Effects of intraoperative liposomal bupivacaine on pain control and opioid use after pediatric Chiari I malformation surgery: an initial experience

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OBJECTIVE Pediatric Chiari I malformation decompression is a common neurosurgical procedure. Liposomal bupivacaine (LB) is a novel formulation that can have an impact on postoperative recovery for particular procedures, but its potential role in pediatric neurosurgery is largely unexplored. The authors sought to describe and assess their initial experience with LB in pediatric Chiari I malformation decompression to better define its potential role as an analgesic agent in a procedure for which the postoperative course is often remarkably painful.

METHODS A retrospective review of all pediatric Chiari procedures performed at the authors' institution between 2018 and 2020 was conducted. Patients were divided into those who were treated with a single intraoperative dose of LB (LB group) and those who were not (control group). Comparisons of total opioid use and pain control were made using chi-square and Wilcoxon rank-sum tests.

RESULTS A total of 18 patients were identified, 9 (50%) in the LB group and 9 (50%) in the control group. Overall, there were 13 (72%) female and 5 (28%) male patients with a mean age of 15.9 years. No surgical complications were observed over a mean length of stay of 2.7 days. Within the first 24 hours after surgery, the LB group had significantly lower total opioid use than the control group (17.5 vs 47.9 morphine milligram equivalents, respectively; $p = 0.03$) as well as lower mean pain scores reported by patients using a 10-point visual analog scale (3.6 vs 5.5 for the LB vs control groups, $p = 0.04$). However, from the first 24 postoperative hours to discharge, total opioid use ($p = 0.51$) and mean pain scores ($p = 0.09$) were statistically comparable between the two groups. There were 2/9 (22%) LB patients versus 0/9 (0%) control patients who did not require opioid analgesia at any point during hospitalization.

CONCLUSIONS The use of a single intraoperative dose of LB in pediatric Chiari I malformation surgery appears to be safe and has the potential to reduce pain scores and opioid use when administered during the first 24 postoperative hours. From that time period to discharge, however, there may be no significant difference in total opioid use or pain scores.

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KEYWORDS liposomal bupivacaine; Chiari; malformation; pain; opioid; pediatric

CHIARI I malformation is a common pediatric neurosurgical presentation, with a natural incidence as high as 1% in children.^{1,2} Symptomatic treatment is surgical decompression,³ but despite the known risk of persistent opioid use after surgery in the pediatric patient population,⁴ to date there has been only limited investigation of ways to optimize postoperative opioid and pain outcomes following Chiari procedures in pediatric patients. Enhancing recovery after Chiari decompression is particularly important because the postoperative course is remarkably painful and at times administration of oral opioids is required at scheduled times and also for breakthrough pain rescue.⁵

Bupivacaine is a long-acting sodium channel blocker that has been used for many decades by surgeons to target pain-initiating nociceptor neurons and provide postoperative pain relief at the surgical site.⁶ Liposomal bupivacaine (LB) has emerged in recent years as an intraoperative formulation that can be injected into the surgical site at the end of surgery to further enhance postoperative pain control.^{7–9} The novelty of LB lies in its multivesicular liposomal system, which results in a slower release of bupivacaine compared to the more standard liquid formulation and makes LB an attractive alternative for consideration to enhance the patient's postoperative course.¹⁰ LB is an FDA-approved drug,¹¹ and although its safety in adults fol-

ABBREVIATIONS LB = liposomal bupivacaine; MME = morphine milligram equivalents; VAS = visual analog scale.

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lowing spine surgery has been demonstrated in multiple reported studies,^{12–14} the safety and efficacy of LB in Chiari I decompression surgery and pediatric patients have not been explored.

In this study, we sought to describe our initial experience with using a single intraoperative dose of LB in the setting of Chiari I malformation decompression to elucidate if and how this formulation may affect the postoperative course in terms of opioid use and pain control in pediatric patients.

Methods

Surgical Cohort

An institutional database was retrospectively interrogated for all Chiari I malformation procedures between 2018 and 2020 performed at the department of neurosurgery at our institution. During this time, one surgeon (E.S.A.) utilized LB for Chiari procedures, and these outcomes were compared to the outcomes of Chiari procedures without LB use, which were performed in the same neurosurgical department by a different surgeon (D.J.D.). All surgical patients were managed by the same surgical anesthesia and in-hospital care teams, as well as the same postoperative pain control protocol (detailed below). The Chiari procedures included in this study were those that were primary procedures, and revision surgeries were excluded. Surgical posterior decompression was performed by both surgeons with standard means of muscle dissection and suboccipital bone and C1 lamina resection, which could be supplemented with duraplasty if deemed appropriate. The addition of duraplasty to decompression, or the presence of syringomyelia, did not affect patient inclusion in this study. The present study was conducted with the approval of the Mayo Clinic institutional review board.

LB Injection

At our institution, we are approved to use LB off label in pediatric surgery if the following criteria set by our institution's formulary committee are met: 1) patient age > 10 years, 2) patient weight > 40 kg, and 3) the contents of the intraoperative LB injection are not administered in conjunction with any other local anesthetic that includes soluble bupivacaine. When used in the Chiari procedures, the intraoperative injection itself was 40 mL in total volume (20 mL of 13.3 mg/mL LB mixed with 20 mL of saline) and administered into the muscle after a duraplasty and prior to closure of the muscle, fascia, and skin (Fig. 1). A watertight closure following duraplasty was confirmed by close inspection with an induced Valsalva maneuver prior to injection.

Approach to Pain Control

Units for opioid use were morphine milligram equivalents (MME). Pain control after surgery was pursued when necessary to treat breakthrough pain via a combination of 1) opioid analgesia: oxycodone (1.5 MME) by mouth and hydromorphone (4 MME) by mouth and intravenously, and 2) nonopioid analgesia: acetaminophen by mouth and ketorolac intravenously before ibuprofen by mouth. It is standard procedure at our institution to first rely on oxycodone

FIG. 1. Intraoperative administration of LB into the muscle at the end of the Chiari I malformation surgery prior to fascial closure. Figure is available in color online only.

done for opioid analgesia and then utilize hydromorphone in the cases for which oxycodone is contraindicated or pain remains refractory.

Outcomes

Our primary outcome of interest was total opioid use within the first 24 hours after surgery, and then for the remainder of hospitalization. Our secondary outcomes of interest included patient-reported pain as well as nonopioid use at all time points. Pain was patient reported and graded on a visual analog scale (VAS) of 0–10, with 0 being no pain and 10 being the worst pain imaginable. Scores were recorded every hour within the first 12 postoperative hours, and then every 1–4 hours during the remainder of the postoperative stay.

Statistical Analysis

When appropriate, quantitative outcomes were compared between the LB and control (non-LB) groups. Analyses were conducted using chi-square exact and Wilcoxon rank-sum tests for categorical and continuous data, respectively. All analyses were conducted using STATA 14.1 (StataCorp); tests were two-sided, and statistical significance was defined using the alpha threshold of 0.05.

Results

Surgical Cohort

A total of 18 patients were included in this study, with 9 in the LB group and 9 in the control group (Table 1). Overall, there were 13 (72%) female and 5 (28%) male patients with a mean age of 15.9 years (range 12–18 years). The most common symptom at presentation was headache, which occurred in 13 (72%) patients. Syringomyelia was noted in 7 (39%) patients. All patients underwent successful surgical decompression and 15 (83%) had duraplasty performed. There were no postoperative seizures or other complications reported in the LB cohort. The mean length of stay was 2.7 days, with mean values of 2.8 and 2.6 days in the LB and control groups, respectively. These param-

TABLE 1. Characteristics of the surgical cohort with (LB group) and without (control group) LB administration

Parameter	Overall (n = 18)	LB group (n = 9)	Control group (n = 9)	p Value
Age, yrs	15.9 (12–18)	15.4 (12–18)	16.4 (12–18)	0.57
Sex				0.60
Male	5 (28%)	2 (22%)	3 (33%)	
Female	13 (72%)	7 (78%)	6 (67%)	
Presenting symptom				0.54
Headache	13 (72%)	7 (78%)	6 (67%)	
Incidental	2 (11%)	1 (11%)	1 (11%)	
Central sleep apnea	1 (6%)	0	1 (11%)	
Dysphagia	1 (6%)	0	1 (11%)	
Paresthesia	1 (6%)	1 (11%)	1 (11%)	
Syringomyelia present	7 (39%)	3 (33%)	4 (44%)	0.63
Duraplasty performed	15 (83%)	9 (100%)	6 (67%)	0.08
Postoperative complications	0	0	0	0.99
Length of stay, days	2.7 (2–4)	2.8 (2–4)	2.6 (2–3)	0.69

Data are presented as number (%) of patients or mean (range) unless stated otherwise.

eters were statistically comparable between the LB and control groups (Table 1).

Opioid Use

Within the first 24 hours postoperatively (Table 2), in the LB versus the control groups the mean doses of oxycodone were 17.5 versus 30.8 MME, respectively ($p = 0.21$); the mean doses of hydromorphone were 0 versus 17.7 MME, respectively ($p = 0.01$); and the mean total opioid doses were 17.5 versus 47.9 MME, respectively ($p = 0.03$) (Fig. 2A).

After the first 24 postoperative hours until discharge (Table 3), the mean oxycodone doses in the LB versus control groups were 31.7 versus 45.0 MME, respectively ($p = 0.22$); the mean hydromorphone doses were 4.4 versus 29.7 MME, respectively ($p = 0.54$); and the mean total opioid doses were 49.4 versus 61.4 MME, respectively ($p = 0.96$) (Fig. 2B). Of note, 2/9 (22%) patients in the LB

group did not require any opioids during hospitalization, whereas none of the patients in the control group did not require any opioids during hospitalization.

Pain Scores

Within the first 24 hours (Table 2), the mean VAS pain scores after surgery in the LB and control groups were 3.6 (range 1.0–6.1) and 5.5 (range 3.2–8.0), respectively, which were significantly different ($p = 0.04$) (Fig. 3A). During this period, 6/9 (67%) patients in the LB group reported at least one pain score of ≤ 1 compared to 3/9 (33%) patients in the control group ($p = 0.16$).

After the first 24 postoperative hours until discharge (Table 3), the mean pain scores in the LB and control groups were 3.0 (range 0–6.1) and 4.6 (range 1.6–6.2), respectively ($p = 0.09$) (Fig. 3B). During this period, 6/9 (67%) of the LB group reported at least one pain score of ≤ 1 compared to 2/9 (22%) in the control group ($p = 0.06$).

TABLE 2. Pain outcomes during the first 24 hours after surgery in patients treated with (LB group) and without (control group) LB administration

Parameter	Overall (n = 18)	LB Group (n = 9)	Control Group (n = 9)	p Value
VAS pain score	4.5 (1.0–8.0)	3.6 (1.0–6.1)	5.5 (3.2–8.0)	0.04
VAS score ≤ 1	9 (50%)	6 (67%)	3 (33%)	0.16
Opioid use, MME				
Oxycodone	24.2 (0–75)	17.5 (0–46)	30.8 (0–75)	0.21
Hydromorphone	8.5 (0–40)	0 (0–0)	17.7 (0–40)	0.01
Total	32.7 (0–113)	17.5 (0–56)	47.9 (18–113)	0.03
Nonopioid use				
Acetaminophen, g	2.7 (0.7–5.0)	2.4 (0.7–3.6)	3.0 (1.3–5.0)	0.33
Ketorolac, mg	39.2 (0–76)	40.0 (0–60)	38.4 (0–76)	0.64
Ibuprofen, g	0.1 (0–1.8)	0.2 (0–1.8)	0 (0–0)	0.31

Data are presented as number (%) of patients or mean (range) unless stated otherwise.

FIG. 2. Total opioid use (MME) for the LB and control groups during the first 24 hours after surgery (**A**, * $p = 0.03$) and the remainder of the hospitalization (**B**). Data are presented as mean (middle bar) with range (whiskers). Figure is available in color online only.

Nonopioid Use

All patients received nonopioid pain medications as part of their postoperative management. Across all patients, within the first 24 hours (Table 2), the mean doses of acetaminophen, ketorolac, and ibuprofen were 2.7 g, 39.2 mg, and 0.4 g, respectively.

Across all patients after the first 24 postoperative hours until discharge (Table 3), the mean doses of acetaminophen, ketorolac, and ibuprofen were 4.8 g, 40.0 mg, and 0.9 g, respectively. All doses were statistically comparable between the LB and control groups.

Discussion

With this study, we sought to describe our initial observations of postoperative recovery with LB injection into the muscle layer after Chiari I malformation surgery. Our initial findings suggest a significant reduction in total opi-

oid use and pain scores within the first 24 hours of surgery in the LB group compared to the control group. From then to discharge, total opioid use and pain scores were statistically comparable. Future studies are required to explore the clinical and pharmacological merit of intraoperative LB injections and determine if the benefits to the patient are more pronounced immediately after surgery but diminish by the time of discharge.¹⁵

To date, although the use of LB in pediatric neurosurgery and broader surgery has not been widely reported, the limited published results appear to support our findings. In a study by Crowley et al.¹⁶ investigating LB in pediatric alveolar cleft surgery, the authors reported that in the first 24 postoperative hours total opioid use was significantly less in patients who had been treated with an intraoperative LB injection than in their control cohort, which is what we observed in our study in the first 24 postoperative hours. Cloyd et al.,¹⁷ however, did not observe any differ-

TABLE 3. Pain outcomes after the first 24 hours from surgery to discharge in patients treated with (LB group) and without (control group) LB administration

Parameter	Overall (n = 18)	LB Group (n = 9)	Control Group (n = 9)	p Value
VAS pain score	3.8 (0–6.2)	3.0 (0–6.1)	4.6 (1.6–6.2)	0.09
VAS score ≤1	8 (44%)	6 (67%)	2 (22%)	0.06
Opioid use, MME				
Oxycodone	38.3 (0–90.0)	31.7 (0–90.0)	45.0 (0–90.0)	0.42
Hydromorphone	17.1 (0–243.0)	4.4 (0–40.0)	29.7 (0–243.0)	0.54
Total	55.4 (0–243.2)	49.4 (0–90.0)	61.4 (0–243.2)	0.96
Nonopioid use				
Acetaminophen, g	4.8 (1.5–8.5)	5.1 (2.5–8.5)	4.6 (1.5–8.0)	0.69
Ketorolac, mg	40.0 (0–120.0)	48.3 (0–105.0)	31.7 (0–120.0)	0.37
Ibuprofen, g	0.9 (0–4.8)	1.4 (0–4.8)	0.4 (0–1.8)	0.10

Data are presented as number (%) of patients or mean (range) unless stated otherwise.

FIG. 3. Mean patient-reported pain scores for the LB and control groups during the first 24 hours after surgery (A, $p = 0.04$) and the remainder of the hospitalization (B). Data are presented as mean (middle bar) with range (whiskers). Figure is available in color online only.

ences in total opioid use by discharge after pediatric spine surgery in patients who were administered single-dose LB intraoperatively and those who were not. Similarly, Day et al.¹⁸ reported no significant differences in pain scores following pediatric pharyngoplasty 3 days after surgery in patients who did compared with those who did not receive LB. These pediatric findings are comparable to our results of no difference in total opioid use after the first 24 hours postoperatively until discharge in patients administered LB compared with those who were not, with our average time to discharge being 2.7 days.

More data regarding the use of LB have been published in the adult than in the pediatric neurosurgical and spine literature, and we note that many of the reported observations are congruent with our results. In terms of opioid use, Tomov et al.¹⁴ noted a significant reduction within the immediate postoperative period in their spinal fusion cohort who were treated with LB, which corresponds to our findings within the first 24 postoperative hours. On the other hand, for multiple spinal fusion studies of LB analgesia,^{12,14,19} the authors reported no difference in total opioid use by the time of discharge, which parallels our findings after the first 24 postoperative hours to discharge. In terms of pain scores, Brusko et al.¹³ showed in their spinal fusion cohort that the only significant difference between their LB and control cohorts was on the first postoperative day, with the LB cohort reporting lower scores, but this difference was no longer observed up until discharge, a trend that was also reported by Puffer et al.,¹⁹ and both studies ultimately mirror the experiences we report here for the use of LB for pain relief in pediatric patients undergoing Chiari decompression.

A primary concern surrounding the use of LB in a pediatric cohort is the risk of associated adverse events, particularly in cases in which the central nervous system is exposed to the drug. In large adult series,^{9,12} the most common adverse events associated with LB in general

are nausea, emesis, constipation, and hypotension events. More specific to neurosurgery and Chiari surgery, central nervous system toxicity has been reported. Although intrathecal injection was shown to be safe in an animal study,²⁰ in a few cases, local and intravascular administration of LB has been associated with postoperative seizures in animal models²¹ and human patients.²² We did not encounter any seizure event in our limited cohort, and note that prior to LB injection, we confirmed the presence of a solid dural barrier between the injection site and the central nervous system, which may be an additional step necessary to avoid unwanted nervous system exposure to LB. Admittedly, there remains a risk of LB migration into the CSF, because in rare instances a watertight duraplasty at closure does not guarantee permanent closure. Although we suspect this risk to be very low, verification of closure by close visual inspection utilizing induced Valsalva maneuvers is highly supported. Despite these concerns, in addition to our cases, a large series²³ of over 300 pediatric spine, orthopedic, and gastrointestinal surgery patients treated with intraoperative LB did not have any reported cases of local anesthetic systemic toxicity syndrome, further supporting the safety of LB in pediatric surgical patients.

Despite the significant reduction of opioid use following LB administration that we observed in our patients during the immediate 24 hours after surgery, the comparable total opioid use for the remainder of hospitalization to discharge suggests that the pain benefits of a single LB injection may not last the entire length of stay. This transient benefit in our series could reflect a similar finding that sensory blockade is only expected to last 12–24 hours after epidural LB injection.¹⁰ LB can dissipate away from the tissue site of injection via the circulation as early as 12 hours after surgery, peaking in the blood supply at approximately 72 hours.²⁴ We posit that the exact pharmacokinetics of LB may depend on intrinsic surgical and

physiological factors of the patient, which contribute to the interpatient variation we observed in our outcomes.

Furthermore, once the effects of LB have waned or dissipated, it is possible that natural triggers of headache may reemerge, which will require medication during patient hospitalization and increase breakthrough medication demands to amounts comparable to those seen without LB during the short number of days to discharge. It is also possible, however, that the biological origins of pain subside naturally within the first 24 hours after closure, leading to no significant difference in pain scores between cohorts after 24 hours. Although we did observe trends, which were not statistically significant, of lower reported pain scores in the later portion of the hospital stay in our small LB cohort, it is possible that in the future, a study with a larger cohort size may tease out statistical differences at higher power. It is worth noting that there were individual patients in the LB cohort who required no opioid use whatsoever, which suggests that continued LB pain relief beyond the first 24 hours after surgery is possible, but its incidence is lower than the immediate pain relief from LB.

Whether or not these effects on opioid use and pain control we report are dose dependent in the setting of pediatric Chiari decompression remains to be seen. We utilized the recommended FDA-approved dose volume and formulation of LB for adults in our reported cases,¹¹ and the possibility that increasing LB concentration provides greater pain control cannot be ruled out at this point. Yet, the pharmacology of LB in adults would suggest that the outcomes may not change drastically, as plasma concentrations over time are quantitatively similar at both double and half the FDA-approved dose.²⁴ Whether or not total dose volume can impact subsequent dissipation away from the surgical site is also a consideration that may support future investigation of dose volumes less than 40 mL in pediatric patients. Last, given that the administered dose involves saline, it should be recognized that injection of normal saline into muscle is known to bring about pain relief for particular trigger points.²⁵ It is conceivable then that some of the significant pain relief observed in the LB cohort may derive from the mechanical process of injecting 40 mL of fluid (20 mL of LB and 20 mL of saline) into the muscle. Future comparative studies that include a placebo arm of 40 mL of saline only would allow better ascertainment of the pain relief attributable to the LB component of the injected dose.

Given the initial nature of our experience, there are limitations to this study. The size of our cohort was small, and therefore statistical power was limited, which means that more subtle differences in outcomes may not have been revealed. It is therefore promising to note that even at such a small sample size, we were able to identify statistical differences in total opioid use and pain control within the first 24 postoperative hours that are congruent with the wider literature. Based on our preliminary results, we are now utilizing single-dose LB in our practice where possible for these procedures and hope to accumulate larger cohorts in the future to overcome concerns that possible outliers may be biasing comparison results.

Another limitation is that this study was retrospective, and therefore, controlling of the cohorts for various man-

agement parameters could not be performed. In terms of the surgery, intraoperative anesthesia and duraplasty use and type, as well as incision length, varied between cohorts. We do note, however, that no other local anesthetic was given at the completion of decompression, irrespective of LB use, and that no laminectomies were performed outside the suboccipital bone and C1 lamina resections. Other patient-dependent performance outcomes, such as postoperative activity levels and physical therapy use, could not be clarified, and neither could psychological parameters, such as preexisting anxiety and depression. The lack of clarification of these parameters limits the validity of the pain outcomes and conclusions we report. Nonetheless, we note that although the surgeons for each group were different, all reported patients shared the same care personnel and pain management protocols regarding as-needed medications during hospitalization, and statistically there were no obvious inconsistencies in basic demographic features of the patients. Future studies that utilize a standardized protocol for nonopioid pain control will also improve opioid use inferences.

Other observed differences that we have anecdotally seen in practice, such as seemingly improved activity and rest in those patients who had LB compared with those who had only short-acting bupivacaine HCL, also cannot be inferred in a retrospective study like this. Future comparisons between LB and its more standard counterpart of bupivacaine with epinephrine with known shorter efficacy may prove useful for future cost-benefit analyses should LB be seriously considered for standard practice. We acknowledge the need for these analyses given that the cost of LB is much higher than that of bupivacaine with epinephrine.

Finally, we recognize that pain outcomes are difficult to quantify consistently between patients in retrospect, particularly given that a number of patient characteristics, such as age, sex, and cultural factors, can influence pain perception.²⁶ There are limitations in utilizing a pain-ranking VAS scale of 0–10 as the sole metric of pain outcome, as pediatric patients in particular have a wide range of pain tolerances and perceptions.²⁷ We anticipate that future prospective studies of larger cohorts, preferably blind to LB administration, using standardized pain management and assessment methods will provide the most robust data, as well as establish if differences may be detectable at higher statistical power.

Conclusions

Our initial experience demonstrates that a single intraoperative dose of LB administered at the end of pediatric Chiari I malformation decompression surgery is safe and has the potential to result in reduced pain scores and opioid use in the first 24 postoperative hours, a period that is typically marked by substantial pain in these patients. After this period, there appears to be no significant effect on total opioid use or pain scores associated with LB use for the remainder of the patient's hospitalization. Although the trends we report here require validation, our initial experience also highlights that a completely nonopioid postoperative analgesia course may be possible in some patients who have received LB during Chiari decompression surgery.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Ahn, Lu, Haile. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ahn. Statistical analysis: Lu. Study supervision: Ahn.

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