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Retrospective cohort-based comparison of intraoperative liposomal bupivacaine versus bupivacaine for donor site iliac crest analgesia during alveolar bone grafting

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Summary *Introduction:* Bone grafting of alveolar clefts is routinely performed with cancellous bone harvested from the iliac crest. Graft site morbidity is frequently seen, with early postoperative pain being one of the most common complaints. Liposomal bupivacaine (LB) has been demonstrated to provide improvement in postoperative pain for patients undergoing bunionectomy or hemorrhoidectomy, which may translate to patients requiring iliac crest bone graft harvest.
Methods: Thirty-eight patients undergoing iliac crest bone harvest were included in the study. Twenty-one patients underwent open iliac crest bone graft harvest with administration of 0.25% bupivacaine at the hip donor site, while 17 patients received local infiltration of 1.3% liposomal bupivacaine. Patient-reported pain scores, total narcotic use, length of stay, and postoperative steps were monitored.
Results: There were no significant differences in age, weight, distribution of clefts, or choice of donor hip between the two groups. There were no significant differences in length of

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hospitalization stay. However, differences were noted in average postoperative pain scores at five of six time points in the first 24 h, total oral morphine equivalents administered (4.7 ± 5.3 vs. 14.3 ± 12.0), and steps at postoperative days one to three ($p < 0.001$, for all three days) for patients receiving 1.3% LB versus 0.25% bupivacaine, respectively.

Conclusion: Reduced pain scores and increased postoperative activity highlight the potential of LB to improve postoperative pain management in children undergoing iliac crest bone harvest for alveolar bone grafting.

Introduction

Bone grafting of alveolar clefts is a routine procedure performed to restore function and contour to the maxilla. Cancellous bone utilized in the graft may be harvested from a multitude of locations including the iliac crest, proximal tibia, calvarium, and mandibular ramus.[1-3] A majority of centers prefer iliac crest donor sites because of the ease of procurement, large volumes of bone, and relatively low morbidity.[1-3] Although all sites provide adequate quantity and quality of bone, efforts are continually made to limit donor site morbidity and postoperative pain. Following iliac crest bone harvest, more than 90% of patients report pain at the donor site, with the incidence of long-term pain as high as 41%.[2,4,5] Studies also suggest pain duration and severity on postoperative day one to be significantly associated with the incidence of chronic pain.[6] As a result, there is substantial emphasis on the adequate treatment of pain in the immediate postoperative period. Dashow et al. first reported the efficacy of bupivacaine-soaked gel foam at the osteotomy site for patients receiving an iliac crest bone harvest for alveolar bone grafting.[7] Following the usage of bupivacaine-soaked gel foam, patients experienced less postoperative pain, reduced opioid consumption, and expedited early ambulation.[7] A subsequent study by Gamli et al. reported similar findings with reduced postoperative opioid requirements but no significant reduction in pain scores.[8]

Current postoperative analgesic regimens include acetaminophen, NSAIDs, steroids, and opioid-based medications, among other modalities.[6,9,10] A multimodal approach involving a combination of medications provides analgesia affecting both central and peripheral nociceptive pathways.[6,9,10] Guidelines for perioperative pain management place increased emphasis on local anesthetics and non-opioid analgesic strategies but still acknowledge the role of opioids in the treatment of severe pain.[6,9,10] However, because of the rising concern of opioid misuse, side effects, and risk of dependency, new practice guidelines and methods of analgesia are being explored.

Liposomal bupivacaine (LB), trademarked under the name Exparel® (Pacira Pharmaceuticals, Parsippany, New Jersey, USA), was approved by the FDA in 2011 for analgesic use through surgical site infiltration. Pharmacokinetic studies of bupivacaine have demonstrated analgesia through 72 h following administration.[11-14] LB incorporates bupivacaine into liposomal vesicles to reduce immediate absorption and prolong the analgesic effect, with some studies reporting efficacy as long as 96 h.[15] An increased duration of this local anesthetic through the postoperative period would theoretically reduce opioid analgesic requirements at a time point where its use is traditionally elevated.

Since its approval, results from clinical trials have expanded the FDA's indications of LB to incorporate bunionectomy and hemorrhoidectomy citing reduced postoperative pain, opioid requirements, and length of stay.[14,16-21] Additional randomized controlled trials have also demonstrated efficacy in colorectal surgery and vascular surgery.[14,19,20] Other reports show negligible or no benefit with the use of liposomal bupivacaine, such as in total shoulder arthroplasty and sternotomy.[11,22,23] It is unclear what factors account for the differences between studies, and to the best of our knowledge, there have been no reports of its use in children. Our aim is to assess the efficacy of single-dose intraoperatively administered LB as compared to that of bupivacaine with gel foam in children undergoing iliac crest bone graft harvesting for the repair of alveolar clefts.

Methods

A total of 40 patients were included in the study. Exclusion of patients greater than or equal to 18 years of age and patients unable to record activity tracking at postoperative day one resulted in 38 patients meeting the inclusion criteria. Patients undergoing alveolar bone grafting with an open iliac crest bone harvest at the Lucille Packard Children's Hospital were retrospectively included in the study under IRB approval (39,096) from December 2016 to March 2018. STROBE guidelines were followed for standardized reporting of cohort-based studies. Patients received either LB infiltration following completion of the bone harvest or a combination of bupivacaine infiltration prior to the incision along with bupivacaine with gel foam at the hip donor site during completion of the bone harvest. The two cohorts were created at different time points during a single surgeon's experience. Up to the introduction of LB as the standard of care for alveolar bone grafting patients, the patients received bupivacaine-soaked gel foam at the site of the osteotomy. Following this time period, LB was offered to patients and their families as an off-label alternative to bupivacaine. Protocol 39,096 was initially created to retrospectively review five patients electing to use LB and compare it to five patients receiving bupivacaine-soaked gel foam. Following an initial analysis, the protocol was subsequently amended at a later time to retrospectively include all patients receiving LB. Data gathered from the electronic medical record system included patient age, length of stay, postoperative pain scores, numbness or paresthesia, and total

Table 1 Patient demographics.

		1.3% LB $n=17$	0.25% Bupivacaine $n=21$	*P* value
Age (years)	Mean ± SD	11.7 ± 3.0	12.1 ± 3.5	0.669
Weight (kg)	Mean ± SD	39.9 ± 16.6	41.4 ± 17.5	0.790
BMI (kg/m^2)	Mean ± SD	18.9 ± 5.3	18.6 ± 3.7	0.821
Sex				0.847
Male	N	10	13	
Female	N	7	8	
Cleft Side				0.274
Right	N	5	11	
Left	N	10	7	
Bilateral	N	2	3	
Iliac crest donor site				0.337
Right	N	4	8	
Left	N	13	13	

narcotic use in total oral morphine equivalents (OME). Postoperative steps were prospectively measured using an activity tracker.

Iliac crest bone graft harvest

A 3 cm site along the inferior border of the crest was marked. The patients in the 0.25% bupivacaine group had the anesthetic agent administered subcutaneously prior to making an incision, whereas the patients in the 1.3% LB group did not receive 0.25% bupivacaine prior to the incision to prevent confounding bupivacaine usage in the LB group. An incision was then made, and electrocautery dissection was continued through to the iliac crest. The external oblique aponeurosis was then divided with care to prevent injury to the lateral femoral cutaneous, hypogastric, and ilioinguinal nerves. An osteotomy was performed to facilitate the harvest of the cancellous bone. Once adequate volumes of bone were obtained, either 0.25% bupivacaine in gel foam or 1.3% LB was administered at the osteotomy site for anesthesia. The external oblique aponeurosis, subcutaneous, and skin layers were then primarily closed.

Postoperative pain assessment and activity tracking

Postoperatively, subjective pain scores were assessed on a scale from zero to ten every four hours for a 24-h duration. Nonopioid analgesic regimens included 15 mg/kg of acetaminophen scheduled every 6 h. No additional nonsteroidal anti-inflammatory medications were prescribed. Opioid consumption was reported as an oral morphine equivalent, which is equivalent to 1 mg of morphine. 1.5 mg of oxycodone, 1 mg of hydrocodone, or 4 mg of hydromorphone are equivalent to 1 mg of morphine or 1 oral morphine equivalent.[24] Patients were also provided with an activity tracker to be worn on the ankle and secured through a removable strap. The tracker was used while hospitalized and after discharge. Steps were recorded on the device each postoperative day, and data were collected following removal. Inability to record steps at least on postoperative day one resulted in their exclusion from the study.

Statistical analysis

Statistical analysis was performed using SPSS (version 24.0, Chicago, IL). Chi-square test and Fisher's exact test were used to compare categorical data as listed in Table 1. After confirming that the data had a normal distribution, independent t-tests were used to compare continuous variables as listed in Table 2 and Figure 2. The Mann-Whitney U test was performed to compare nonparametric variables as shown in Figure 1. *P* values <0.05 were considered statistically significant.

Results

A total of 38 patients were included in the study, with 17 in the LB treatment group and 21 in the bupivacaine control group. All patients were children with a mean age (years) of 11.7 ± 3.0 standard deviation (SD) and 12.1 ± 3.5 (SD) for the LB and bupivacaine groups, respectively. As shown in Table 1, there were no significant differences in age, weight, BMI, distribution of clefts, or iliac crest donor sites between groups as measured by the chi-square test.

Operative time, complications, and length of stay were comparable between the LB and bupivacaine groups (Table 2). Mean dosages of 1.3% LB and 0.25% bupivacaine were 4.4 ± 1.6 ml (SD) and 9.3 ± 1.1 ml (SD), respectively. Mean operative times were 93.6 ± 18.0 (SD) minutes for the LB group and 97.2 ± 21.0 (SD) minutes for the bupivacaine group. Two patients in the LB group and one in the bupivacaine group experienced transient treatment-sided lateral thigh paresthesia, with all patients experiencing full recovery. The administration of LB significantly reduced opioid consumption in the immediate postoperative period as compared to that of bupivacaine. Average OME consumption was 4.7 ± 5.3 (SD) for the LB group versus 14.3 ± 12.0 (SD) for the bupivacaine group, with a mean difference of 9.6 (95% CI 3.3-16.0, $p=0.002$) (Table 2). When the weight of patients was factored into oral morphine equivalent

Table 2 Perioperative parameters.

		1.3% LB	0.25% Bupivacaine	Mean difference [95% CI]	*P* value
Operative time (minutes)	Mean ± SD	93.6 ± 18.0	97.2 ± 21.0	3.6 [−9.6, 16.8]	0.578
Oral morphine equivalents (mg)	Mean ± SD	4.7 ± 5.3	14.3 ± 12.0	9.6 [3.3, 16.0]	**0.002**
Oral morphine equivalents by patient weight (mg/kg)	Mean ± SD	0.11 ± 0.13	0.34 ± 0.22	0.23 [0.11, 0.35]	**<0.001**
Complications[a]	n/a	2	1	n/a	0.557
Length of stay (days)	Mean ± SD	1.1 ± 0.3	1.2 ± 0.4	0.1 [−0.2, 0.3]	0.553

[a] Two patients in the LB group and one patient in the bupivacaine group experienced transient treatment-sided lateral thigh paresthesia.

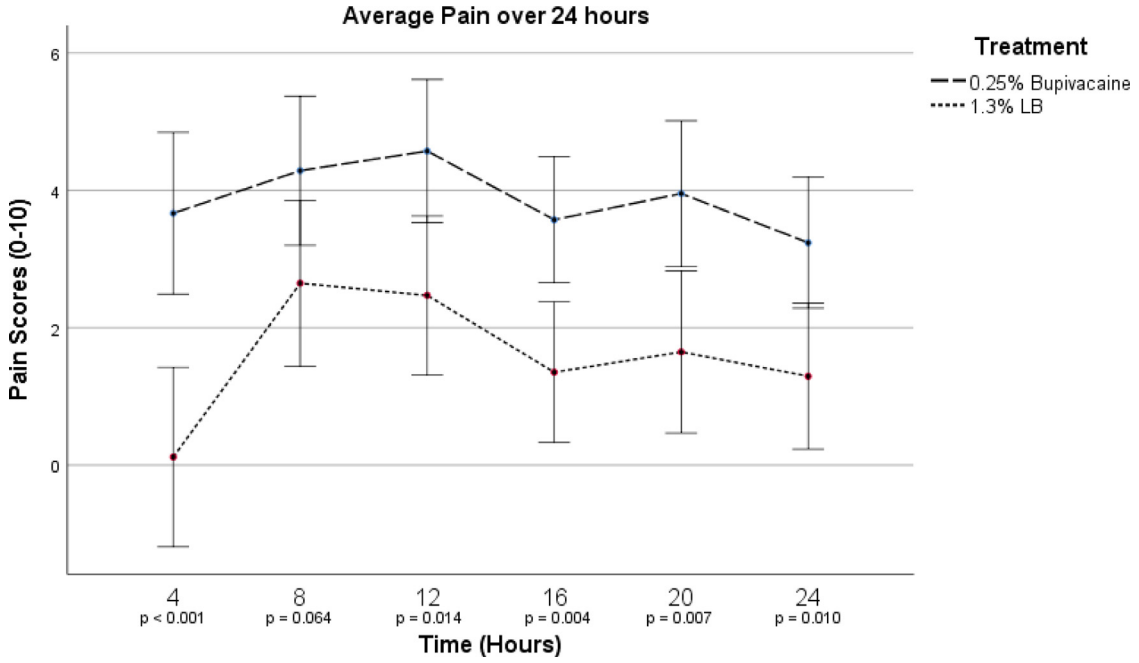

Figure 1 Average donor site pain scores for patients receiving 1.3% LB and 0.25% bupivacaine at 4-h time points during the first 24 h in the postoperative period. Mann–Whitney U tests at each time point demonstrated patient-reported pain scores to be significantly reduced in the LB group at the 4- ($p < 0.001$), 12- ($p = 0.014$), 16- ($p = 0.004$), 20- ($p = 0.007$), and 24-h ($p = 0.010$) time points.

requirements, the LB group maintained its reduction in opioid consumption with a mean difference of 0.23 (95% CI 0.11–0.35, $p < 0.001$) (Table 2). Operative time, opioid use, and length of stay were compared using the independent samples *t*-test, while complications were compared using the chi-square test.

The patients receiving LB had significantly reduced pain scores in the first 24 h of the postoperative period (Figure 1). Pain scores were compared at individual time points using a Mann–Whitney U test. Notably, patient-reported pain scores at four hours following surgery averaged 0.1 ± 0.5 (SD) in the group receiving LB as compared to those of 3.7 ± 3.5 (SD) in the group receiving bupivacaine ($p < 0.001$). Significant differences continued at the 12- ($p = 0.010$), 16- ($p = 0.002$), 20- ($p = 0.006$), and 24- ($p = 0.009$) hour time points, with a trend toward significance at the 8-h time point ($p = 0.064$).

Using steps recorded with an activity tracker as an objective surrogate and functional assessment of pain, the average number of steps recorded each day to postoperative day eight is illustrated in Figure 2. Steps were compared using the independent samples *t*-test at individual time points. At postoperative days one, two, three, and five, activity trackers of patients in the LB group recorded a significantly increased number of steps when compared with those of patients in the bupivacaine group ($p < 0.001$ for days one to three; $p = 0.032$ for day five). Steps recorded on day four approached significance ($p = 0.056$), while those recorded on day six did not ($p = 0.343$). Most patients continued to wear the activity tracker up to postoperative day six. Because of the battery life of the activity tracker, data recorded at postoperative days seven and eight were limited to four patients. As a result, statistical analysis was not performed at these time points.

Discussion

The rising concerns surrounding the prescription and usage of opioid medications have encouraged new approaches to pain management. Because of the increased consumption of narcotics in the postoperative period and resulting side

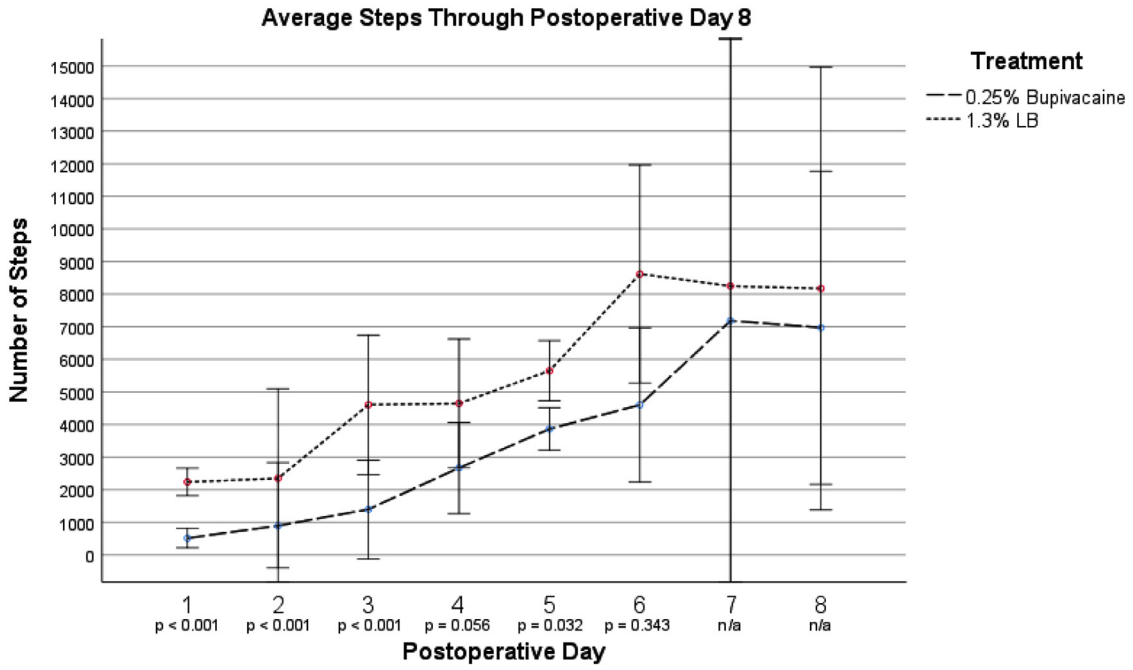

Figure 2 Average steps taken by patients receiving 1.3% LB and 0.25% bupivacaine during eight days in the postoperative period. Independent samples *t*-test at each time point demonstrated the recorded steps to be significantly increased at postoperative days 1 ($p < 0.001$), 2 ($p < 0.001$), 3 ($p < 0.001$), and 5 ($p = 0.032$) in patients receiving LB as compared to those receiving bupivacaine.

effects, there is additional focus on local anesthetics for pain control. Long-acting local analgesics such as liposomal bupivacaine, administered intraoperatively and extending beyond the immediate postoperative period, may theoretically reduce the need for narcotics and provide durable pain control.[14,25]

FDA indications for the usage of LB include infiltration at surgical sites to provide analgesia. Given these nonspecific recommendations, a multitude of clinical trials have explored its use following various surgical procedures.[14,17,18,20-22,25] Although some studies have questioned the efficacy of LB, literature supporting its use generally describes findings of a reduction in opiate use, pain scores, and improvement in patient satisfaction.[14] Results from clinical trials have expanded FDA indications for LB to include bunionectomy and hemorrhoidectomy.[17,18] Other randomized controlled trials evaluating LB in augmentation mammoplasty have shown reductions in narcotic usage but similar pain scores between groups.[26] The efficacy of bupivacaine in iliac crest bone harvesting has already been established.[8,27] Randomized controlled trials evaluating the use of bupivacaine during iliac crest bone harvest have shown reductions in pain scores at 5- and 12-week follow-up without an increase in complications.[27] Studies exploring the use of bupivacaine-soaked gel foam demonstrated efficacy in reducing postoperative pain, opioid consumption, and time to ambulation.[7,8] Gamli et al. showed patients treated with bupivacaine-soaked gel foam consumed approximately 7.5 mg of hydromorphone within 48 h postoperatively and an average weight of 87.2 kg, which translates to 0.022 mg/kg OME by weight. Mean pain scores for these patients were 3.98 ± 0.10 at either the 24-h or the 48-h timepoint. Dashow et al. also presented data that use of bupivacaine-soaked gel foam resulted in an oral morphine equivalent requirement by weight of 0.14 mg/kg. The maximum immediate postoperative pain scores reported was 4.3, while the average was 1.3. Within this context, the current study had oral morphine equivalent consumption by weight, which was 0.11 ± 0.13 mg/kg for the LB group and 0.34 ± 0.22 mg/kg for the bupivacaine group. Pain scores for the LB group were 3.7 ± 3.5 (SD) at the 4-h timepoint and 3.2 ± 2.3 (SD) at the 24-h timepoint, while those for the bupivacaine group were 0.1 ± 0.5 (SD) and 1.3 ± 1.9 (SD), respectively. Overall, pain scores and oral morphine equivalent consumption by weight were higher than those reported by Gamli et al. and Dashow et al.[7,8] Although differences between studies are relatively small, they may be due to the increased weight of adult patients driving the oral morphine equivalent by weight (mg/kg) value artificially low. Additionally, pain tolerance thresholds may be reduced in children as compared to those in adults, and as a result, children may be more prone to more hyperbolic reporting of pain scores, resulting in higher rates of opioid consumption.[28]

However, for patients undergoing alveolar bone grafting with iliac crest bone harvest, there is lack of data comparing outcomes of LB and bupivacaine. Our approach provided cumulative bupivacaine doses to be below 3 mg per kg, and the volume of LB administered was also in line with that stated in other reports adjusted for weight in our patient population.[18] However, there is also paucity of data elucidating comparative doses between LB and bupivacaine, and as such, it precluded the administration of standardized equivalent volume dosages between patients. Although some studies utilize volumetric comparisons for LB versus bupivacaine, this metric is still not an ideal estimate to adequately compare the two formulations. Equivalent volumes are not a perfect estimate of equivalency for local

anesthetics because the percentage composition of the solutions is not identical. In the same regard, maintaining the exact equivalency dose also provides little value in directing a comparison study between the medications. Because the liposomal formulation has a slower pharmacokinetic release profile than traditional bupivacaine, an exact equivalent dose may underdose the patient in the immediate postoperative period, prematurely yielding a negative result. It is the delivery of this medication that provides the most poignant effects we aim to study. As a result, we believe there is no standardized fashion to compare the two medications. However, the average dosage for patients receiving bupivacaine and bupivacaine-soaked gel foam was approximately 2.33 mg, while the LB group received an average of 5.66 mg.

Results from the current study's LB group demonstrated a reduction in average pain scores at most time points within the first 24 h as compared to those of the 0.25% bupivacaine group. It is interesting to note that increased pain was observed in the bupivacaine group despite the administration of preemptive local anesthetic, which was not employed in the LB group. The patients also consumed fewer OME in the LB group than in the bupivacaine group with a mean difference of 9.6 OME (95% CI 3.3–16.0, $p = 0.002$), suggesting more durable and effective pain control. Additionally, the activity tracker recorded increased ambulation, which may be an indirect measure of improved pain control. With reductions in postoperative pain and increased ambulation, there is the potential for a decreased incidence of chronic pain and expedited return of function. Overall, these results advocate the use of LB in iliac crest bone harvest at the hip donor site.

Originating in Denmark, Enhanced Recovery After Surgery (ERAS) protocols provide comprehensive guidelines for the management of patients in the perioperative period.[29] Standardization of perioperative care is the goal of ERAS programs, with results showing reductions in length of stay, complication rates, and improved patient satisfaction. Unfortunately, there are limited quality data for implementation in the pediatric population, and as a result, most programs are extrapolated from adults. Because local anesthesia is a crucial part of pain control and is included in ERAS programs, our data support the use of LB in the iliac crest donor site for alveolar cleft bone grafting. Amin et al. showed minimal requirements for opioid administration in a series of 100 patients with 86% not requiring any opioids but did not provide any pain score data.[30] In the current study, only one patient in the bupivacaine group had no requirements, while eight patients in the LB group had no requirements, suggesting it may be possible to avoid opioid therapy. Other delivery mechanisms of nonopioid analgesia have also been explored in this context, including the transversus abdominis plane block and donor site multiple-infusion catheter-based strategies.[31-34] These studies suggest a reduction in opioid consumption overall, with some reporting earlier discharge, reduced time to ambulation, and reduction in pain scores. Although these avenues are efficacious for the treatment of donor site pain, drawbacks may include potential for tracking infections in catheter-based strategies and increased operative time to achieve a plane block. LB may provide an alternative quick, safe, and effective method to control pain.

Notably, two patients in the LB and one patient in the bupivacaine group experienced transient treatment-sided lateral thigh paresthesia for three days following bone grafting. Other dysesthesias following iliac crest bone harvest have been reported in literature, with reported rates as high as 34.8%, and predominately associated with a surgical technique and not the use of an anesthetic.[3,5,35,36] All patients in our study recovered within three days without any residual morbidity. Although the duration of these parasthesias correlates with the duration of action, careful dissection is paramount in preventing complications. It is also important for clinicians to understand that other side effects such as cardiotoxicity and neurotoxicity may still occur as with other formulations of this local anesthetic.[13] With the rising cost of healthcare, limiting unnecessarily expensive medications have become a cornerstone of cost-effective care. Despite current data suggesting the price of LB to be approximately 285–315 USD and bupivacaine to be 1–5.24 USD, we believe there may still be a role for LB in this setting.[37] It is increasingly recognized that increased acute postoperative pain predisposed patients to a higher risk of developing chronic pain.[38,39] With a recent meta-analysis showing an incidence of chronic pain at 4.5% and one study reporting an incidence as high as 10%, alleviating acute postoperative pain may translate to reduced morbidity.[40] Although this study is unable to provide such justification with long-term follow-up, we hope further exploration of the use of LB in this setting may provide the required result.

Of note, there are several limitations in this study. Treatment groups were retrospectively divided in a nonstandardized, unblinded, and underpowered manner. Additionally, it is difficult to ascertain whether the control group was given equivalent 0.25% bupivacaine as compared to the administration of LB. As there is no standard approach for the volume to be administered in our patient population, confounding factors influencing outcomes are possible. Usage of the activity tracker may also have been patient dependent subject to the correct usage of the device. With such a multitude of variables, standardization of practices regarding the dosing of LB in children and further randomized controlled trials may provide more definitive answers.

Conclusion

LB may be used intraoperatively for effective pain reduction, expeditious return to activity, and reduction in opioid requirements for patients undergoing iliac crest bone harvest for alveolar bone grafting.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose relevant to the content of the manuscript. Dr. Momeni is a consultant for Allergan, AxoGen, and Stryker.

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