MATERNAL

A randomized controlled trial of liposomal bupivacaine for pain following obstetrical laceration

Katherine L. Dengler, MD; Kelsey J. Simpson, MD; Christopher J. Strauchon, DO; Angela K. Shaddeau, MD; Daniel I. Brooks, PhD; Daniel D. Gruber, MD

BACKGROUND: Postpartum pain management is critical after vaginal delivery involving a second, third, or fourth degree laceration as patients heal from their repair. Uncontrolled postpartum pain can affect both the physical and mental recovery period, extend hospital stays, and increase the potential for serious adverse reactions with pain medications. In light of the opioid crisis and increase in dependency after utilization, finding alternatives for pain management after procedures is paramount. The need for a safe, effective, long-acting medication to treat postpartum and postoperative pain has reached a critical point in the current healthcare climate.

OBJECTIVE: To minimize pain after vaginal delivery, we assessed the effectiveness of liposomal bupivacaine vs plain bupivacaine injected into the perineum after second, third, or fourth degree lacerations. We hypothesized that the liposomal bupivacaine study group would have less vaginal pain, analgesic usage, and improved quality of life compared with the plain bupivacaine control group.

MATERIALS AND METHODS: This is a single-blinded randomized controlled trial with 120 subjects enrolled at Walter Reed National Military Medical Center, Bethesda, Maryland, from February 2018 to February 2019. After vaginal delivery and repair, study participants were randomized into 20-mL liposomal bupivacaine (study group) or 20-mL 0.25% plain bupivacaine (control group) injected into and around the perineal body bilaterally. On postpartum days 1, 3, and 7, pain scores and analgesics were recorded. Our primary outcome was vaginal pain score at postpartum day 3, analyzed with Wilcoxon rank-sum test. Our secondary outcomes included vaginal pain at postpartum days 1 and 7, pain with bowel movement, sleep disturbance, and pain's impact on activity, stress, and mood. Desired statistical power was achieved with 48 patients per group (total of 96 patients).

RESULTS: A total of 60 patients were randomized to each group; 108 patients completed the study. Most patients (94%) had regional anesthesia. There was no statistically significant difference in the demographics between these groups. There were 25 obstetric anal sphincter injuries, equally distributed between the 2 groups ($P>.99$). There was no significant difference between vaginal pain scores at postpartum day 3 (control, 2 [1−3]; study, 2 [0−3]) ($P=.63$). This was also seen at postpartum day 1 (control, 2 [0−3]; study, 2 [0−3]) ($P=.82$) and postpartum day 7 (control, 1 [0−3]; study, 1 [0−2]) ($P=.47$). Cumulative pain scores for postpartum days 1, 3, and 7 failed to reach significance (study, 5 [3−8]; control, 6 [3−8]) ($P=.83$). Secondary analysis of pain with bowel movement and impact on sleep, activity, stress, and mood found no differences. Given that only 3 patients required outpatient opioids, there were insufficient data to calculate morphine equivalent differences.

CONCLUSION: After obstetric lacerations, there is no proven benefit to lateral and intraperineal injection of liposomal bupivacaine over plain bupivacaine in postpartum vaginal pain scores, quality of life scores, or pain medication utilized. This may be due to low pain scores and opioid usage, both groups benefiting from the intervention, or ineffective perineal injection location.

Key words: liposomal bupivacaine, OASIS, obstetrical laceration, perineal injection, plain bupivacaine, postpartum pain, quality of life scores, vaginal pain

Postpartum pain management is critical after a vaginal delivery involving a second, third, or fourth degree laceration. Lacerations typically result in postpartum vaginal pain. Uncontrolled pain can affect physical and mental recovery periods, extend hospital stays, and increase the potential for serious adverse reactions with pain medications. Postpartum analgesia involves a multimodal approach of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids, if indicated.

The long-term use of opioids has adverse reactions and dependency concerns. The Joint Commission on Accreditation of Healthcare Organizations has issued advisories regarding better pain management and heightened awareness of adverse reactions with opioid use.[1] A recent study published opioid dependency after vaginal and cesarean deliveries to be 1.7% and 2.2%, respectively.[2] The need for a safe, effective, long-acting medication to treat postpartum and postoperative pain has reached a critical point.

Intrapartum analgesia is beneficial in reducing immediate and long-term postpartum pain. Intrapartum analgesia modalities include regional anesthesia, acetaminophen, opioids, and local anesthetic such as amides. Amides, such as lidocaine and bupivacaine, contribute minimally to postpartum pain control because of their relatively short duration of action. Lidocaine provides pain control for 1.5−3 hours and bupivacaine for 7 hours, with neither providing a long-acting result.[3]

Liposomes bind bupivacaine and provide a slow release, which allows for prolonged analgesia. Colorectal, orthopedic, urogynecology, and general surgery literatures have reported on an extended-release liposomal bupivacaine

Cite this article as: Dengler KL, Simpson KJ, Strauchon CJ, et al. A randomized controlled trial of liposomal bupivacaine for pain following obstetrical laceration. Am J Obstet Gynecol MFM 2020;2:100115.

2589-9333/$36.00
Published by Elsevier Inc.
https://doi.org/10.1016/j.ajogmf.2020.100115

AJOG MFM at a Glance

Why was this study conducted?

Given the necessity to decrease opioid usage and reduce pain for patients, a perineal injection of liposomal bupivacaine vs plain bupivacaine to block the pudendal nerve was performed to determine if postpartum vaginal pain scores decreased after obstetrical laceration.

Key findings

In this single-blinded randomized controlled trial, there was no difference in postpartum vaginal pain scores, quality of life scores, or pain medication utilized between patients receiving perineal injection of liposomal bupivacaine and plain bupivacaine after repair of second, third, or fourth degree obstetrical lacerations.

What does this add to what is known?

There is no literature on liposomal bupivacaine use following obstetrical laceration repair, and this study adds to the literature on postpartum pain control.

injection, which was shown to provide up to 96 hours of postoperative analgesia with minimal adverse effects.[4–9] Gorfine et al[10] reported that extended-release bupivacaine reduced postoperative pain over 72 hours and decreased narcotic needs after hemorrhoidectomy. Similarly, most obstetric literature on liposomal bupivacaine during cesarean delivery showed decreased narcotic usage and lower pain scores.[11,12] Although we found studies on the positive use of liposomal bupivacaine, a study by Prabhu et al[13] revealed no difference in pain or opioid usage during cesarean delivery vs placebo. A review of recent orthopedic literature comparing the efficacy of liposomal bupivacaine vs plain bupivacaine or ropivacaine showed no advantage in total knee arthroplasty or wrist operations.[14–16] We did not find any publications on liposomal bupivacaine use after vaginal delivery. Given the pudendal nerve distribution and successful injection during hemorrhoidectomy, the obstetric patient population may show benefit during delivery.

This study primarily aimed to assess the effectiveness of long-acting liposomal bupivacaine in providing pain control after vaginal deliveries involving a second, third, or fourth degree obstetric laceration on postpartum day (PPD) 3. The control arm of plain bupivacaine would have been eliminated by 72 hours; hence we anticipated the largest delta pain scores between the 2 groups at PPD 3.

Secondary outcomes included determining whether liposomal bupivacaine improved vaginal pain scores at PPDs 1 and 7, decreased pain medication usage (specifically opioids), and improved patient's quality of life during the postpartum period.

Methods

This was a randomized, single-blinded trial conducted at Walter Reed National Military Medical Center (WRNMMC) with institutional board (IRB) approval (WRNMMC-2017-0054) and was registered with ClinicalTrials.gov (NCT03152877) before enrolling patients. Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed (Figure 1).

We included all pregnant women over the age of 18 years, eligible to deliver vaginally at WRNMMC Mother Infant Care Center (MICC) who consented before induction of labor or active labor (>5 cm) from February 2018 to February 2019. Exclusion criteria included regular use of narcotic pain medication (defined as use on most days in 3 months before delivery), fetal demise, history of alcohol or narcotic abuse requiring treatment, unstable cardiac arrhythmias, hepatic impairment, or known allergy to amide local anesthetics.[9] Patients with chronic pain or regular narcotic usage were excluded because of concern of higher risk of pain and increased narcotic usage owing to opioid tolerance.

Patients who requested regional anesthesia received an epidural or spinal anesthesia (n=1) with a combination of fentanyl and bupivacaine per provider's discretion. Epidural anesthesia was terminated at the completion of the repair. Intrapartum monitoring was done for 2 hours after anesthesia induction.

Subjects who met inclusion criteria after vaginal or operative delivery were assessed for the presence of a second, third, or fourth degree laceration. They were randomized to receive either a 20-mL injection of 0.25% plain bupivacaine or a 20-mL injection of liposomal bupivacaine in their perineum following the completion of laceration repair. These repairs were performed per delivering provider' discretion. Local anesthetic was used if indicated for immediate pain control because liposomal bupivacaine cannot be effectively used for immediate anesthetic relief. When local anesthetic (1% lidocaine) was used during the repair, injection of the study medication was delayed for 20 minutes. The injection was administered after repair completion in order not to delay the repair or increase blood loss while the medication was prepared in a separate location.

Randomization was performed using a computer-generated block randomization program, in blocks of 40, carried out by the Investigational Pharmacy at WRNMMC. Each randomization was blinded to the researcher and delivering provider until after delivery and repair completion. To blind the patient, the researcher opened a sequentially numbered opaque sealed envelope (SNOSE) in a different room, revealing which medication the patient was randomized to receive. Plain bupivacaine or liposomal bupivacaine was drawn into a 20-mL syringe, and syringe barrels were covered with solid white labels to mask the content because liposomal bupivacaine is cloudy, whereas plain bupivacaine is clear.

The medication was injected in the patient's perineum after aspiration using

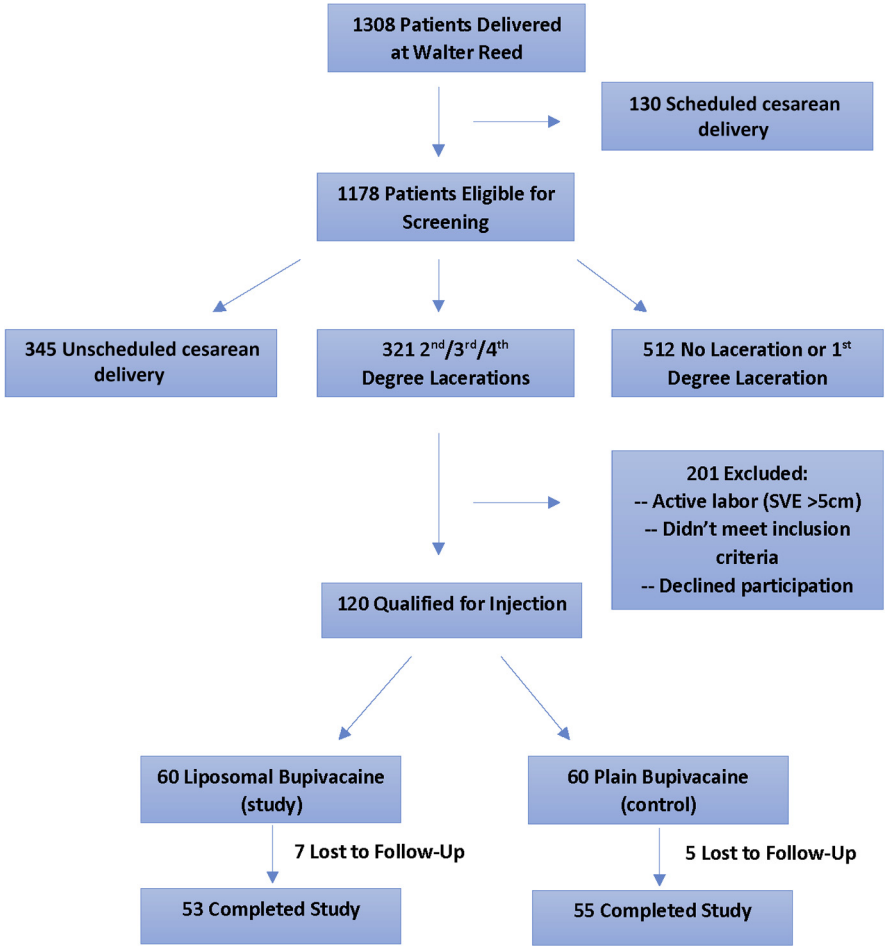
a 21-gauge 1.5-inch needle in a fan-like distribution pattern to cover the pudendal nerve distribution (Figure 2, A). Two milliliters were injected at the top of the perineum and 9 mL on both sides at the midperineum, 1-needle length lateral to the midline (2 mL injected directly and remaining 7 mL injected in a fan-like distribution bilaterally) (Figure 2, B).

Certified nurse midwives, obstetrics and gynecology residents, and attending physicians performed all the deliveries. Providers administered the injections after receiving simulation training. After injection administration, the patient received routine postpartum care based on the SMFM position statement on pain management, to include perineal ice packs and witch hazel pads. Patients were prescribed acetaminophen and NSAIDS as needed and oxycodone (or equivalent opioid) if requested for breakthrough pain.[17]

At PPD 1, patients were asked to rate their baseline pain in the vaginal area and with bowel movement according to the Defense and Veterans Pain Rating Scale, an 11-point visual pain scale (Figure 3). Patients were then asked questions regarding their current pain level in the vaginal area and pain with bowel movements and its impact on 4 quality of life measures (activity, sleep, mood, and stress) using the same scale.

Once patients were discharged home, total postpartum pain medication usage was calculated. Patients were contacted at PPDs 3 and 7 and asked the same questions, and pill counts were totaled. Subjects were given the same visual pain scale at discharge so that it could be referenced during follow-up calls. At the PPD 7 phone call, patients were asked what study medication they thought they received. Patients were included for analysis if they reported pain scores at PPDs 1, 3, and 7 and if they answered what medication they thought they received. One patient in each group did not have a recorded baseline vaginal pain score and was excluded from analyses that controlled for baseline vaginal pain.

FIGURE 1
Consolidated Standards of Reporting Trials flow diagram .



A flow diagram describing enrollment for the study.

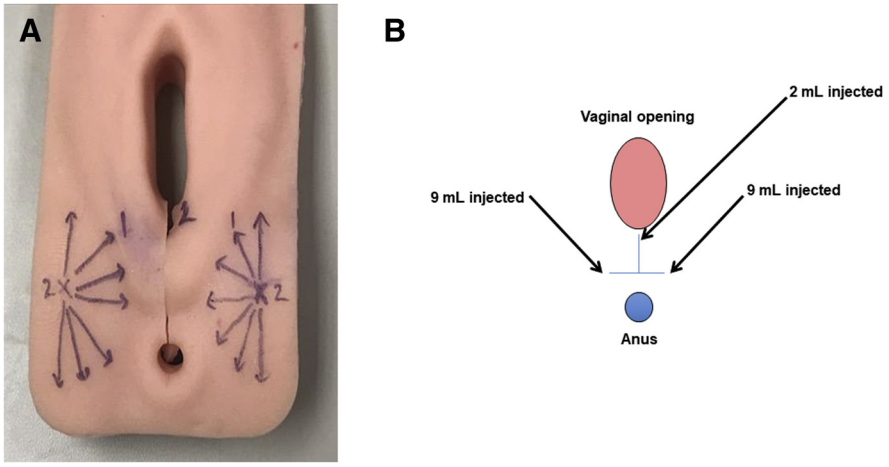
SVE, sterile vaginal exam.

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

In a study by Gorfine et al[10], a randomized controlled trial comparing liposomal bupivacaine and normal saline after hemorrhoidectomy, the overall pain level for the entire 72-hour period was reported as 141.8 for the study group compared with 202.5 for the placebo group with a common standard deviation (SD) of 104.3. This reference was used to calculate the sample size needed for this study. Given the plain bupivacaine half-life of 2.7 hours, the clearance would occur by 24 hours postpartum when differentiating pain scores between groups.

To detect a 30% difference in pain level at 72 hours postpartum between the study medication (liposomal bupivacaine) and control groups (plain bupivacaine), a sample size of 96 patients was needed to have 80% power with an alpha of 0.05.[9,10] Average postpartum pain score was calculated in our population through an internal quality review. Based on historical data at our institution, we anticipated that 5%−10% of all patients would have second, third, or fourth degree vaginal tears. In practice, we observed a higher rate (Figure 1), although this did not affect the actual number of subjects enrolled. Therefore, up to 2400 participants may have been needed for screening, with up to 120 participants eligible for randomization

FIGURE 2
Perineal injection distribution



A, Simulation model used to teach perineal injection distribution. "X" shows the injection site bilaterally and the numbers are the volume injected at each site. The direction of the needle from the original insertion site with the amount instilled at each line is shown (*arrows*). **B,** Schematic showing perineal injection distribution. The 3 areas where the needle was injected are delineated (*arrows*).

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

(2400×5%=120; 120×80%=96]. A total of 120 patients were selected to account for a 20% dropout rate.

All statistical analyses were completed using R (R Core Team, Vienna, Austria). Normally distributed continuous variables, such as age and BMI, were reported as means with SDs. Pain scores and other secondary outcomes were reported as medians with interquartile ranges (IQRs). To approximate a measure of total pain across the study period, pain scores were summed up. For continuous measures, data were reported as mean and SD, whereas for categorical measures, data were reported as number and percentage. The Wilcoxon rank-sum test was used to evaluate group differences for continuous variables. Fisher exact test was used to compare categorical outcomes, such as perceived drug, and binomial confidence intervals (CIs) were calculated using the method by Agresti and Coull (1998). To evaluate the possible contribution of multiple covariates to reported pain score, a linear model including additional covariates of BMI, parity, and age was used after visual inspection confirmed that residuals were normally distributed.

Results

A CONSORT flow diagram (Figure 1) describes enrollment, consent, and randomization to the liposomal bupivacaine and plain bupivacaine groups. We included 53 patients in the liposomal bupivacaine study group and 55 patients in the plain bupivacaine control group for analysis. Patient demographics and clinical features are presented in Table 1. There was no difference in demographics. The patient's estimated gestational age, regional anesthesia usage (94%), operative delivery rates, birthweight, and delivery estimated blood loss were also not statistically significant (Table 1). Of all vaginal deliveries, there was an overall 3% rate of obstetric anal sphincter injuries (OASIS). There were 25 (23.1%) OASIS in our randomized population, with statistically equivalent distribution between the liposomal bupivacaine and plain bupivacaine groups.

For the primary outcome of postpartum vaginal pain at 72 hours, there was no significant difference in vaginal pain scores between the liposomal bupivacaine and plain bupivacaine groups (Table 2). There was in fact no significant difference at any time point or in summed pain scores between the groups. In addition, changes in pain scores from baseline were not significant.

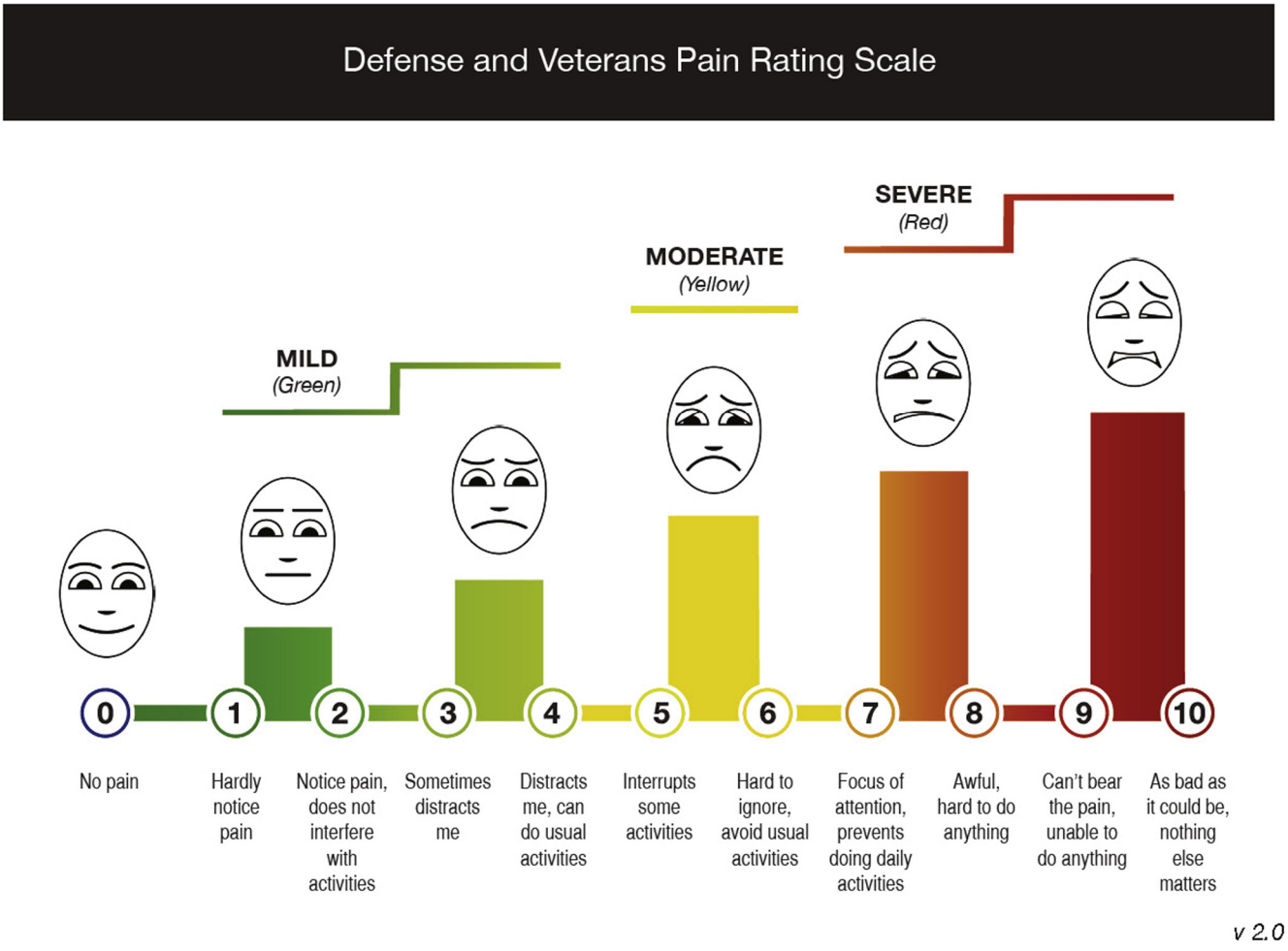
Patients in both treatment groups believed that they were given the study drug (liposomal bupivacaine, 75.5%, 95% CI [62.3%−85.2%]; plain bupivacaine, 70.9%, 95% CI [57.8%−81.3%]). There was no significant difference in perceived drug as a function of actual drug (P=.67).

To account for demographic covariates, a linear model was used that found no significant difference in vaginal pain between the liposomal bupivacaine and plain bupivacaine groups at PPDs 1 (P=.93), 3 (P=.85), or 7 (P=.68).

Secondary analysis of quality of life measures are summarized in Table 3. There were no differences between the liposomal bupivacaine and plain bupivacaine groups in our secondary analysis. Generally, patients required low amounts of opioids, with only 3 patients receiving outpatient opioids at any time point. Given the low amounts of opioid used, statistical analysis was not performed. There were no differences in reported usage of ibuprofen or its equivalent (P=.30) (plain bupivacaine, 3629 mg; liposomal, 3872 mg) or acetaminophen (P=.15) (plain bupivacaine, 3678 mg; liposomal, 4175 mg). There were 18 patients in the plain bupivacaine group and 17 patients in the liposomal bupivacaine group who had bowel movements at PPD 1 that were included in the analysis and 44 patients in plain bupivacaine and 48 liposomal bupivacaine groups at PPDs 3 and 7. Among all patients, 4 patients had no bowel movement at PPD 7 (3 liposomal and 1 plain bupivacaine). All patients voided at the time of hospital discharge.

Primary and secondary outcomes were analyzed separately for patients with OASIS with no statistical difference found at PPD 1 or 3. A likely false significant difference was found at PPD 7, with lower pain (P=.02) reported in the liposomal group (median, 0; IQR, 0−2) than the plain bupivacaine group (median, 2; IQR, 1−2.25). However, our

FIGURE 3
Defense and Veterans Pain Rating Scale (DVPRS) version 2.0[18]



Courtesy of Walter Reed National Military Medical Center.

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

study was not powered to detect a difference in this group. Of note, there was no statistically significant difference in vaginal pain between patients with a second degree laceration vs patients with OASIS (third and fourth degree lacerations) regardless of medication received (P=.17) (Table 4). This is contrary to the popular belief that a higher degree of laceration equates to more pain.

Adverse outcomes for this study included 2 patients receiving plain bupivacaine with bilateral perineal contusions (1.9%) and had no additional issues. There were 3 patients with third-degree (3c) lacerations receiving plain bupivacaine who had wound breakdown requiring repair in the operating room (2.8%). Finally, 1 patient receiving liposomal bupivacaine with persistent granulation tissue required revision.

Structured Discussion and Comments

Principal findings

Following second, third, or fourth degree obstetrical lacerations in our population, there was no proven benefit to perineal injection of liposomal bupivacaine over plain bupivacaine in postpartum vaginal pain scores at PPDs 1, 3 (our primary outcome), and 7. There was also no difference in pain medications consumed between the 2 groups. Moreover, there was no statistical difference in quality of life factors that include impact of vaginal pain on stress, mood, sleep, and activity between groups.

Results

To the best of our knowledge, this is the first study to evaluate vaginal pain scores and other secondary analysis after perineal injection of liposomal bupivacaine vs plain bupivacaine after obstetrical laceration.

Although most patients thought they received the study medication, both groups were equally distributed, and their vaginal pain scores were not statistically significant. This could have been due to overall low pain scores between the 2 groups or both groups

TABLE 1
Demographic and clinical features from analyzed patients

Demographics	Plain BP (n=55)	Liposomal BP (n=53)	*P* value
Age (y), mean (SD)	30.1 (4.9)	30.4 (4.9)	.72
Race, n (%)			.97
White	38 (69.1)	38 (71.7)	
Black	4 (7.3)	5 (9.4)	
Asian	5 (9.1)	4 (7.5)	
Other	7 (12.7)	5 (9.4)	
Unknown	1 (1.8)	1 (1.9)	
Weight (kg), mean (SD)	88.4 (6.9)	84.9 (6.9)	.13
Height (cm), mean (SD)	165.4 (7.6)	166.6 (7.6)	.46
BMI (kg/m^2), mean (SD)	32.5 (7.1)	30.5 (3.9)	.12
Parity, median (IQR)			
Gravida	2 (1–2)	2 (1–2)	.93
Term	0 (0–1)	0 (0–1)	.7
Preterm	0 (0–0)	0 (0–0)	>.99
Abortion	0 (0–1)	0 (0–1)	.83
Living children	0 (0–1)	0 (0–1)	.58
Estimated gestational age (wk), median (IQR)	40 (39–40)	39 (38–40)	.06
Epidural, n (%)	52 (94.5)	50 (94.3)	>.99
Delivery method, n (%)			.90
SVD	46 (83.6)	44 (83.0)	
Operative delivery	9 (16.4)	9 (17.0)	>.99
Forceps	9 (16.4)	8 (15.1)	
Vacuum	0 (0)	1 (1.9)	
Lacerations, n (%)			.81
2	43 (78.1)	40 (75.5)	
OASIS	12 (21.8)	13 (24.5)	
3	12 (100)	11 (84.6)	
4	0 (0)	2 (15.4)	
Episiotomy	2 (3.6)	1 (1.9)	>.99
Baby birthweight (g), mean (SD)	3559.2 (376.4)	3472.3 (449.6)	.28

OASIS and operative delivery denominators include randomized patients only.

BMI, body mass index; *BP*, bupivacaine; *IQR*, interquartile range; *OASIS*, obstetric anal sphincter injuries; *SD*, standard deviation; *SVD*, spontaneous vaginal delivery.

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

benefiting from their intervention. Current practice after laceration repair does not include routine local anesthetic injection. With regard to baseline vaginal pain scores in the postpartum period, a previous study by Komatsu et al[19] followed nulliparous women after both vaginal and cesarean deliveries and monitored self-reported pain scores to determine a time frame to a pain- and opioid-free functional status. No studies are available that specifically compare pain scores in women after sustaining second, third, or fourth degree lacerations. Given that pregnant patients are automatically categorized as a high-risk study population, we could not obtain a placebo arm from our institution.

Given that only 7 patients required inpatient opioids and 3 were discharged home with these medications, there were insufficient data to calculate a difference in morphine equivalents. This may have been due to low narcotic usage in our study population or that postpartum patients, in general, may not require opioids after delivery. Previously, providers may have automatically prescribed opioids to patients after more significant tears, but with our protocol, opioids were prescribed only upon the patient's request. Overall, fewer opioids were used than originally anticipated. There are multiple gynecologic studies after hysterectomy that showed significantly less postoperative opioid use than prescribed by the provider.[20–22] This suggests that prescribing physicians provide more narcotics than medically needed, thus contributing to the opioid epidemic. The low narcotic use in our study could also be because both groups may have benefited from the injection, but baseline postpartum narcotic usage was not available for comparison. NSAID and acetaminophen usage was also not statistically significant. These routine nonopioids are considered safe for most patients postpartum.

Clinical implications

Immediate postpartum goals for patients include newborn bonding, early ambulation, and tolerable pain scores, all of which could be influenced by inadequate postpartum pain control. Although the immediate postpartum period can have a significant impact on quality of life factors (stress, mood, sleep, and activity), questions in this study were posed directly in relation to vaginal pain and not in relation to the newborn. There may have been some underlying bias when answering these questions; however, absolute incidence of quality of life scores was quite low and had no clinical significance between the 2 groups.

The negative findings of this study could have potentially been due to ineffective perineal injection site. For liposomal bupivacaine to be effective, it needs to be dispersed throughout the tissues. Jones et al[9] studied bilateral perineal injection with liposomal bupivacaine vs placebo in an older urogynecology population after posterior colporrhaphy. They injected 9 mL of unmixed liposomal bupivacaine in a single perineal injection bilaterally and 2 mL at the level of the introitus. This study found no statistical difference in vaginal pain scores between the 2 groups but suspected that this could have been due to limited tissue distribution of the liposomal bupivacaine. In our younger patient population with more "active" nerves, it was anticipated that an improved injection technique may provide clinically significant results. In an attempt to best diffuse the study medication throughout the perineal tissues in the pudendal nerve distribution, it was injected using a fan-like pattern (Figure 2, A).

At the time of IRB approval, regional blocks with liposomal bupivacaine were not approved; thus, future research could consider a pudendal block for additive pain control postpartum. To perform the cleanest study, liposomal and plain bupivacaine were not mixed to further distribute the medication in the tissue; however, this could also be considered in future research.

Research implications

A future epidemiologic study could look at baseline pain scores after vaginal delivery and specific risk factors that increase pain postpartum. Bateman et al[23] looked primarily at risk factors after cesarean delivery and found that psychiatric comorbidities, substance use and abuse, and chronic pain conditions increased the risk of persistent narcotic use postpartum. Although we suspect the risk factors to be similar after vaginal delivery, there is limited literature available. We anticipated that patients with second, third, and fourth degree lacerations would have more vaginal pain than those without and would benefit from our intervention. Specifically in our study, there was no statistically significant difference in pain scores between patients with second degree lacerations and OASIS. If the characteristics of these patients with higher pain scores could be proven in vaginal deliveries, they may

TABLE 2
Postpartum vaginal pain scores at each time point, including several within participant calculated values

Vaginal pain scores	Plain BP (n=55)	Liposomal BP (n=53)	*P* value
Baseline pain	0 [0–0]	0 [0–0]	.22
PPD 1[b]	2 [0–3]	2 [0–3]	.82
PPD 3[a]	2 [1–3]	2 [0–3]	.63
Summed PPDs 1+3	4 [2–6]	4 [3–6]	.85
PPD 7[b]	1 [0–3]	1 [0–2]	.47
Total summed score	6 [3–8]	5 [3–8]	.83
Change from PPD 1–3	0 [−1 to −1]	0 [−1 to −2]	.60

Scores are expressed as median value [interquartile range].

BP, bupivacaine; *PPD*, postpartum day.

[a] Primary outcome PPD 3; [b] Secondary outcomes PPDs 1 and 7.

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

TABLE 3
Secondary outcome of the impact of vaginal pain on quality of life measures at each time point

Quality of life measures	Plain BP (n=55)	Liposomal BP (n=53)	*P* value
PPD 1			
Bowel movement (n=35/108)[a]	0 [0–2.5]	2 [0–3]	.45
Activity	1 [0–4]	2 [0–4]	.6
Sleep	0 [0–2]	0 [0–0]	.24
Mood	0 [0–1]	0 [0–0]	.24
Stress	0 [0–1]	0 [0–0]	.52
PPD 3			
Bowel movement (n=92/108)[a]	0 [0–2.25]	0 [0–2]	.49
Activity	1 [0–3]	2 [0–3]	.38
Sleep	0 [0–1]	0 [0–0]	.41
Mood	0 [0–1]	0 [0–1]	.77
Stress	0 [0–1]	0 [0–2]	.29
PPD 7			
Bowel movement (n=92/108)[a]	1 [0–2]	0 [0–2]	.3
Activity	0 [0–2]	0 [0–2]	.97
Sleep	0 [0–0]	0 [0–0]	.96
Mood	0 [0–0.5]	0 [0–0]	.92
Stress	0 [0–0.5]	0 [0–1]	.82

Scores are expressed as median value [interquartile range].

BP, bupivacaine; *PPD*, postpartum day.

[a] Bowel movement n's vary by the number of patients who reported that outcome.

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

TABLE 4
Vaginal pain scores for second degree laceration vs OASIS (third and fourth)

Vaginal pain scores	Second degree	OASIS	*P* value
All patients (N=108)	2 [0–3]	3 [1–4]	.28

Scores are expressed as median value [interquartile range].

OASIS, obstetric anal sphincter injuries.

Dengler et al. Liposomal bupivacaine for pain after obstetrical laceration. AJOG MFM 2020.

benefit the most from additional nonopioid pain management.

An additional modality with minimal literature is neuraxial analgesia at time of vaginal delivery. Neuraxial analgesia injects morphine, or an opioid equivalent, into the intrathecal space, commonly given at time of cesarean delivery because a spinal block is performed. A literature search did not produce any studies pertaining to postvaginal delivery pain control with neuraxial morphine. When expanding the search to include combined epidural-spinal blockade, no studies were found. A potential research study would be a randomized controlled trial looking at pain scores after neuraxial blockage.

Strengths and limitations

One of the strengths of this study was that it is a randomized controlled trial with only a 10% dropout rate, while a 20% dropout was anticipated. Patients were blinded to randomization. Using block randomization and SNOSEs and performing randomization only after the vaginal delivery and laceration repair led to a low selection bias. A large number of skilled providers performed the deliveries, laceration repairs, and injections, making this more generalizable to the population. By training the researchers via simulation, creating a reference video, and posting injection pictures in the main work area in labor and delivery, we aimed to improve the reproducibility and validity of our study.

This study also had limitations. This study was not double blinded because our investigational pharmacy is only open during routine business hours and would have limited involvement with patients who delivered at night. Overall, low pain made it difficult to detect a difference in pain scores between groups. Patients who were dependent on narcotics were excluded from this study owing to a low number in our population; however, it could be argued that these patients would benefit the most from this type of intervention and should be considered in future trials. A true placebo, such as normal saline, was not used. Without a placebo, it is unknown if both groups benefited from their injections. However, given the short duration of action of plain bupivacaine and the assessment of pain scores at PPDs 1, 3, and 7, it is likely that this group acted as its own control.

Conclusion

Postpartum pain control is of paramount importance. Any methodology that decreases opioid analgesia usage and improves pain and quality of life scores is clinically imperative and should continue to be researched. ■

References

1. The Joint Commission. Pain management. Available at: http://www.jointcommission.org/pain_management/. Accessed February 1, 2014.

2. Peahl AF, Dalton VK, Montgomery JR, Lai YL, Hu HM, Waljee JF. Rates of new persistent opioid use after vaginal or cesarean birth among US women. JAMA Netw Open 2019;2:e197863.

3. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. J Pain Res 2012;5:107–16.

4. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee 2012;19:530–6.

5. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. Curr Med Res Opin 2012;28:1609–15.

6. Marcet JE, Nfonsam VN, Larach S. An extended pain relief trial utilizing the infiltration of a long-acting multivesicular liposome formulation of bupivacaine, EXPAREL (IMPROVE): a phase IV health economic trial in adult patients undergoing ileostomy reversal. J Pain Res 2013;6:549–55.

7. Vogel JD. Liposome bupivacaine (EXPAREL®) for extended pain relief in patients undergoing ileostomy reversal at a single institution with a fast-track discharge protocol: an IMPROVE phase IV health economics trial. J Pain Res 2013;6:605–10.

8. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig 2013;33:109–15.

9. Jones CL, Gruber DD, Fischer JR, Leonard K, Hernandez SL. Liposomal bupivacaine efficacy for postoperative pain following posterior vaginal surgery: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 2018;219:500.e1–8.

10. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2011;54:1552–9.

11. Baker BW, Villadiego LG, Lake YN, et al. Transversus abdominis plane block with liposomal bupivacaine for pain control after cesarean delivery: a retrospective chart review. J Pain Res 2018;11:3109–16.

12. Parikh P, Sunesara I, Singh Multani S, Patterson B, Lutz E, Martin JN Jr. Intra-incisional liposomal bupivacaine and its impact on postcesarean analgesia: a retrospective study. J Matern Fetal Neonatal Med 2019;32:966–70.

13. Prabhu M, Clapp MA, McQuaid-Hanson E, et al. Liposomal bupivacaine block at the time of cesarean delivery to decrease postoperative pain: a randomized controlled trial. Obstet Gynecol 2018;132:70–8.

14. Bravin LN, Ernest EP, Dietz MJ, Frye BM. Liposomal bupivacaine offers no benefit over ropivacaine for multimodal periarticular injection in total knee arthroplasty. Orthopedics 2020;43:91–6.

15. Dale EL, Kluemper CT, Cowart SJ, et al. Bupivacaine extended-release liposomal injection versus bupivacaine HCl for early postoperative pain control following wrist operations: a prospective, randomized control trial. J Hand Surg Am 2019 [Epub ahead of print].

16. Schneider J, Broome B, Keeley D. Narcotic-free perioperative total knee arthroplasty: does the periarticular injection medication make a

difference? J Knee Surg 2019 [Epub ahead of print].
17. Ecker J, Abuhamad A, Hill W, et al. Substance use disorders in pregnancy: clinic, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society of Maternal–Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine. Am J Obstet Gynecol 2019;221:B5–28.
18. Polomano RC, Galloway KT, Kent ML, et al. Psychometric testing of the defense and veterans pain rating scale (DVPRS): a new pain scale for military population. Pain Med 2016;17:1505–19.
19. Komatsu R, Carvalho B, Flood PD. Recovery after nulliparous birth: a detailed analysis of pain analgesia and recovery of function. Anesthesiology 2017;127:684–94.
20. As-Sanie S, Till SR, Mowers EL, et al. Opioid prescribing patterns, patient use, and postoperative pain after hysterectomy for benign indications. Obstet Gynecol 2017;130:1261–8.
21. Griffith KC, Clark NV, Zuckerman AL, Ferzandi TR, Wright KN. Opioid prescription and patient use after gynecologic procedures: a survey of patients and providers. J Minim Invasive Gynecol 2018;25:684–8.
22. Wong M, Vogell A, Wright K, Isaacson K, Loring M, Morris S. Opioid use after laparoscopic hysterectomy: prescriptions, patient use, and a predictive calculator. Am J Obstet Gynecol 2019;220:259.e1–11.
23. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid naïve women. Am J Obstet Gynecol 2016;215:353.e1–18.

Author and article information

From the Departments of Obstetrics and Gynecology (Drs Dengler, Simpson, Strauchon, Shaddeau, and Gruber) and Research Programs (Dr Brooks), Walter Reed National Military Medical Center, Bethesda, Maryland; Department of Obstetrics and Gynecology, Naval Medical Center Portsmouth, Portsmouth, Virginia (Dr Strauchon); and Department of Obstetrics and Gynecology, Johns Hopkins University School of Medicine, Baltimore, Maryland (Dr Shaddeau).

Received March 10, 2020; accepted March 14, 2020.
The authors report no conflict of interest.
C.J.S. and D.D.G. obtained grant funding from Pacira Pharmaceuticals. The research was funded, in part, by a grant (Pacira IIT 2016-040) from Pacira Pharmaceuticals Inc, Parsippany, NJ. Pacira Pharmaceuticals Inc supplied the liposomal bupivacaine (Exparel, Pacira Pharmaceuticals Inc, Parsippany, NJ) for the study arm. They had no involvement or input in the study design, implementation of the study protocol, data collection, statistical analysis, or manuscript creation.
The opinions expressed in this manuscript are those of the authors and do not represent the Department of Health and Human Services or the Department of Defense.
This research was presented regionally as an oral presentation at the Annual ACOG Armed Forces District Meeting in San Diego, CA, Sept. 7—11, 2019, and won the Host Award for best clinical research. It was presented internationally as an oral scientific salon presentation at AUGS/IUGA Joint Scientific Meeting 2019 in Nashville, TN, Sept. 24—28, 2019.

Corresponding author: Katherine L. Dengler, MD, FACOG. katidengler13@gmail.com