






Postoperative Analgesia in Neonates and Infants Using Epidural Chloroprocaine and Clonidine

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Introduction: In neonates and infants, epidural analgesia has gained popularity as a means of providing postoperative analgesia, limiting opioid-related adverse effects and improving the postoperative course. In addition to a local anesthetic agent, adjunctive agents may be added to further augment analgesia. Clonidine is an α_2 -adrenergic agonist that is frequently added to single-shot caudal analgesia, but there are limited data regarding its use in a continuous epidural infusion, especially in patients ≤ 12 months of age.

Methods: We retrospectively reviewed the hospital records of neonates and infants who received postoperative epidural infusions with 2-chloroprocaine, and clonidine was identified over a 4-year period.

Results: The study cohort included 52 neonates and infants ranging in age from 0 to 12 months and in weight from 2.1 to 10.1 kilograms. The catheters were dosed with either 1.5% 2-chloroprocaine (n=47) or 3% 2-chloroprocaine (n=5) with clonidine (median concentration 0.2 $\mu\text{g}/\text{mL}$) infused at a median rate of 0.72 mL/kg/hour. Pain scores were uniformly ≤ 3 at all evaluation points during the first 72 postoperative hours with a limited need for supplemental systemic opioids. No serious adverse effects were noted.

Conclusion: With the recognized limitations of a retrospective study, these preliminary data demonstrate the safety of adding clonidine to an epidural infusion of 2-chloroprocaine in neonates and infants less than 12 months of age. Future studies are needed to determine its analgesic efficacy compared to 2-chloroprocaine alone and the optimal clonidine concentration for postoperative epidural infusions.

Keywords: chloroprocaine, epidural analgesia, clonidine, neonatal anesthesia

Introduction

Regional anesthesia has been shown to be a safe and effective option for intraoperative and postoperative analgesia in neonates, infants, and children.¹ In neonates and infants, epidural analgesia has gained popularity as a means of limiting postoperative opioid-related adverse effects, facilitating earlier tracheal extubation, and encouraging the resumption of normal gastrointestinal function.¹⁻³ Although bupivacaine and ropivacaine remain the most commonly used local anesthetic agents for postoperative epidural infusions in infants, clinical concerns exist regarding the potential for local anesthetic systemic toxicity (LAST) with these agents.⁴⁻⁸ Given these concerns, there has been expanding use of 2-chloroprocaine especially for continuous postoperative epidural infusions in neonates and infants.^{4,9-11} Chloroprocaine is an ester that undergoes rapid metabolism by plasma cholinesterases with a serum half-life of approximately 60 seconds.¹²

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In addition to local anesthetic agents, adjunctive agents such as opioids, ketamine, or clonidine may be added to epidural infusions to potentiate analgesia and limit the infusion requirements for local anesthetic agents.^{13–15} Clonidine is commonly added to local anesthetic agents for single-shot caudal blockade in infants and children; however, there remains limited data on its addition to solutions for continuous epidural infusions in neonates and infants.¹⁵ We retrospectively reviewed our experience with the addition of clonidine to 2-chloroprocaine for continuous postoperative infusions in neonates and infants.

Methods

This study was approved by the Institutional Review Board of Nationwide Children's Hospital (STUDY00000544) and conducted in accordance with the regulations of the Declaration of Helsinki for research involving human subjects. As a large retrospective cohort study, it was deemed to have no more than minimal risk. With the use of de-identified data for publication, the need for informed consent was waived. Neonates and infants who received postoperative epidural infusions with 2-chloroprocaine and clonidine were identified over the time period from January 2015 to August 2019. The institutional electronic medical record was reviewed for these patients and data regarding each patient's surgery, anesthesia, and postoperative course was obtained.

Data collected included the following patient demographic characteristics: age at time of procedure, gestational age, height, weight, gender, race, and ethnicity. Surgical data collected included the primary diagnosis, surgical procedure, American Society of Anesthesiologists (ASA) physical status, and length of surgery. Epidural data collection consisted of location of epidural catheter placement, whether the epidural infusion was started intraoperatively or postoperatively, length of endotracheal intubation and timing of tracheal extubation, duration of epidural therapy, adverse effects related to the epidural infusion (hypotension, bradycardia, or excessive sedation) and the reason for removal of the epidural catheter. Data were obtained on the administration of bolus epidural doses and the administration of analgesic or sedative adjuvants including acetaminophen, lorazepam, diazepam, and ketorolac. Consumption of fentanyl, morphine, hydromorphone, and oxycodone were determined in 24-hour intervals up to 72 hours after surgery (postoperative days 1, 2, and 3). Morphine, hydromorphone, and oxycodone were combined and converted to oral morphine equivalents (OMEs) in mg/kg/day.¹⁶ Intravenous fentanyl administration was calculated

separately as $\mu\text{g}/\text{kg}/\text{day}$. The consumption of fentanyl was tabulated separately due to its comparatively divergent half-life and potency, particularly in neonates and infants. Two validated methods were used to assess pain levels in our study population. These assessment tools were the Faces, Legs, Agitation, Cry, and Consolability (FLACC) Scale and the Neonatal Pain, Agitation and Sedation Scale (NPASS).^{17,18} Both tools are based on a 10-point scale with zero being most comfortable or no pain.

Information gathered on each patient was stored on the secure, on-site server REDCap. Patient and procedure characteristics are described as median and interquartile range (IQR) for continuous variables or count and percentage for categorical variables. Medications and pain scores are described as median (IQR). All analyses were performed using SAS 9.4 (Cary, NC).

Results

The study cohort included 52 neonates and infants ranging in age from 0 to 12 months and in weight from 2.1 to 10.1 kilograms. Four patients were ≤ 1 month of age and 19 were ≤ 3 months of age. Gestational age ranged from 23 to 41 weeks. Forty-three patients (83%) identified as white (96%), four identified as Black or African American (8%), and five as other (9%). During their preoperative evaluation, most patients were assigned an ASA physical status of II (35%) or III (48%). The demographic data are outlined in Table 1. The epidural catheter was placed in the operating room after the induction of anesthesia and endotracheal intubation in all patients. There were ten surgical procedures on the airway, lung or diaphragm; thirty-eight

Table 1 Demographic Data of the Study Cohort (n=52)

Variable	Median (IQR) or N (%)
Age at time of procedure (months)	4 (2, 7)
Gestational age at birth (weeks)	37 (34, 39)
Weight (kilograms)	4.9 (3.5, 7.5)
Gender (female)	26 (49%)
Race	
White	43 (83%)
Black or African American	4 (8%)
Other	5 (9%)
ASA physical status	
II	18 (35%)
III	25 (48%)
IV	9 (17%)

Abbreviations: IQR, interquartile range; N, number; ASA, American Society of Anesthesiologists.

on the gastrointestinal tract; and four on the genitourologic tract. Twenty catheters were placed from a caudal approach and threaded cephalad so that the tip of the catheter was positioned at T5-T11, 30 catheters were placed at the thoracic level (T6-T10), and two catheters were placed at the lumbar level (L2-3). The decision regarding the eventual location of the tip of the catheter was based on the site of the surgical incision and the dermatomes involved. Documentation of the appropriate placement of the epidural catheter was verified by real-time ultrasound in the operating room or by a postoperative radiograph. Forty-four patients (85%) had their tracheas extubated in the operating room while 8 (15%) required postoperative mechanical ventilation. The tracheas of four of these patients were extubated within 72 hours while the four others required a more prolonged course of mechanical ventilation (6, 9, 15, and 24 days) due to the surgical procedure, secondary medical issues or associated comorbid conditions.

The catheters were dosed with either 1.5% 2-chloroprocaine (47 patients or 90%) or 3% 2-chloroprocaine (5 patients or 10%). The clonidine concentration in the epidural solution varied from 0.1 to 0.4 µg/mL (median concentration of 0.2 µg/mL). No other adjunctive agents were added to the epidural infusions. The epidural infusion was dosed and administered intraoperatively in two patients, intraoperatively and postoperatively in 31 patients or only postoperatively in 19 patients. Nineteen patients (37%) received a bolus dose of 2-chloroprocaine followed by an infusion while the remaining 33 patients (63%) had the infusion started without a bolus dose. During the entire course and subsequent use of the catheter, seven patients received one bolus dose, five patients received two bolus doses, and seven patients received three bolus doses. Per our usual clinical practice, the initial bolus dose in the operating room after the epidural catheter was placed included only 2-chloroprocaine (1.5% or 3%). The bolus doses administered during the postoperative course used the 2-chloroprocaine with clonidine solution. The median bolus dose was 2 mL (range 1–3 mL, IQR 2–2.5 mL). The continuous infusion was started at a median dose of 0.73 mL/kg/hour (range 0.32–1.67 mL/kg/hour, IQR 0.59–0.93 mL/kg/hour). Table 2 shows the duration of catheter use in the 52 patients. The catheter was discontinued because it was no longer needed in 47 patients (90%) and due to concerns regarding sterility or status of the dressing in five patients (10%). No change was required in the infusion rate in 29 patients (56%), one change in 18 patients (34%), two

Table 2 Duration of Catheter Use

Duration (Days)	Number of Patients (Percentage)
≤1 day	4 (8%)*
2	4 (8%)
3	15 (29%)
4	23 (44%)
≥ 5	6 (11%)

Note: *Includes 2 patients in whom the catheter was used only intraoperatively.

changes in five patients (10%). In all patients that had a change in the infusion rate, the result was an increase in the infusion to improve the level of analgesia. The starting infusion rate and the subsequent rates after the first and second change in the infusion are outlined in Table 3. No adverse effects including excessive sedation, bradycardia or hypotension were noted in the study cohort following bolus dosing or during the continuous infusion. None of the patients required a decrease in the infusion rate, discontinuation of the infusion or change in the infusion medications due to adverse effects.

Postoperative analgesia was supplemented as needed by the administration of opioids including intravenous morphine, fentanyl, hydromorphone, and oral oxycodone (Table 4). In the entire cohort of 52 patients, the median (IQR) consumption of OMEs for the first, second, and third 24-hour postoperative periods were 0.3 (0, 0.7), 0.3 (0–0.6), and 0.15 (0–0.5) mg/kg (Figure 1). To exclude sedation and analgesia needs impacted by the presence of an endotracheal tube and ongoing mechanical ventilation, the consumption of opioids was also calculated for 72 postoperative hours in the

Table 3 Infusion and Subsequent Infusion Rates

Rate	Median (IQR)	Range
Initial rate (n=52)	0.73 (0.59–0.93)	0.32–1.67
Second rate in patients with one change (n=23)	0.75 (0.58, 1.09)	0.38–1.43
Third rate in patients with two changes (n=5)	0.79 (0.69, 0.87)	0.44–1.40

Note: Data are listed in mL/kg/hour.

Abbreviation: IQR, interquartile range.

Table 4 Postoperative Opioid Use

Opioid	Number of Patients*
Morphine	37
Fentanyl	21
Oxycodone (enteral)	10
Hydromorphone	1

Note: *The number is greater the study cohort of 52 as some patients received more than one opioid over the postoperative course.

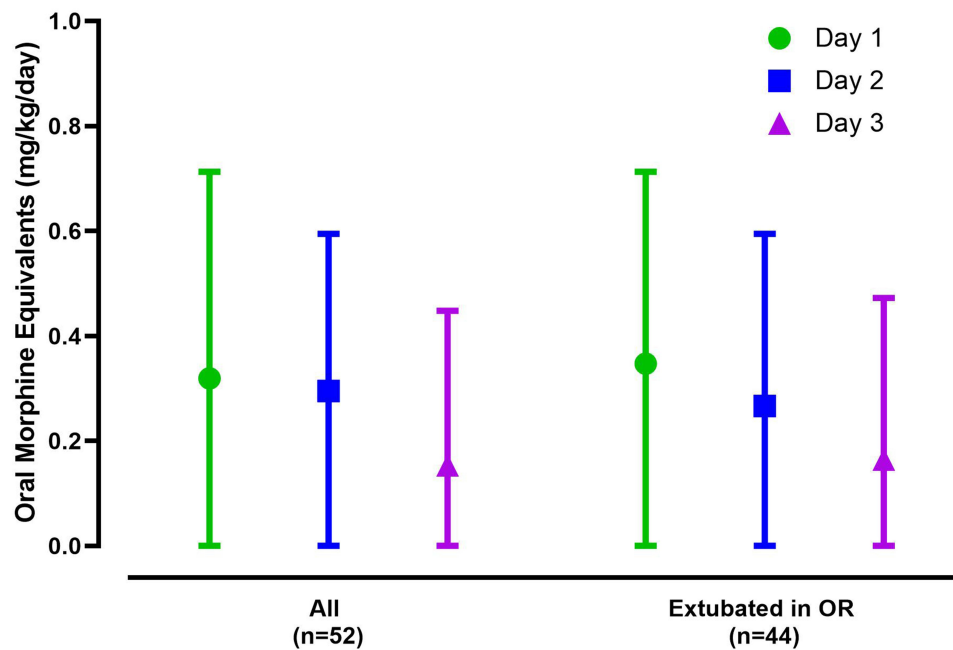


Figure 1 The median (interquartile range) values of opioid consumption over a 72-hour postoperative period in oral morphine equivalents (mg/kg) for all patients (n=52) and patients who were had their tracheas extubated in the operating room (n=44).

44 patients who had their tracheas extubated in the operating room resulting in OMEs use of 0.4 (0–0.7), 0.3 (0–0.6), and 0.2 (0–0.5) mg/kg, respectively, on postoperative days 1, 2, and 3. For fentanyl consumption, the median (IQR) for the first, second, and third 24-hour postoperative periods was 0 (0, 1.1), 0 (0, 0.4), and 0 (0, 0) μ g/kg/day, respectively, on postoperative days 1, 2, and 3 (Figure 2).

In addition to the opioids noted, the following analgesic or sedative adjunctive agents were administered.

Acetaminophen (intravenous or enteral) was administered around the clock every six hours to 51 of 52 patients (98%), ketorolac was administered every 6–8 hours to 19 patients (36%), and a benzodiazepine (diazepam or lorazepam) was administered as needed to 14 patients (27%). Pain scores using either the N-PASS or FLACC scoring are listed in Figure 3. Values were uniformly less than 3 of 10 at all assessment points. Neonates were more commonly assessed using the N-PASS pain scale, while

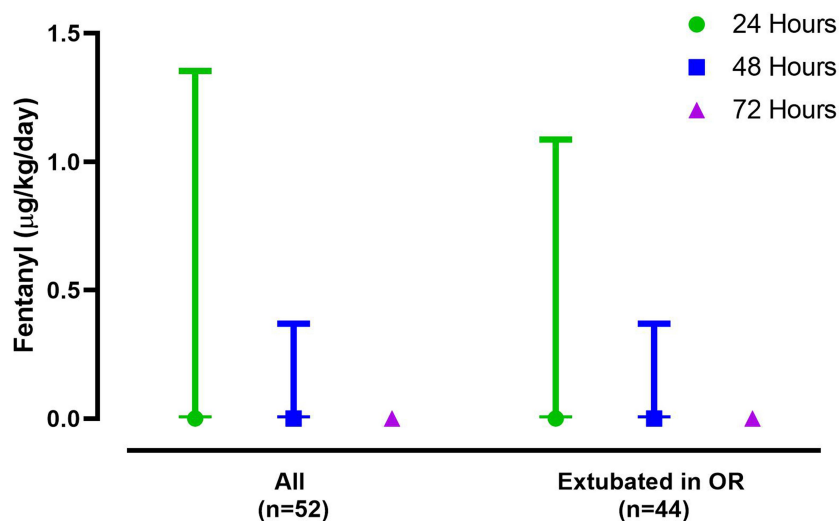


Figure 2 The median (interquartile range) values of fentanyl (μ g/kg/day) consumption over a 72-hour postoperative period for all patients (n=52) and patients who were had their tracheas extubated in the operating room (n=44).

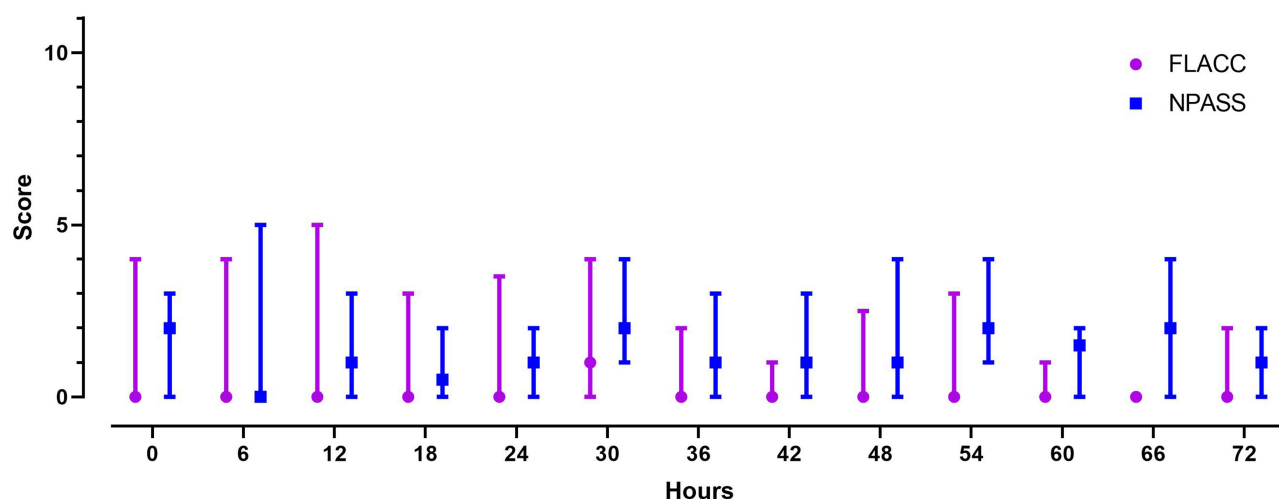


Figure 3 Median (interquartile range) values of pain scores using the FLACC (Face, Limbs, Activity, Cry, Consolability) scale and N-PASS (Neonatal Pain Agitation and Sedation Scale) scores assessed postoperatively every 6 hours for 72 hours.

infants and children were more commonly assessed using the FLACC pain scale.

Discussion

Despite the benefits of continuing epidural analgesia into the postoperative period, neonates and infants present unique challenges. In the early 1990s, the expanded use of continuous epidural analgesia resulted in several instances of LAST in the pediatric population.^{5,19,20} Dose restrictions with consideration of the volume and concentration is needed in neonates and infants when using continuous infusions of epidural bupivacaine or ropivacaine.^{7,21} Even with these considerations, toxicity may occur as more recent information has demonstrated that with epidural infusion rates of bupivacaine at 0.2 mg/kg/hour, increasing serum concentrations were noted at 48 hours leading the authors to caution against infusions beyond that time period.²¹

Concerns with the variable pharmacokinetics of amide local anesthetic agents during prolonged infusions in neonates and infants have led to a resurgence with interest in the use of 2-chloroprocaine for continuous epidural infusions. These studies have demonstrated effective analgesia with acceptable pain scores and limitation of postoperative opioid needs with the use of a postoperative epidural infusion with 2-chloroprocaine.⁹⁻¹¹ The reader is referred to the manuscript of Veneziano and Tobias for a full review of the use of chloroprocaine for epidural infusions in neonates, infants, and children.⁹

The addition of adjunctive agents is frequently chosen to improve analgesia and limit local anesthetic dosing

requirements (volume and concentration) of postoperative epidural infusions. Clonidine is a centrally acting α_2 -adrenergic agonist, that provides neuraxial analgesia through its effects on α_2 -adrenergic receptors in the dorsal horn of spinal cord, central nervous system, and peripheral nervous system. It was first used for epidural analgesia in 1984, and since then has been shown to be a valuable adjunct for continuous epidural analgesia in adults in various clinical scenarios.²²⁻²⁵ Similar efficacy was subsequently demonstrated in infants and children with clonidine added as an adjunct to caudal analgesia.²⁶⁻²⁸ However, there are limited data regarding the use of epidural clonidine in a continuous epidural infusion in infants and children.²⁹⁻³¹ In an open-label, prospective trial, clonidine was evaluated for epidural analgesia following abdominal surgery in a cohort of 40 children, less than three years of age.²⁹ The children were randomly allocated to receive a bolus of epidural clonidine (2 μ g/kg) followed by a 24-hour epidural infusion of clonidine (1 μ g/mL) at 0.2 mL/kg/hour or clonidine added to a 0.1% ropivacaine infused at 0.2 mL/kg/hour. Approximately 77% of the clonidine group and 59.3% of the clonidine and ropivacaine group required ≤ 1 dose of tramadol over a 24-hour period. Except for those patients who exhibited frequent coughing during the night (four patients in the clonidine group and five patients in the clonidine-ropivacaine group), no patient required supplemental analgesia and all had good sleep quality during the first postoperative night. Sedation and decreased systolic blood pressure were observed after the administration of the initial epidural clonidine bolus. A subsequent prospective study sought

to determine the optimal concentration of clonidine when added to epidural 0.1% ropivacaine for postoperative analgesia.³¹ The authors concluded that the addition of clonidine (0.08–0.12 µg/kg/hour) was the optimal concentration and was found to improve postoperative pain relief in children without clinically significant adverse effects.

However, there remains no information regarding epidural clonidine infusions in neonates and the suggestion that its use in children less than six months of age may be limited in current clinical practice.³² The current retrospective study evaluates a practice change in epidural analgesia at our institution with the addition of clonidine to continuous 2-chloroprocaine infusions. As noted above, 2-chloroprocaine is chosen given its improved safety profile when compared to local anesthetics of the amide class. Given the popularity and efficacy of adding clonidine to local anesthetic solutions for single-shot caudal epidural blockade, we decided to evaluate the addition of this agent to our continuous epidural infusions in patients less than one year of age. As there is no control group, an evaluation of its efficacy is not feasible; however, the current practice which we described demonstrates acceptable pain scores without the need for excessive supplementation with systemic opioids. Pain scores were uniformly ≤3 at all evaluation points during the first 72 postoperative hours. While the need for systemic opioids was limited, supplemental parental agents must be available to treat agitation in patients that are nil per os, for patient agitation related to other factors (presence of an endotracheal tube) or in the event that epidural analgesia is not complete.

Of note in our cohort was the lack of adverse effects. Although generally safe and effective, adverse effects reported with epidural clonidine related to direct neuraxial actions or systemic absorption have included bradycardia, hypotension, respiratory depression or apnea.^{33–37} These effects are more likely in neonates and infants, with higher doses, and following bolus administration.^{33,37,38} In our patient population, no hemodynamic effects were noted and none of the infusions were discontinued or the rates decreased due to hypotension or bradycardia. The majority of the cohort had their tracheas extubated in the operating room and breathed spontaneously during the administration of epidural clonidine. This was feasible with epidural clonidine infusion rates at a median dose of 0.15–0.16 µg/kg/hour (0.73–0.79 mL/kg/hour with a clonidine concentration of 0.2 µg/mL).

Given the retrospective nature of this study, there are specific limitations that must be recognized. There was variability in practice according to the physicians on the Acute Pain Service including the starting infusion rate of the

epidural infusion, the concentration of 2-chloroprocaine used (1.5% or 3%), and the concentration of clonidine in the epidural solution. However, in the majority of patients, the starting dose for clonidine was 0.1–0.2 µg/kg/hour. Although pain scores (FLACC or N-PASS) were recorded, assessments did not routinely include the use of a separate sedation score. Additionally, given that the identification of adverse effects may be problematic during a retrospective chart review, our ability to definitely comment on the adverse profile of epidural clonidine may be limited.

Within the constraints of these limitations, our preliminary data demonstrate the safety of adding clonidine to an epidural infusion of 2-chloroprocaine in infants less than 12 months of age with a large number (n=19) that were ≤3 months of age. The description of our clinical practice outlines dosing suggestions regarding both the 2-chloroprocaine infusion rates as well as the clonidine concentration. Future prospective studies are needed to compare 2-chloroprocaine with clonidine to 2-chloroprocaine alone to clearly determine if the combination is superior. Additionally, determination of the optimal clonidine concentration is currently speculative and based on limited pediatric data.

Disclosure

The authors have no conflicts of interest or funding sources to disclose.

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