Assessment of Outcomes With a Sedation Protocol During Laser Photocoagulation in Preterm Infants With Retinopathy of Prematurity

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OBJECTIVES To evaluate the success of a sedation protocol of fentanyl and midazolam infusions for infants undergoing laser photocoagulation for retinopathy of prematurity.

METHODS This retrospective study included infants receiving a sedation protocol for laser photocoagulation during a 4-year period. The primary objective was protocol success, defined as completion without interruption, absence of protocol dose deviations, and absence of interventions. Secondary objectives compared outcomes between those with and without opioid/benzodiazepine exposure. A logistic regression was used to assess the effect of prior opioid/benzodiazepine exposure on requirement for fentanyl infusion increases.

RESULTS Twenty-six infants were included. Seven (26.9%) had protocol success. Sixteen (61.5%) had protocol success, excluding dose deviations. Seventeen (65.4%) experienced ≥ 1 cardiopulmonary adverse events. Photocoagulation was completed in all cases.

CONCLUSIONS Most achieved protocol success, when eliminating dosing deviations. These data indicate that flexibility is needed in fentanyl and midazolam infusion titration, based on clinical response.

ABBREVIATIONS AEs, adverse events; aOR, adjusted odds ratio; CI, continuous infusion; CRI, cardiorespiratory index; EMR, electronic medical record; IV, intravenous; NICU, neonatal intensive care unit; N-PASS, Neonatal Pain Agitation and Sedation Scale; OU, both eyes; PMA, postmenstrual age; ROP, retinopathy of prematurity

KEYWORDS fentanyl, midazolam; neonatal intensive care; retinopathy of prematurity; sedation

J Pediatr Pharmacol Ther 2018;23(5):410–416

DOI: 10.5863/1551-6776-23.5.410

Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide and affects nearly 16,000 preterm infants in the United States annually. An estimated 1100 to 1500 progress to severe disease requiring medical intervention.^{1,2} Cryotherapy has traditionally been the treatment of choice. However, during the last 2 decades, there has been a general shift in treatment of ROP to favor laser photocoagulation surgery or intravitreal injection of vascular endothelial growth factor inhibitors over cryotherapy owing to fewer side effects and more positive outcomes.^{2–5}

Even though laser photocoagulation surgery has been commonly used for over 20 years, there is not a widely accepted guideline regarding sedation during the procedure. It may be performed in an operating room under general anesthesia or at the bedside under intravenous (IV) sedation. However, many practitioners prefer IV sedation owing to improved patient stability, avoidance of routine intubation, and shorter

recovery periods.^{6–9} Given this perceived justification for IV sedation during ROP laser photocoagulation surgery, there remains a paucity of data supporting the most appropriate sedation regimen. Three studies have evaluated an opioid continuous infusion (CI).^{8,10,11} One study evaluated morphine CI monotherapy, and another evaluated fentanyl CI monotherapy.^{8,11} Another study used an opioid CI along with supplemental doses of IV benzodiazepines.¹⁰ It is difficult to compare these studies, as the investigators used different endpoints and different regimens. None of the studies used an opioid and benzodiazepine CI regimen. Our institution implemented an IV fentanyl and midazolam CI protocol for infants undergoing ROP laser photocoagulation surgery in the neonatal intensive care unit (NICU) (Table 1). The rationale for this protocol was that it would maintain more of a consistent serum concentration of midazolam and fentanyl and avoid some of the potential adverse events (e.g., chest wall rigidity, hypotension) associated with intermittent dosing. The purpose of this study was to identify the number of patients with sedation success

Table 1. Retinopathy of Prematurity Laser Surgery IV Protocol

Medication	Dosing
Atropine	0.02 mg/kg as needed every 10-15 min for bradycardia (maximum of 0.04 mg/kg)
Cyclomydril ophthalmic	2 drops OU every 15 min times 2, starting 1 hr prior to procedure
Fentanyl	2 mcg/kg IV bolus 2 hrs before procedure 2 mcg/kg/hr CI Discontinued 30 minutes after procedure complete
Midazolam	0.1 mg/kg IV bolus 2 hrs before procedure 0.06–0.12 mg/kg/hr CI Discontinued at completion of procedure
Naloxone	0.1 mg/kg IV as needed for respiratory distress
Proparacaine HCl 0.5%	2 drops OU every 15 min times 2, starting 1 hr before procedure

CI, continuous infusion; OU, both eyes

receiving a standard protocol of fentanyl and midazolam CI during ROP laser photocoagulation surgery.

Materials and Methods

Study Design and Population. This retrospective, descriptive study was conducted in a tertiary care academic hospital with 88 NICU beds. This study included infants receiving a fentanyl and midazolam CI protocol for ROP laser photocoagulation surgery between January 1, 2012, and December 31, 2015. After Institutional Review Board approval, patients were identified within the electronic medical record (EMR) database. Children were excluded if they had incomplete records or if their procedure occurred under general anesthesia.

Study Objectives and Data Collection. Demographic data included postmenstrual age (PMA) (weeks) and chronologic age (weeks) at time of surgery, weight, and sex. Additional data were collected regarding baseline ventilation status prior to surgery, previous exposure to an opioid/benzodiazepine regimen in the 2 weeks prior to surgery (i.e., tolerant), and highest stage of ROP. The fentanyl and midazolam CI data collection included initial dose, final dose, cumulative exposure, and duration (hours). Additional data collected included need for termination or delay of surgery as reported in the EMR, dosage deviations from sedation protocol, and life-sustaining interventions (i.e., intubation and mechanical ventilation, atropine, naloxone).

The primary objective was to assess the success of the current sedation protocol for ROP laser photocoagulation surgery. Success was defined as completion of the procedure without interruption, a life-sustaining intervention required, and absence of a dose deviation from the sedation protocol. A secondary objective was to compare protocol outcomes between those patients who had opioid or benzodiazepine CI exposure within 2 weeks prior to ROP surgery and those who did not. An additional secondary objective was to identify the number of cardiopulmonary adverse events (AEs) including apnea, bradycardia, and hypotension. Apnea was defined as cessation of breathing ≥ 20 seconds.

Bradycardia was defined as heart rate < 60 beats per minute. For this study, hypotension was defined as mean arterial pressure < 30 mm Hg for patients < 37 weeks' PMA and mean arterial pressure < 45 mm Hg for patients ≥ 37 weeks' PMA.

Statistical Analysis. Descriptive statistics were computed for demographic and clinical variables. Point estimates for means and proportions were computed along with corresponding 95% confidence intervals. Data were dichotomized into opioid and benzodiazepine tolerant and naïve subjects. Comparisons of categorical variables were made by using a chi-square test or the Fisher exact test, as appropriate. Continuous variables were assessed for normality and compared between groups by using the Shapiro-Wilk test. To test the initial versus final dose protocol changes for fentanyl and midazolam, either the McNemar test or Bowker test for symmetry was used to assess whether subjects starting at a particular initial dose concentration changed to a different final dose concentration. Additionally, a logistic regression was performed to assess the requirement for a fentanyl CI dose increase while controlling for the independent variables of opioid exposure, benzodiazepine exposure, opioid and benzodiazepine exposure, chronologic age, and initial fentanyl dose classification. For the purpose of this analysis, initial fentanyl dosing was classified as subprotocol (i.e., dosing < 2 mcg/kg/hr), supraprotocol (dosing > 2 mcg/kg/hr), and per-protocol. The *a priori* level of significance was < 0.05 .

Results

Baseline Characteristics. Thirty-one patients underwent retinal photocoagulation for ROP during the study period. Of these, 5 were excluded from analysis. One patient was excluded because she received a hydromorphone and midazolam CI, and 1 patient was excluded for incomplete records. An additional 3 patients were excluded because their ROP laser photocoagulation surgery was completed under general anesthesia in the operating room in conjunction with other surgical procedures.

Table 2. Baseline demographics (n = 26)

Variable	Number (%) or Mean $\pm$ SD
Postmenstrual age (wks)	36.7 $\pm$ 1.72
Chronological age (wks)	11.5 $\pm$ 1.96
Sex, male	18 (69.2)
Weight (kg)	2.22 $\pm$ 0.50
Mechanical ventilation at baseline	5 (19.2)
Retinopathy of prematurity staging:	
Stage II	2 (7.7)
Stage II with plus disease	4 (15.4)
Stage III	8 (30.8)
Stage III with plus disease	12 (46.1)
Opioid and benzodiazepine prior exposure:	
Opioids	6 (23.1)
Benzodiazepines	5 (19.2)
Opioids AND benzodiazepines	2 (7.7)
Opioids OR benzodiazepines	9 (34.6)

A total of 26 patients were included in the analysis. Table 2 provides an overview of demographics. The mean PMA was 36.7 ± 1.7 weeks, and the mean chronological age was 11.5 ± 1.96 weeks at the time of procedure. Most were male (69.2%). Five (19.2%) were mechanically ventilated at baseline, while 15 (57.7%) required non-invasive modes of respiratory support (e.g., continuous positive airway pressure). The remaining patients (23.1%) required no respiratory support just prior to the procedure. Nine (34.6%) had been exposed to opioid or benzodiazepine CI in the 2 weeks prior to the procedure. There were significantly more infants with opioid or benzodiazepine CI exposure who were intubated at baseline versus those receiving non-invasive ventilation or room air at baseline, 4 (80.0%) versus 5 (23.8%), $p = 0.034$.

Sedation Protocol Outcomes. Table 3 provides an overview of IV fentanyl and midazolam exposure during the procedure. The mean initial fentanyl CI dose was 1.9 ± 0.7 mcg/kg/hr. Infants received their fentanyl CI for a mean duration of 4.5 ± 1.2 hours with a mean cumulative fentanyl dose of 10.6 ± 4.7 mcg/kg. The mean initial midazolam CI dose was 0.06 ± 0.02 mg/kg/hr. The mean duration of midazolam CI was 4.3 ± 1.2 hours, resulting in a mean cumulative dose of 0.4 ± 0.2 mg/kg.

Twenty patients (76.9%) were initiated on the recommended initial doses of fentanyl and midazolam CI. Fifteen (57.7%) had at least 1 dosage deviation with fentanyl and/or midazolam to achieve adequate sedation (Table 4). Four of these (26.7%) were initiated on fentanyl CI at a dose lower than protocol (i.e., 0.5 or 1 mcg/kg/hr) and 2 of these (13.3%) at a dose larger than the protocol (i.e., 2.5 and 4 mcg/kg/hr). Of those who were initiated at the protocol dose of 2 mcg/kg/hour ($n = 20$), 4 (20.0%) required an increase to a mean fentanyl CI dose of 3.2 ± 0.8 mcg/kg/hr owing to undersedation and increased movement and 5 (25.0%) required a

decrease to a mean of 0.74 ± 0.2 mcg/kg/hr secondary to development of hypotension and/or bradycardia. For midazolam CI, 3 patients (11.5%) were initiated on a dose lower than the protocol dose of 0.06 mg/kg/hour (i.e., 0.02 mg/kg/hr). Of those patients initiated at the protocol dose of 0.06 mg/kg/hr, 3 patients required a reduction in dose to a mean of 0.03 ± 0.01 mg/kg/hr owing to hypotension.

Table 5 provides an overview in vital sign changes during the procedure. Seventeen (65.4%) experienced at least 1 cardiopulmonary AE. There were significantly fewer AEs noted in infants who were intubated at baseline than in those receiving non-invasive ventilation or room air at baseline, 1 (20.0%) versus 16 (76.2%), $p = 0.034$. Six (23.1%) experienced apnea, and 7 (26.9%) developed bradycardia. Twelve (46.2%) met the criteria for hypotension.

Overall, 7 patients (26.9%) met the study definition for protocol success. Ten (38.5%) required a life-sustaining intervention; all of these patients were receiving non-invasive ventilation or room air at baseline (Table 4). Nine of these (34.6%) required intubation and mechanical ventilation. Most (77.8%) received the initial midazolam and fentanyl dose per protocol and did not receive

Table 3. Exposure of IV Fentanyl and Midazolam

Agent	Mean $\pm$ SD
Fentanyl	
Initial dose (mcg/kg/hr)	1.9 $\pm$ 0.7
Final dose (mcg/kg/hr)	2.0 $\pm$ 1.0
Cumulative dose (mcg/kg)	10.6 $\pm$ 4.7
Duration (hrs)	4.5 $\pm$ 1.2
Midazolam	
Initial dose (mg/kg/hr)	0.06 $\pm$ 0.02
Final dose (mg/kg/hr)	0.07 $\pm$ 0.03
Cumulative dose (mg/kg)	0.4 $\pm$ 0.2
Duration (hrs)	4.3 $\pm$ 1.2

Table 4. Reasons for Protocol Failure

Reason	Number (%)
Termination of procedure	0
Delay of procedure	3 (11.5)
Requiring an intervention:	
Intubation with mechanical ventilation	9 (34.6)
Naloxone	1 (3.8)
Atropine	0
Fentanyl or midazolam dose deviations:	
Midazolam OR fentanyl dose deviation	15 (57.7)
Smaller dose of fentanyl	9 (34.6)
Larger dose of fentanyl	6 (23.1)
Smaller dose of midazolam	6 (23.1)
Larger dose of midazolam	0

opioids or benzodiazepines in the 2 weeks prior to the procedure. One patient received naloxone secondary to respiratory depression. None of the patients with bradycardia were noted to receive atropine secondary to poor perfusion. Despite this, only 3 (11.5%) required a significant delay in their procedure as reported in the EMR, and no patient required early termination. If dose deviations were excluded from the definition of success, 16 patients (61.5%) achieved protocol success.

Regression Analysis. A logistic regression was performed to assess the requirement for a fentanyl CI dose increase while controlling for selected independent variables. Infants with no prior opioid or benzodiazepine exposure were 3 times more likely to require a fentanyl CI dose increase, but this was not statistically significant (adjusted odds ratio [aOR] 3.1, 95% CI: 0.3–33.1, $p = 0.35$). Two separate logistic regression models evaluated opioids and benzodiazepine exposure separately. Infants with no prior exposure to opioids (aOR 1.3, 95% CI: 0.09–18.0, $p = 0.85$) and no prior exposure to benzodiazepines (aOR 1.4, 95% CI: 0.1–15.9, $p = 0.80$) had increased odds of requiring a fentanyl CI dose increase, but these findings were not statistically significant. Chronologic age was not significantly associated with an increase in fentanyl dose.

Only 20 infants (76.9%) were initiated on the initial fentanyl CI protocol dosing. An attempt was made to perform a post hoc logistic regression in these patients who received the initial fentanyl CI dosing per-protocol to assess the requirement for a fentanyl CI dose increase while controlling for the independent variables of opioid exposure, benzodiazepine exposure, opioid and benzodiazepine exposure, chronologic age, and initial fentanyl dose classification. Owing to the limited sample size, this analysis was not performed.

Discussion

This is the first study to evaluate the use of an opioid and benzodiazepine CI sedation protocol in infants undergoing ROP laser photocoagulation surgery at the bedside. Intravenous sedation negates the need

for anesthesiology intervention, operating room availability, routine intubation, the possibility of prolonged mechanical intervention, and patient transfer, saving time and money.^{6,7} In addition, recent studies have suggested an association with neurocognitive delays and general anesthetics. Ing et al¹² performed a case-control analysis of children born from 1989–1992 exposed to general anesthetics before age 3 years. They found that children exposed to even 1 course of general anesthetics had an increase in language and cognitive deficits as compared to non-exposed children. Thus, these data have prompted clinicians to explore suitable alternatives for ROP laser photocoagulation surgery without general anesthesia.

Several studies have suggested IV opioid analgesia with or without benzodiazepine sedation may be a suitable and potentially safer alternative to general anesthesia for ROP laser photocoagulation surgery.^{8–13} Orge et al¹³ evaluated intermittent IV morphine versus fentanyl with or without IV benzodiazepines. Three studies evaluated the use of opioid CI with or without benzodiazepines.^{8,10,11} Sammartino and colleagues¹⁰ were the first to report their findings. They used a remifentanyl CI along with an IV midazolam bolus just prior to the procedure in 6 infants. All infants were intubated and mechanically ventilated at baseline. No episodes of hemodynamic instability were noted. They also noted that infants receiving fentanyl and/or morphine prior to the procedure required 2- or 3-fold larger doses of remifentanyl than opioid-naïve patients. It is difficult to compare their findings with our own considering the difference in opioid CI used and the fact that our protocol includes a midazolam CI. In addition, the authors did not define cardiopulmonary AEs.

Kirwan and colleagues⁸ retrospectively evaluated the efficacy of morphine CI as an alternative to general anesthesia in 109 infants, representing 136 ROP laser photocoagulation surgeries. Four (2.9%) were intubated and mechanically ventilated at baseline owing to chronic respiratory distress. Thirteen (9.6%) were electively intubated prior to the procedure owing to concerns

Table 5. Vital Sign Changes

Vital Signs	Baseline (Mean $\pm$ SD)	Lowest (Mean $\pm$ SD)	Percent Change (%) (Mean $\pm$ SD)
Heart rate (bpm)	147 $\pm$ 19.4	117 $\pm$ 26.4	20.0 $\pm$ 16.0
Respiratory rate (bpm)	43.0 $\pm$ 9.95	30 $\pm$ 7.6	28.0 $\pm$ 20.0
Systolic blood pressure (mmHg)	68.5 $\pm$ 6.99	57 $\pm$ 7.66	16.0 $\pm$ 12.0
Diastolic blood pressure (mmHg)	41.0 $\pm$ 11.3	28.5 $\pm$ 9.44	29.0 $\pm$ 18.0
Mean arterial pressure (mmHg)	50.4 $\pm$ 9.26	38.6 $\pm$ 8.29	22.0 $\pm$ 14.0

for apnea and poor procedure tolerance. Most (85.3%) patients remained on the same respiratory support they received prior to surgery. Twenty (14.7%) required an increase in respiratory support with 6 (4.4%) requiring intubation with mechanical ventilation. They noted only minor alterations in oxygen saturations, bradycardia, or tachycardia. These findings are difficult to compare to our study considering they used morphine CI and that they also did not define cardiopulmonary AEs.

A recent study by Jiang and colleagues¹¹ retrospectively evaluated the efficacy of fentanyl CI ($n = 47$), topical anesthesia ($n = 31$), and general anesthesia ($n = 19$) at the single center. At this institution, the standard anesthesia practice changed from topical anesthesia to general anesthesia, and then ultimately to fentanyl CI. Patients in the general anesthesia and fentanyl CI groups were intubated and mechanically ventilated prior to the procedure. The fentanyl group received a bolus of 2 mcg/kg, followed by 2 mcg/kg/hr. A cardiorespiratory index (CRI) score was calculated for each patient to facilitate comparisons of cardiorespiratory stability between groups preoperatively and postoperatively. There was no difference in cardiorespiratory stability between the general anesthesia and fentanyl CI group. In the fentanyl group, 8 infants (17.0%) demonstrated mild instability and 2 infants (4.2%) exhibited marked instability based on the CRI score. The Neonatal Pain Agitation and Sedation Scale (N-PASS) was documented every 20 minutes in the fentanyl group. The mean N-PASS score in the fentanyl group at baseline was 0.2 ± 0.8 and during the procedure was 1.8 ± 1.1 , but it is difficult to interpret these findings since the N-PASS scores were not documented in the other groups. Although the fentanyl CI dosing used in this study is the same as our protocol, it is difficult to directly compare the results to our study. First, they reported the mean CRI score for each of the groups, while we reported the individual events of apnea, bradycardia, or desaturations. In addition, to calculate their CRI score the authors used different definitions for cardiopulmonary AEs, so it is difficult to compare the rates of cardiopulmonary AEs. They collected N-PASS scores for the infants in the fentanyl group. We attempted to collect pain and sedation scores for our study; however, we noted that these were inconsistently documented. Lastly, all patients in the study by Jiang and colleagues¹¹ were

intubated prior to the procedure.

Only 1 study has evaluated the use of an IV fentanyl and midazolam protocol. In a letter to the editor, Spector and colleagues⁹ reported success with a fentanyl and midazolam protocol used in 15 infants who were not intubated prior to the procedure, but it is not clear from the letter if this was a fentanyl and midazolam CI versus intermittent dosing. They noted 9 (60%) tolerated the procedure well with no change in respiratory support. The other 6 (40%) required intubation during the procedure for apnea. No other details including cardiopulmonary AEs and dosing were provided.

Our opioid and benzodiazepine CI protocol for ROP laser photocoagulation surgery was adopted in 2011. This sedation protocol is used in most patients. By our definition, 7 patients (26.9%) had protocol success. Fifteen (57.7%) had at least 1 dosage deviation with fentanyl and/or midazolam, but 6 of these were not started on the recommended initial protocol dose. Of the 20 patients who were initiated at the recommended protocol dose, 9 (45.0%) required an upward or downward fentanyl titration. Possible explanations for these findings could include tolerance and interpatient variability. Nine (34.6%) had previous exposure to scheduled opioid or benzodiazepine CIs. Tolerance has been reported in 16% to 78% of children receiving fentanyl infusions, and risk factors include concomitant midazolam CI.^{14,15} To account for tolerance, we performed a logistic regression that included all 26 patients to assess the requirement for an increased fentanyl CI dose, controlling for factors including opioid and benzodiazepine exposure. We found that infants who were not exposed to benzodiazepines or opioid CIs had a 3.1 odds increase in requiring a fentanyl CI dose increase, but this was not statistically significant. It is difficult to interpret these results owing to the wide confidence intervals. In addition, it is possible that our definitions of benzodiazepine and opioid exposure may have been too conservative. Previous studies have noted that the risk for opioid tolerance is increased for children receiving scheduled opioids within a 1-year timeframe.^{14,15} It is possible that these infants may have received opioids and benzodiazepines during their NICU admission and thus required an increased fentanyl CI dose.

Another possible explanation for dosing deviations is interpatient variability. Katz and Kelly¹⁶ previously re-

ported wide interpatient variability in weight-normalized clearance of fentanyl CI, ranging from 207 to 2045 mL/kg/hr, so it could be proposed that the protocol should include a dosage range versus a set dose. This would allow for dose titration based on clinical response, similar to our midazolam dosing range. We propose that the fentanyl CI dose could be initiated at 2 mcg/kg/hr, titrated up or down by 0.5 mcg/kg/hr, with a minimum of 1 mcg/kg/hr and a maximum of 3 mcg/kg/hr, based on the mean doses received by those with a dose deviation in our study. Additionally, we recommend an initial midazolam CI dose at 0.06 mg/kg/hr, with an increase to 0.12 mg/kg/hr if inadequately sedated. Considering the potential for interpatient variability and fentanyl and midazolam tolerance, it may be likely that patients would require frequent dose changes to achieve optimal sedation. If dose deviations were taken out of the study definition, 16 (61.5%) would have had protocol success.

Seventeen (65.4%) had at least 1 cardiopulmonary AE. Of note, a significantly higher rate of AEs occurred in patients who were not mechanically ventilated at baseline. It is important to consider that there was also a significantly larger number of infants with opioid or benzodiazepine exposure in patients who were mechanically ventilated at baseline. Based on this finding, it is possible that these infants developed tolerance, and therefore may have been less prone to bradycardia and hypotension. Nine (34.6%) patients required intubation and mechanical ventilation. In 4 of the studies evaluating sedation protocol in non-intubated patients, approximately 4.4% to 40% had to be intubated owing to a cardiopulmonary AE.^{8–10,13} In the study by Kirwan and colleagues,⁸ 17 infants (15.6%) were either electively intubated or intubated at baseline, and they noted only 4.4% had to be intubated during the procedure. Thus, it is possible that the rate of intubation may have been greater if some of their high-risk infants were not electively intubated prior to the procedure. The decision to electively intubate prior to the procedure was not a part of our protocol, but rather, this decision was based on the infant's clinical status by the provider. By our study definition, 12 infants (46.2%) developed hypotension, and 7 (26.9%) developed bradycardia. In contrast, Kirwan et al⁸ found minimal changes in heart rate. It is difficult to compare our findings given that they did not define cardiopulmonary AEs. At this time, there also remains significant controversy over appropriate blood pressure goals in preterm infants.

There are limitations to this study that must be noted. First, this study included a small sample size and is subject to type II errors such as the observation that opioid- and benzodiazepine-naïve patients were 3.1 times more likely to require an increase in their fentanyl CI dose. Next, this was a descriptive study, which lacks the rigor

of a randomized, controlled trial comparing outcomes of infants receiving various opioid and sedation regimens during their ROP laser photocoagulation surgery. Given the prevalence of disease requiring treatment, it is difficult to overcome these barriers within a single center setting. Third, owing to inconsistent documentation of sedation and pain scores, we were unable to correlate dosing titration with adequate sedation and analgesia. Despite this, all patients successfully completed the procedure, and a significant delay was only noted in the EMR for 3 subjects.

Conclusions

This is the first study to evaluate the use of an opioid and benzodiazepine CI sedation protocol in infants undergoing ROP laser photocoagulation surgery. Sixteen (61.5%) patients had protocol success, when dose deviations were excluded from the definition. All patients successfully completed the procedure. These data indicate that in this population, physicians should prepare for frequent intraoperative dose titration based on clinical response, and more flexibility may be needed for fentanyl in our sedation protocol. A future prospective study is needed to compare efficacy and outcomes with different dosing strategies or alternative opioid and sedative agents to determine the optimal regimen for sedation and analgesia.

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Disclosures At the time of publication Dr Jamie L. Miller was on the speaker's bureau for Chiesi, USA, Inc. The rest of the authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data and take responsibility for the integrity and accuracy of the data analysis.

Acknowledgments Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Accepted May 31, 2017

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