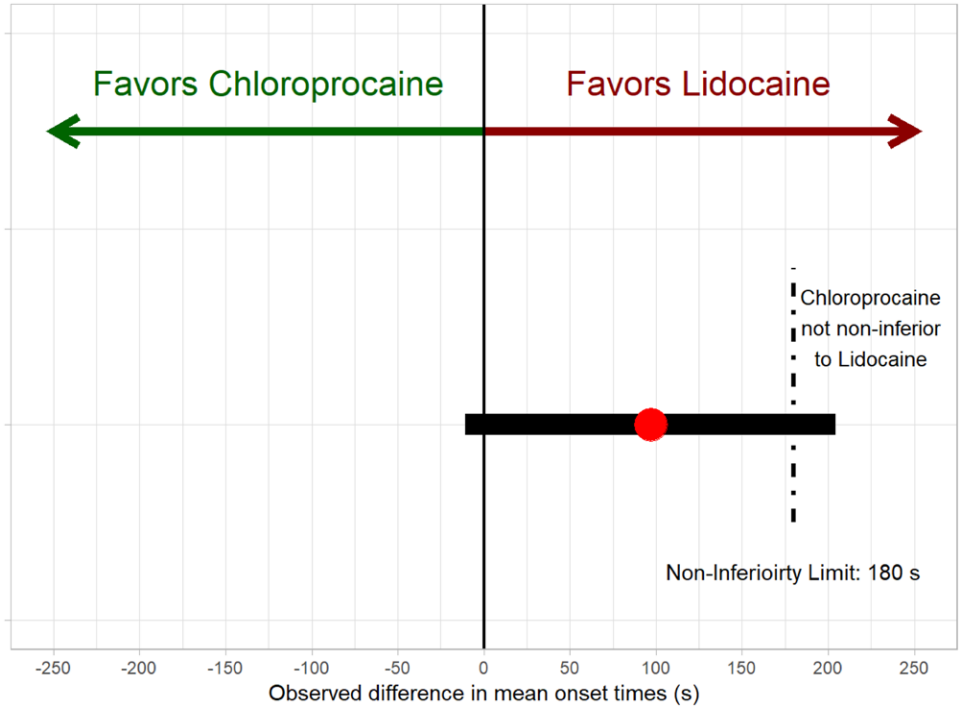

Figure 2. Noninferiority diagram with observed difference of onset time to T7 sensory block between the CP and LEBF groups. The dashed line represents the noninferiority margin. The error bars designate the 90% CI of the difference between the CP and LEBF groups. CI indicates confidence interval; CP, chloroprocaine; LEBF, lidocaine, epinephrine, bicarbonate, and fentanyl.

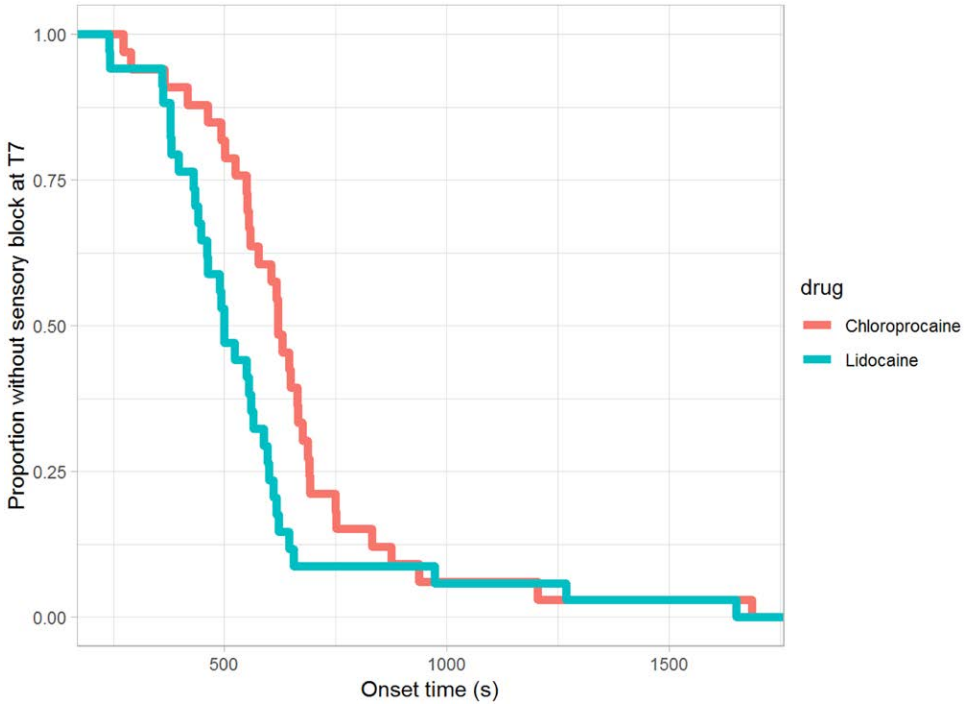

Figure 3. Kaplan-Meier survival curve for time to onset of sensory block to touch at T7.

found with regard to neonatal outcomes, including APGAR scores at 1 and 5 minutes, umbilical vein pH, and base excess, which were all comparable between the 2 groups (Table 3). There were no incidences of high spinal block or LAST; however, one patient in the CP group did develop a postural headache suggestive of PDPH on postoperative day 2. This was assumed to be due to dural puncture with the 27-G spinal needle because there were no signs of inadvertent intrathecal drug administration during the study. This was treated successfully with an epidural blood patch.

DISCUSSION

This is the first randomized trial that has directly compared 2 commonly used local anesthetic mixtures (CP and LEBF) for epidural extension anesthesia for

Table 3. Postoperative Pain Scores, Oxycodone Consumption, and Neonatal Outcomes

	CP (n = 33)	LEBF (n = 34)	*P*
Patient satisfaction, n (%)			
0–3	0 (0)	0 (0)	>.99[a]
4–7	1 (3)	1 (3)	
8–10	32 (97)	33 (97)	
Oxycodone use in the first 24 h after surgery, n (%)	27 (82)	22 (65)	.114[b]
Cumulative oxycodone (mg)			
Median (Q1, Q3)	15 (8.8, 30)	10 (0, 30)	.405[c]
Mean ± SD	19.2 ± 17.1	16.3 ± 16.7	
APGAR score at 1 min, n (%)			
<8	21 (64)	25 (74)	.383[d]
8–10	12 (36)	9 (26)	
APGAR score at 5 min, n (%)			
<8	7 (21)	4 (12)	.297[a]
8–10	26 (79)	30 (88)	
Umbilical vein pH			
Median (Q1, Q3)	7.28 (7.24, 7.30)	7.29 (7.28, 7.31)	.054[c]
Mean ± SD	7.26 ± 0.06	7.29 ± 0.04	
Umbilical vein BE			
Median (Q1, Q3)	−4.2 (−5.1, −3.1)	−4.0 (−5.4, −2.9)	.985[c]
Mean ± SD	−4.3 ± 2.2	−3.9 ± 2.5	

Patient satisfaction rating from 0 (extremely dissatisfied) to 10 (extremely satisfied).

Abbreviations: APGAR, appearance, pulse, grimace, activity, and respiration; BE, base excess; CP, chloroprocaine; LEBF, lidocaine, epinephrine, bicarbonate, and fentanyl; Q1, first quartile; Q3, third quartile; SD, standard deviation.

[a]Fisher exact test.

[c]Wilcoxon rank-sum test.

[b]Pearson's χ^2 test.

CD. Both study solutions had a rapid onset of surgical anesthesia, with a mean of 655 seconds in the CP group and 558 seconds in the LEBF group. The absolute difference between the 2 groups was 97 seconds. However, the upper bound limit of the CI between the groups was 204 seconds which exceeded the 180 seconds prespecified margin. Noninferiority trials can be interpreted as noninferior, inconclusive, or inferior according to the location of the CIs in relation to the noninferiority margin.[21,22] Because the upper limit of the CI exceeded this margin, our trial provides insufficient evidence to conclude that CP is noninferior to LEBF in this patient population. Therefore, the results are inconclusive and further research is required to determine noninferiority.

The intraoperative analgesic supplementation rate in this study was comparable to other studies, with 21% and 12% of patients in the CP and LEBF groups, respectively, requiring analgesia intraoperatively.[4,10,19,23] In all cases, neuraxial supplementation was adequate to maintain satisfactory neuraxial blockade. Patient satisfaction scores were high in both groups, and no participants required conversion to another type of neuraxial or general anesthetic.

This study design featured a randomized controlled trial with carefully standardized study drug administration and sensory block assessment. The sensory modality of touch was chosen because of its binary endpoint. The patient either feels the stimulus or she does not. When the sensations of cold or sharp are used, the end point is not as clear due to the graded intensity of the stimulus.[10] Numerous studies have also used touch as the preferred sensory modality when assessing speed of anesthetic onset for CD.[9–11] Although a block to T7 level seems low, it is generally accepted that this corresponds to a much higher sensory level when compared to cold or pinprick sensation, and that the majority of women never achieve a block height to T6 for touch but have adequate surgical anesthesia.[11,27] Our results are similar to other studies.[10,19,20] A previous study using a solution of lidocaine, epinephrine, and fentanyl reported an onset of 13 minutes to a T7 block to touch.[10] Another study demonstrated no difference between CP and a solution of lidocaine with epinephrine to achieve a loss of cold sensation at T5 (8 and 5 minutes, respectively).[19] However, it would not be valid to make direct comparisons due to major differences in methodology, sensory modality assessment, and differing drug combinations.

In this study, we used a unique clinical model of simulating "labor analgesia" by establishing and maintaining a T10 sensory block before the time of scheduled CD. This model and the method of drug administration were designed to closely represent the clinical environment that requires the rapid conversion of epidural analgesia to surgical anesthesia for emergent CD.

We opted for a noninferiority study design because each study solution has its own distinct advantages. Hence, our aim was to prove that the current practice at our institution of administering CP for the unanticipated emergency CD was not unacceptably less efficacious than LEBF. This becomes especially important during times of local anesthetic drug shortages.[28] The use of epidural CP to extend labor analgesia to anesthesia is appealing and has many advantages. The risk of systemic toxicity to the fetus and mother is lower when compared to amide local anesthetics.[16,17] It has a short half-life of only a few minutes in both maternal and fetal blood, and is not influenced by fetal acidosis and, therefore, may have an advantage over lidocaine when fetal asphyxia is present.[16,29,30] By avoiding the use of additives, the risk of bacterial contamination and drug errors from mixing 4 different drugs is minimized, as well as the time required to prepare and administer the medication.[2]

Several limitations apply. First, there is a paucity of studies that directly compare CP to lidocaine-containing solutions, so our sample size calculation was based on limited data[10,18,19] and reduced our ability to detect noninferiority. There is widespread belief among clinicians that CP provides the most

rapid form of anesthesia[31,32]; however, the evidence for this is questionable, and is based primarily on retrospective data or a limited number of smaller studies.[19,20,33,34] The data collected in the current study suggest that LEBF may have a faster onset than CP; a future superiority randomized control trial is needed to test this hypothesis. Second, some clinicians may consider a noninferiority margin of 3 minutes to be too great, but this difference reflects a combination of the known difference in time needed to prepare the 2 solutions and the smaller clinically important difference in time that would allow the team to avoid the need for general anesthesia in the event of an unanticipated emergency. For noninferiority trials, a more conservative α-level of .025 is recommended as opposed to a 0.05 significance level we used, which can be considered a limitation of our study, although this would not have altered the results. We also assumed that the dosages of CP and lidocaine administered were equipotent based on previous studies.[19,20,34,35]

In conclusion, we were unable to demonstrate that CP was noninferior to LEBF. Both drugs have a rapid onset of anesthesia when used to extend low-dose epidural sensory block to surgical anesthesia for elective CD, but further research is required to determine noninferiority. ■

DISCLOSURES

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Contribution: This author helped conduct the study, analyze the data, and write the manuscript.
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Name: Prannal Bansal, MD.
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