Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Paravertebral nerve block catheters using chloroprocaine in infants with prolonged mechanical ventilation for treatment of long-gap esophageal atresia

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What is already known

- Regional anesthesia is effective in controlling postoperative pain.

What this study adds

- The results of this study show that short-term paravertebral nerve block catheter placement decreases opioid and benzodiazepine exposure, weaning days and ICU stay in infants undergoing prolonged mechanical ventilation after long gap esophageal atresia repair.

Keywords
infants; long-gap esophageal atresia; pain; paravertebral nerve block; regional anesthesia

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Section Editor: Adrian Bosenberg

Accepted 30 June 2015

doi:10.1111/pan.12736

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Summary

Background: Infants with long-gap esophageal atresia (LGEA) undergo repeated thoracotomies for staged surgical repair known as the Foker process (FP). Associated prolonged mechanical ventilation results in exposure to high doses of opioids and benzodiazepines, and prolonged weaning times and ICU stays.

Aim: The aim of this study was to determine the effectiveness of short-term paravertebral nerve block (PVNB) catheters in reducing opioid/benzodiazepine exposure and effects on clinical variables.

Methods: The medical records of seventeen infants were retrospectively reviewed; 11 with PVNB and six without (CG). PVNB were placed using ultrasound-guidance and chloroprocaine infusions implemented in the ICU. Opioids and benzodiazepines were administered via the protocol for 5 days following thoracotomies for Foker-I and Foker-II.

Results: Foker-I: Average reduction in morphine and midazolam consumption was 36% (2.18 vs 3.40 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$; $P < 0.001$) and 31% (2.25 vs 3.25 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$; $P = 0.033$), respectively, in the PVNB compared with CG. Foker-II: Average reduction in morphine and midazolam consumption was 39% (3.19 vs 5.27 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) and 38% (3.46 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ vs 5.62; $P < 0.001$), respectively in the PVNB compared with CG. 24-h prior to extubation: Average reduction in morphine and midazolam consumption was 50% (2.91 vs 5.85 $mg{\cdot}kg^{-1}{\cdot}24\ h^{-1}$; $p = 0.023$) and 61% (2.27 vs 5.83 $mg{\cdot}kg^{-1}{\cdot}24\ h^{-1}$; $P = 0.004$), respectively, in the PVNB compared with CG. Infusion wean time, (independence from opioid/midazolam infusions) following extubation was 5 days in the PVNB group and 15 days in CG

($P = 0.005$). Median ICU stay (IQR) was 40 days (34–45 days) in PVNB patients and 71 days (42–106 days) in controls ($P = 0.02$). PVNB catheters were left an average of 7 days and there were no complications associated with the nerve blocks.

Conclusion: Short-term PVNB placement decreases opioid and benzodiazepine exposure, weaning days and ICU stay in infants undergoing prolonged mechanical ventilation for LGEA repair in this small pilot study. Larger studies are warranted to confirm results.

Introduction

Long-Gap Esophageal Atresia (LGEA) is a neonatal disease characterized by esophageal atresia with or without a tracheoesophageal fistula (1). This group of patients can undergo serial thoracotomies, the Foker process, for repair of the esophagus as a neonate or infant (2). The Foker process is made up of two stages, where Foker-I is placement of external traction to the esophagus to promote esophageal growth; Foker-II is the anastomosis of the esophageal pouches. Patients undergoing this process must remain chemically paralyzed and mechanically ventilated for prolonged periods of time and are best served by aggressive multimodal postoperative sedation and pain management currently characterized in our institution by large amounts of benzodiazepines and opioids.

Although very high dose opioid and benzodiazepine exposure is associated with iatrogenic tolerance and dependence and prolonged ICU length of stay (3), poor pain management also negatively impacts patient outcomes suggesting that the choice of analgesia determines patient outcomes (4,5). While regional anesthesia is effective in controlling postoperative pain, evidence of benefit in patients requiring sedation for prolonged intubation and ventilation is lacking (6). Epidural anesthesia is commonly used to decrease pain and stress in some infant surgical populations, but many LGEA patients have contraindications to epidurals such as prolonged chemical paralysis, low body weight, spinal anomalies, minor alterations in coagulation, and poor immune function.

Use of paravertebral nerve block (PVNB) catheters as an alternative to epidural to control postoperative pain in children was first described in 1992 demonstrating segmental, localized analgesia without negating concurrent use of adjunct systemic agents (7). Traditionally, a landmark-based technique was used to place catheters in children. Recently, ultrasound-guided (UG) techniques are described for both adult and pediatric patients including infants (8).

The feasibility and benefit of PVNB catheters for patients undergoing prolonged mechanical ventilation has not been well described in the literature. In an attempt to provide a regional anesthesia-based pain management plan as an alternative to anticipated high–dose opioid and benzodiazepine administration, we developed a preliminary study to trial PVNB catheters using chloroprocaine infusions in a series of LGEA patients. We hypothesized that PVNB would reduce opioid and benzodiazepine consumption in LGEA patients. Secondary outcomes were to determine any effects on the number of esophageal growth days, wean times, ventilator days and ICU length of stay.

Methods

Methods and clinical variables

Following IRB approval (IRB-P00004344), a retrospective review of the medical records of patients undergoing the Foker process of staged repair for LGEA treated from 2006–2014 at a single institution, Boston Children's Hospital (BCH), was performed. Patients prior to 2006 were excluded as the multidisciplinary esophageal treatment team (EAT) had not been formed and patient perioperative care was not standardized. Inclusion criteria included age <1 year, two or more thoracotomies within 45 days, all thoracotomies performed by or under the supervision of a single surgeon, and continuous intubation between thoracotomies.

Prior to January 2014, no patients received a PVNB (5/5). After January 2014, informed consent for general anesthesia alone (1/12) or general anesthesia with PVNB (11/12) was obtained after extensive discussion of the risks and benefits and trial nature of the PVNB. We reviewed patient characteristics including age, weight, weight-for-age Z-score at ICU admission

(WAZ), primary vs secondary esophageal atresia patients, presence of other anomalies, and preoperative gap length.

PVNB placement technique

PVNB were placed at the end of each thoracotomy surgery with patients in the lateral decubitus position using the surgical sterile field. The target thoracic spinal nerve level was determined by the location of the incision. A 3.5 cm high frequency linear array transducer oscillating at 6–18 MZ (8870; Analogic Corp) connected to a portable ultrasound machine (Flex-Focus 400EXP or 500; Analogic Corp, Peabody, MA USA) was used to identify characteristic echogenic landmarks and to facilitate real-time insertion of an 18G 5 cm echogenic ally enhanced needle (Pajunk Medical Inc., Geisingen, Germany) into the paravertebral space using a previously described technique (8).

Ropivacaine hydrochloride 0.2% at a dose of 0.5–1 $ml \cdot kg^{-1}$ was bolused through the needle and a single orifice catheter (B. Braun Medical Inc., Bethlehem, PA, USA) inserted and advanced 1 cm beyond the needle tip. In all patients, we attempted to tunnel the catheter subcutaneously for added security against accidental dislodgement and to prevent local anesthetic (LA) leakage. All catheters were secured with liquid adhesive and an occlusive, clear plastic dressing allowing observation of the insertion site. All catheters were inserted by or under the supervision of anesthesia faculty with training in pediatric regional anesthesia. PVNB catheter infusions of 1.5% chloroprocaine were initiated upon arrival in the ICU at a rate of 0.5–0.8 $ml \cdot kg^{-1} \cdot h^{-1}$. and continued for up to eight postoperative days. All patients received concurrent IV morphine and midazolam hydrochloride, and until successful esophageal anastomosis was established, vecuronium bromide infusions. A pain and sedation management protocol developed for this population and implemented in this pilot group.

Protocol Infusions

Following Foker-I, patients with PVNB catheters were started on morphine sulfate (morphine) at 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$. and midazolam hydrochloride (midazolam) at 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$. Patients without a PNVB catheter, were started on morphine at 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$. and midazolam at 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$. Patients who had prior exposure had protocol adjustment to meet the patient's anticipated needs. Following Foker-II, the protocol called for an increase in the opioid by 10% (an increase in opioid by 20% if no paravertebral catheter was present), an increase in the benzodiazepine by 10% and scheduled intravenous or rectal acetaminophen doses for 72 h.

Protocol boluses

All patient groups had pretreatment with boluses of opioid and benzodiazepine for suctioning or procedures. If patient with sustained tachycardia or hypertension: a non-procedure bolus was administered. Drips were increased 10–20% if >3 non-procedural boluses were administered per shift.

PVNB catheter management

Catheters were followed daily and managed by a dedicated Pain Treatment Team. No adjustments to the local anesthetic infusion were made. Catheters were discontinued after a maximum of 8 days and replaced at each thoracotomy. All patients were intubated and chemically paralyzed from the Foker-1 through their Foker-II post-anastomosis fluoroscopy study. Chemical paralysis was lifted following successful anastomosis. The administration of all medications was recorded and converted to $mg \cdot kg^{-1} \cdot day^{-1}$ for analysis. The NICU protocol for weaning from versed and morphine was started upon extubation.

Outcome measures

Morphine and midazolam consumption were recorded as average consumption of morphine equivalents ($mg \cdot kg^{-1} \cdot day^{-1}$) and midazolam ($mg \cdot kg^{-1} \cdot day^{-1}$), respectively, for the 5 days following the Foker-I (traction) and Foker-II (anastomosis) process (all but one study patient had the PVNB for at least 5 days). Baseline for opioid and benzodiazepine weaning periods was defined as the total opioid and benzodiazepine consumption ($mg \cdot kg^{-1}$) in the 24 h prior to extubation. Axial tension days were defined as number of esophageal growth days from the incision for the Foker-I until day of incision for the Foker-II. Ventilator days were defined as number of days from initial incision for Foker-I until successful extubation following esophageal anastomosis/ICU stay was defined as days from initial incision for Foker-I until discharge from the ICU.

Statistical analysis

A repeated-measures mixed model analysis of variance (ANOVA) was used to determine average opioid (morphine) consumption ($mg \cdot kg^{-1} \cdot day^{-1}$) and average benzodiazepines (midazolam) consumption ($mg \cdot kg^{-1} \cdot day^{-1}$) over a 5-day period for patients with PVNB and con-

trols following Foker-I and Foker-II. This model uses a compound symmetry covariance structure to account for the repeated measurements within the same patient and the Greenhouse-Geisser *F*-test to assess significance with a conservative Bonferroni adjusted two-tailed *P*-value and 95% confidence intervals (CI) around the average consumption to provide precision of the estimated effects (IBM/SPSS Statistics, version 21.0, IBM, Armonk, NY, USA). The Akaike information criterion was used to judge the fit of the model (9,10). The nonparametric Mann–Whitney *U*-test was employed to compare median ICU stay between the two study groups with box-and-whisker plots.

Based on an unbalanced study design with unequal sample sizes (11 PVNB, six controls), measurements of opioid (morphine) and benzodiazepine (midazolam) intravenous consumption analyzed each day over a 5-day period (during both Foker-I and Foker-II), the power was 82% for detecting 30% mean reductions or more between the two groups using the *F*-test in repeated-measures ANOVA with a Greenhouse-Geisser correction for nonsphericity (11). The power calculations were determined using the nQUERY ADVISOR software package (version 7.0; Statistical Solutions, Cork, Ireland).

Results

Eleven patients with PVNB were identified. Six patients were defined as historical controls. (Table 1).

Significant reductions in both morphine and midazolam were seen postoperatively (Figures 1 and 2). Average reduction in morphine consumption following Foker-I was 36%; average morphine consumption was 2.18 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ with PVNB (95% CI: 1.78–2.58 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) and 3.40 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ (95% CI: 2.86–3.54 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) without PVNB ($F = 12.95$, $P < 0.001$). Percent reduction in morphine consumption following Foker-II was 39%; average morphine consumption was 3.19 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ with PVNB (95% CI: 2.65–3.72 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) and 5.27 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ without PVNB (95% CI: 4.54–6.00 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) ($F = 21.16$, $P < 0.001$) (Table 2).

Average percent reduction in midazolam consumption following Foker-I was 31%; midazolam consumption over 5 days was 2.25 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ (95% CI: 1.71–2.78 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) with PVNB and 3.25 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ (95% CI: 2.52–3.97 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) without PVNB

Table 1 Baseline characteristics of long-gap esophageal atresia patients according to use of paravertebral nerve block catheters

Variable	LGEA with PVNB ($n = 11$)	LGEA without PVNB ($n = 6$)
Gender (M/F)	6/5	4/2
Age at Foker-I (months)	4.5 (4.5)	2.7 (2.0)
Weight at Foker-I (kg)	4.8 (1.9)	4.1 (1.0)
WAZ at ICU admission	−2.2 (1.8)	−2.5 (2.0)
Initial gap length (cm)	4.1 (1.0)	4.8 (1.7)
Congenital heart disease	4 (36%)	2 (33%)
VACTERL	3 (27%)	3 (50%)

LGEA, Long-gap esophageal atresia; ICU, intensive care unit; WAZ, weight-for-age Z-score; VACTERL, association of anomalies. Continuous data are mean (SD).

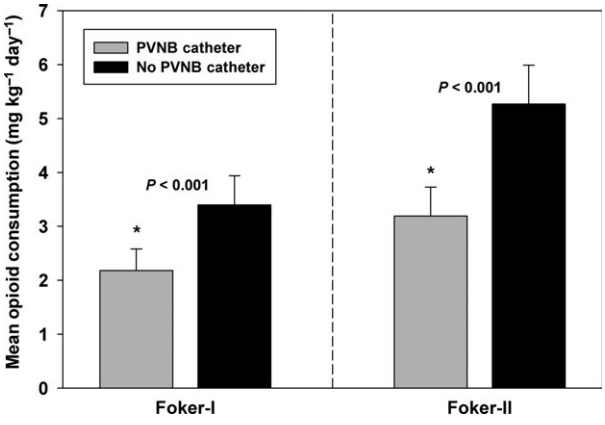

Figure 1 Graph depicting significant reductions in averaged morphine equivalents over 5-days following placement of PVNB at both Foker-I and Foker-II. These were denoted by asterisks (*) and associated *P*-values. The 95% confidence interval is denoted by error bars.

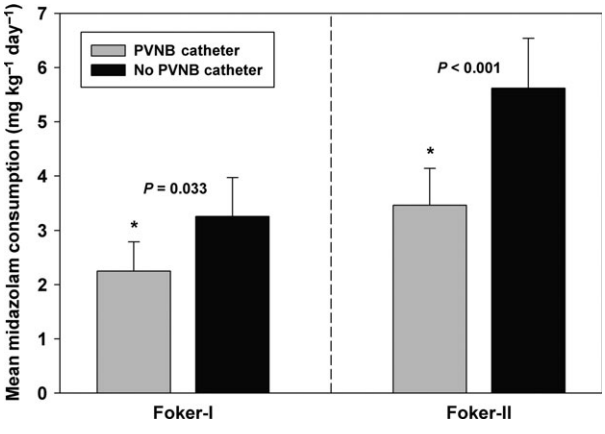

Figure 2 Graph depicting significant reductions in averaged midazolam equivalents over 5 days following placement of PVNB at both Foker-I and Foker-II. These were denoted by asterisks (*) and associated *P*-values. The 95% confidence interval is denoted by error bars.

Table 2 Effectiveness of paravertebral nerve block catheters in reducing intravenous opioid and benzodiazepine consumption

Intravenous Medication	With PVNB (n = 11) Mean (mg·kg^{-1}·day^{-1})	Without PVNB (n = 6) Mean (mg·kg^{-1}·day^{-1})	Difference (mg·kg^{-1}·day^{-1})	Percent Reduction	ANOVA (F-test)	P value
Opioids (Morphine)						
Foker-I	2.18	3.40	1.22	36%	12.95	<0.001*
Foker-II	3.19	5.27	2.08	39%	21.16	<0.001*
Benzodiazepine (Midazolam)						
Foker-I	2.25	3.25	1.00	31%	4.75	0.033*
Foker-II	3.46	5.62	2.16	38%	13.95	<0.001*

PVNB, paravertebral nerve block.

Data are in equivalent units.

*Statistically significant based on repeated-measures ANOVA aggregating across 5-day time period to provide a more robust estimate of average intravenous consumption with and without short-term PVNB.

catheters (F = 4.75, P = 0.033). Average reduction in midazolam consumption following Foker-II was 38%; average midazolam consumption over 5 days was 3.46 mg·kg^{-1}·day^{-1} (95% CI: 2.78–4.14 mg·kg^{-1}·day^{-1}) with PVNB and 5.62 (95% CI: 4.69–6.54 mg·kg^{-1}·day^{-1}) without PVNB catheters (F = 13.95, P < 0.001) (Table 2).

As seen in Table 3, the opioid consumption in the 24 h prior to extubation of the PVNB group was 2.91 ± 1.14 mg·kg^{-1}·24 h^{-1} while the historical control group's was 5.85 ± 3.60 mg·kg^{-1}·24 h^{-1} (P = 0.023). The midazolam consumption in the 24 h prior to extubation was 2.27 ± 1.00 mg·kg^{-1}·24 h^{-1} and 5.83 ± 3.31 mg·kg^{-1}·h^{-1} in the PVNB and control groups, respectively (P = 0.004). Infusion wean time, defined as independence from both opioid and midazolam infusions, in days following extubation was 5 (interquartile range {IQR} 2–11) days in the PVNB group and 15 (IQR: 11–18) days in the control group (P = 0.005) (Table 3).

Median effective ICU days for PVNB catheter patients was 40 days (IQR 34–45 days). This was compared to 71 days (IQR 42–106 days) for the control group (P = 0.02) (Figure 3). Number of esophageal growth days (P = 0.12) did not differ between the two groups. The number of ventilator days (P = 0.40) also did not differ between the two groups.

Ultrasound landmarks were identified in all patients and all catheters could be placed without technical difficulty. In 9 of 11 patients, the catheter was tunneled subcutaneously for added security against accidental dislodgement. The duration of the PVNB catheters ranged from 3–8 days. Premature catheter dislodgement occurred in 2/11 patients. There were no serious complications including local anesthetic systemic toxicity, bleeding or infection.

Discussion

In this small consecutive series of patients representing our pilot program, preliminary data suggest that placement of PVNB in LGEA patients undergoing prolonged mechanical ventilation offers a technically feasible form of pain management. Use of PVNB is associated with a significant decrease in intensive care stay, decreased weaning days as well as a reduction in aggregate opioid

Table 3 Effect of PVNB on dose and weaning from opioid and benzodiazepine infusions

Variable	LGEA with PVNB (n = 11)	LGEA without PVNB (n = 6)	P value
Dose in 24 h just prior to extubation Opioid dose (mg·kg^{-1}·day^{-1})	2.91 (1.14)	5.85 (3.60)	0.023*
Benzodiazepine dose (mg·kg^{-1}·day^{-1})	2.27 (1.00)	5.83 (3.31)	0.004*
Days from extubation to stop infusion			
Opioid	4 (3–6)	10 (6–16)	0.048*
Benzodiazepine	4 (2–9)	8 (6–15)	0.068†
Days from extubation until wean of both opioid and benzodiazepine infusions	5 (2–11)	15 (11–18)	0.005*

LGEA, Long-gap esophageal atresia; ICU, intensive care unit.

Dose is expressed in terms of mean (SD) and days as median (interquartile range).

*Statistically significant.

†Trend.

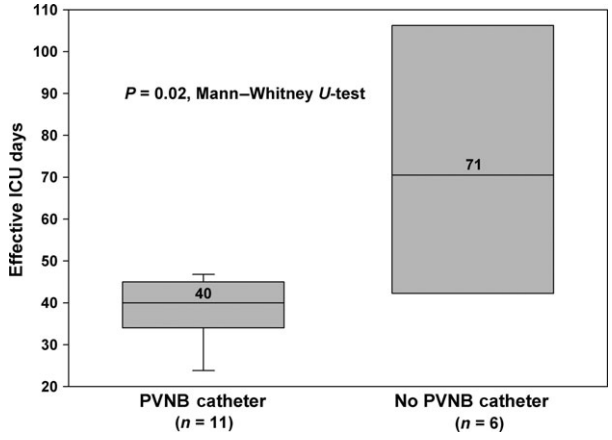

Figure 3 Graph depicting a significant reduction (40 vs 71 days, Mann–Whitney *U*-test, $P = 0.02$) in effective intensive care unit (ICU) days following the placement of the paravertebral nerve block (PVNB) catheter. Each box-and-whisker plot is characterized by a horizontal line through the box that represents the median, whereas the length of the box represents interquartile range.

and benzodiazepine consumption. Although the numbers are small and the retrospective study design allows only limited conclusions, there are several themes worth discussing.

The gold standard for post-thoracotomy pain management in both the adult and pediatric population has been epidural analgesia (12–15) which comes with certain risks and side-effects (16,17). For the LGEA patients in particular, there are several reasons to avoid placement of an epidural catheter with the main concerns being the frequent presence of spinal anomalies and the inability to assess lower extremity motor function as a monitor for possible epidural hematoma.

We can find no studies documenting the value of short-term use of regional anesthesia in surgical patients with prolonged intubation and ventilation beyond the termination of the regional technique and feel this is one of the key findings of our small study. We demonstrate a significant reduction in opioid consumption with PVNB analgesia in the 5 days following thoracotomy. The added decrease in midazolam consumption can be attributed to difficulty discriminating between responses due to pain vs agitation in infants. Using the morphine/midazolam consumption in the 24 h prior to extubation as a surrogate marker of overall opioid/midazolam usage in the time from Foker-I to extubation, we demonstrate the drug sparing effects of the PVNB persisting beyond removal of the nerve blocks. The magnitude of opioid/midazolam sparing necessary for clinical and/or developmental implications are unknown and requires further study.

In our LGEA population, we report no complications associated with the use of PVNB. Recent studies demonstrate a good safety profile and efficacy for non-neuraxial regional analgesia (18–21). Larger prospective studies, however, are required to evaluate safety and frequencies of both common and rare adverse events in our particular patient population. We used ropivicaine, a longer acting drug, for the initial bolus to prevent analgesic gaps prior to initiation of the infusion. Conflicting reports on amide LA elimination and concerns about accumulation in infants <6 months of age (22,23) prompted a switch to an ester LA for the infusion due to the planned prolonged administration. Chloroprocaine perineural administration in infants has only been reported via the epidural route and because PVNB dosing is very similar to epidural we extrapolated the epidural dose to PVNB (24,25). We left PVNBs in for 7–8 days for our study patients in an attempt to maximize potential benefits but chose to analyze morphine and midazolam consumption in the 5 days following thoracotomy since all but one PVNB catheter was still in place at day 5 as well as previous personal experience showing highest benefit from regional anesthesia for up to 5 days after thoracotomy. Although chest tubes remained in place, we felt the risk of infectious complications prevented leaving the PVNB to prevent chest tube discomfort. Additional studies are needed to define the optimal duration for the PVNB and local anesthetic regimen.

Patients in our study had a 43% decrease in number of ICU days. As institutional protocol requires patients to be free of dependence on continuous opioids and benzodiazepines prior to discharge from intensive care unit (ICU), we attributed this decrease in the ICU stays to the decreased weaning times associated with decreased midazolam/opioid exposure. Although our NICU utilizes a weaning protocol, those infants with higher initial exposure are more prone to have interrupted and prolonged weaning (3). Overall, we showed no difference in total days of mechanical ventilation and esophageal growth time, as expected, as these are independent of pain control in this population.

Future directions and conclusions

Concerns about the degree of opioid and benzodiazepine exposure in LGEA infants led to multidisciplinary discussions and the development of a novel approach to pain management in these ICU patients. Preliminary data suggest that placement of PVNB catheters in LGEA infants with prolonged mechanical ventilation decreases averaged opioid and benzodiazepine consumption and ICU length of stay. No PVNB catheter-related morbidity was observed. Further studies are needed to assess this promising approach in pediatric patients undergoing prolonged mechanical ventilation

for this and other procedures, and to evaluate the safety, efficacy, long term benefits and cost-effectiveness of this technique.

Ethics approval

All necessary ethical approval(s) have been accounted for and there are no conflicts in this study.

Funding

The study was funded by departmental resources.

Disclosures

None of the authors have any conflicts of interest to disclose.

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