Sedation Protocol During Bevacizumab Intravitreal Injection in Preterm Infants With Retinopathy of Prematurity

Jamie L. Miller, PharmD; Peter N. Johnson, PharmD; Kari Harkey, ADN; and R. Michael Siatkowski, MD

OBJECTIVES This study describes outcomes of intravenous (IV) analgesics and sedatives for bedside intravitreal bevacizumab injections for retinopathy of prematurity.

METHODS This retrospective study included infants receiving intravitreal bevacizumab injections between January 2012 and May 2016. Infants were excluded if bevacizumab was administered under general anesthesia or for incomplete records. Data collection included demographics, sedation and analgesia regimen, and cardiopulmonary adverse events (AEs). The primary objective was to identify the median doses of the IV analgesics and sedatives. The secondary objectives included the number of patients with cardiopulmonary AEs and those with procedure success, defined as procedure completion without interruption and absence of interventions.

RESULTS Fifteen infants were included. Fourteen (93.3%) were initiated on a fentanyl infusion at a median of 2 mcg/kg/hr (IQR, 2–3.6), and 12 (80%) received midazolam infusions at a median of 0.06 mg/kg/hr. All patients received at least 1 IV neuromuscular blocker dose just prior to the procedure. Only 2 patients (13.3%) required an increase in their fentanyl or midazolam infusions. Procedure success was achieved in 13 patients (86.7%). Five patients (33.3%) experienced 1 cardiopulmonary AE. One patient (6.7%) had a delay in the procedure, and 1 patient (6.7%) required naloxone. Despite this, the procedure was completed in all patients.

CONCLUSIONS Most received fentanyl and midazolam infusions with a dose of vecuronium just prior to the procedure. Thirteen (86.7%) met the criteria for procedure success. One-third experienced a cardiopulmonary AE. Future studies are needed to identify the optimal agents and route of administration for this procedure.

ABBREVIATIONS AE, adverse event; EMR, electronic medical record; ETT, endotracheal tube; IV, intravenous; MAP, mean arterial pressure; NPO, nothing by mouth; PMA, postmenstrual age; ROP, retinopathy of prematurity; SRS, Sedation Rating Scale; VEGF, vascular endothelial growth factor

KEYWORDS bevacizumab; fentanyl; midazolam; neonatal intensive care unit; retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) occurs secondary to abnormal growth of developing blood vessels in the immature retina. It is a leading cause of childhood blindness worldwide and affects nearly 16,000 preterm infants in the United States annually. Among these cases, an estimated 1100 to 1500 progress to severe disease requiring medical treatment.^{1,2} Despite the rarity of this severe disease, significant research in pathogenesis and treatment has occurred. There are currently 2 major treatment strategies for infants with ROP requiring intervention: ablative laser photocoagulation of the avascular retina and intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors.

VEGF is a potent inducer of angiogenesis, and thus

plays a significant role in the pathophysiology of the vasoproliferative phase of ROP. Bevacizumab has been the most widely studied of the currently available anti-VEGF agents;^{3–6} however, intravitreal injection of bevacizumab for ROP is an off-label route and indication.⁶ Intravitreal injection may be painful, and sedation/analgesia is required to optimize safety, as infant movement can increase the risk for iatrogenic cataracts or damage to the sclera. However, there is a paucity of literature regarding the most appropriate regimen for infants receiving intravitreal bevacizumab. Two studies^{7,8} have described the use of analgesic ± sedative agents for these injections. One involved the use of topical agents, and the other report described the use of anesthetic gases in the operating room. Our institution has adopted a protocol for ROP procedures

Table 1. Retinopathy of Prematurity Bedside Protocol

Medication	Dosing
Proparacaine HCl 0.5% ophthalmic	2 drops into affected eye every 15 min times 2, starting 1 hr prior to procedure
Cyclopentolate HCl 0.2% and phenylephrine HCl 1% ophthalmic	2 drops into affected eye every 15 min times 2, starting 1 hr prior to procedure
Atropine	0.02 mg/kg as needed every 10–15 min for bradycardia (maximum of 0.04 mg/kg)
Naloxone	0.1 mg/kg IV as needed for respiratory distress

IV, intravenous

at the bedside, including laser photocoagulation and intravitreal bevacizumab that includes topical anesthetics, mydriatics, and agents to address adverse events (AEs) (Table 1). Clinicians have also used intravenous (IV) sedative and analgesic agents along with a neuromuscular blocker to facilitate the success of the procedure. As a result, all patients are electively intubated and placed on mechanical ventilation for the duration of the procedure. To date, the use of IV sedative and analgesic agents for intravitreal bevacizumab injections at the bedside has not been formally analyzed. The purpose of this study was to describe the IV sedative and analgesic regimens, and its overall effect on procedure success.

Methods

Study Design. This was a retrospective, descriptive case series conducted in a tertiary care academic hospital with 88 Neonatal Intensive Care Unit beds. Patients were included if they received intravitreal bevacizumab for ROP between January 1, 2012, and May 31, 2016. Patients were excluded if they had incomplete medical records or if their procedure was performed in the operating room. Patients were identified through the nurse coordinator's records and the institution's electronic medical record (EMR) database.

Objectives and Data Collection. Demographic data included postmenstrual age (PMA) (weeks) and chronological age (weeks) at time of the procedure, weight, and sex. Additional data were collected regarding baseline respiratory status prior to the procedure (e.g., room air, mechanical ventilation), need for intubation for procedure, previous exposure to an opioid/benzodiazepine regimen in the 2 weeks prior to procedure, and stage of ROP. The IV sedative and analgesic regimens were collected and included initial and final dose. To assess comfort during the procedure, the Sedation Rating Scale (SRS) was documented every 5 minutes, with a goal score of 1 to 2 (1 = No response; 2 = Responds to painful stimuli; 3 = Responds to tactile stimuli; 4 = Arouses easily; 5 = Fully awake). Data collection also included the time to preprocedure feeding status in patients who were receiving feeds prior to the procedure. In addition, the time to extubation was

determined in infants who were specifically intubated for the procedure.

The primary objective was to identify the median doses of the IV sedative and analgesic agents used for the intravitreal bevacizumab injection. The secondary objectives included the number of patients with procedure success and the frequency of AEs. Success was defined as completion of the procedure without interruption and absence of interventions (e.g., atropine and naloxone) for cardiopulmonary AEs. Cardiopulmonary AEs included desaturations, bradycardia, and hypotension. Desaturations were defined as a decrease in oxygen saturation < 85%. Bradycardia was defined as heart rate < 60 beats per minute. For this study, hypotension was defined as mean arterial pressure (MAP) < 30 mm Hg for patients < 37 weeks PMA and MAP < 45 mm Hg for patients ≥ 37 weeks PMA. Descriptive statistics were used.

Results

During the study period, 59 patients underwent an ROP procedure. Thirty-six infants (61.0%) underwent laser photocoagulation. Twenty-three infants (38.9%) received intravitreal bevacizumab injections. Three of these were excluded because their procedure was performed in the operating room under general anesthesia. Five were excluded owing to incomplete medical records.

Table 2 includes the baseline demographics and clinical characteristics of the 15 infants included for analysis. Most were male with a median PMA of 35.0 weeks (IQR, 33.4–36.5). Nine infants (60.0%) had stage III ROP. Seven infants (46.7%) required invasive ventilation via the endotracheal tube (ETT) prior to the procedure. The remaining infants received non-invasive ventilation (n = 7) or room air (n = 1) prior to the procedure. As a result, all 8 of these were electively intubated for the procedure. Ten patients (66.7%) were receiving enteral feeds, while the remaining patients were not given anything by mouth on parenteral nutrition prior to procedure. Most patients (80.0%) were exposed to opioids within the 2 weeks prior to the procedure.

All patients received an opioid continuous infusion with morphine (n = 1) or fentanyl (n = 14) (Table 3). The

Table 2. Patient Demographics and Characteristics (N = 15)

Variable	Number (%) or Median (IQR)
Gestational age, wk	25.5 (24.1–26.3)
Chronological age, wk	9.3 (8.6–11.9)
PMA, wk	35.0 (33.4–36.5)
Male	11 (73.3)
Weight, kg	1.9 (1.7–2.1)
ROP staging	
Stage II with plus disease	6 (40.0)
Stage III	5 (33.3)
Stage III with plus disease	4 (26.7)
Respiratory support at baseline	
Room air	1 (6.8)
High-flow nasal cannula	3 (20.0)
Continuous positive airway pressure	2 (13.3)
Neurally adjusted ventilator assist	2 (13.3)
Mechanical ventilation	5 (33.3)
High-frequency jet ventilator	2 (13.3)
Intubated for procedure	8 (53.3)
NPO at baseline	5 (33.3)
Opioid and benzodiazepine prior exposure	
Opioids	12 (80.0)
Benzodiazepines	5 (33.3)

NPO, nothing by mouth; PMA, postmenstrual age; ROP, retinopathy of prematurity

median initial fentanyl dose was 2 mcg/kg/hr (IQR, 2–3.6), and only 1 patient (6.7%) required an increase in infusion rate. Seven infants (46.7%) required at least 1 fentanyl bolus, with a median cumulative dose of 1 mcg/kg (IQR, 2–3). The patient receiving a morphine infusion was initiated at 0.05 mg/kg/hr and did not require an increase in infusion rate or a bolus dose.

Twelve (80.0%) received midazolam continuous infusions (Table 3). The median initial dose was 0.06 mg/kg/hr, and 1 patient required an increase in infusion rate. Five infants (33.3%) required at least 1 midazolam bolus, with a median cumulative dose of 0.1 mg/kg (0.09–0.14). All patients received at least 1 dose of IV vecuronium (n = 14) or rocuronium (n = 1) (Table 3). Four infants (26.7%) required more than 1 vecuronium dose.

The median duration of the procedure (including preinjection sterile preparation, preparation of injection site, administration of medication, and postinjection measurement of intraocular pressure) was 15 minutes (IQR, 15–27.5). When injections were bilateral, eyes were prepped separately as if it were 2 different procedures. SRS scores were available for 12 patients. The median minimum score was 1 (IQR, 1–1.3), and the median maximum score was 2 (1–2.3).

Table 4 provides an overview of vital sign changes during the procedure. Five patients (33.3%) had at least 1 cardiopulmonary AE (Table 5). Two patients (13.3%) had only 1 event, while another 2 patients (13.3%) had 2 events. One patient had all 3 cardiopulmonary AEs evaluated. This patient was noted to have an obstructed ETT. The patient was extubated, and the ETT was replaced. Following this intervention, the symptoms resolved, and the patient successfully completed the procedure.

Overall, 13 patients (86.7%) met the definition of procedure success. One patient required naloxone secondary to oxygen desaturation, not responding to an increase in oxygen delivery. The other patient required a delay in the procedure owing to the obstructed ETT as described above. In the 10 patients who were receiving enteral feeds prior to the procedure, the median time to return of baseline feeding status was 28 hours (IQR, 7–40). For the 8 patients who required elective intubation for the procedure, the median time to extubation was 33.5 hours (IQR, 17.1–79.9). Six of these (75.0%) were extubated within 48 hours after the procedure, while the other 2 patients required mechanical ventilator support for 171 to 175 hours.

Table 3. Exposure of IV Neuromuscular Blockers, Opioids, and Benzodiazepines

Agent	Median (IQR)
Neuromuscular blocker	
Vecuronium (n = 14)	
Number of doses	1 (1–2.5)
Dose, mg/kg	0.1 (0.1)
Rocuronium (n = 1)	
Number of doses	1
Dose, mg/kg	0.28
Opioid	
Fentanyl (n = 14)	
Initial infusion rate, mcg/kg/hr	2 (2–3.6)
Number of boluses	0 (0–1)
Cumulative bolus dose, mcg/kg	2 (2–3)
Final infusion rate, mcg/kg/hr	2 (2–4)
Morphine (n = 1)	
Initial infusion rate, mg/kg/hr	0.05
Number of boluses	0
Cumulative bolus dose, mg/kg	0
Final infusion rate, mg/kg/hr	0.05
Midazolam (n = 12)	
Initial infusion rate, mg/kg/hr	0.06 (0.06)
Number of boluses	0 (0–1)
Cumulative bolus dose, mg/kg	0.1 (0.09–0.14)
Final infusion rate, mg/kg/hr	0.06 (0.06–0.08)

IV, intravenous

Discussion

This is the first study to evaluate the use of IV analgesic ± sedative infusions for intravitreal bevacizumab injections at the bedside. Although it is of short duration, it is generally understood that this is a very uncomfortable procedure, and it is essential that the infant be immobile to prevent iatrogenic cataract formation or damage to the sclera from inadvertent placement of the needle.⁹ We believe that it is essential that analgesics ± sedative agents be used for the procedure to ensure success and maximize safety, but the optimal agents and routes have not been identified to date. Our institution has an IV sedative and analgesic protocol in place for laser photocoagulation at the bedside.¹⁰ However, clinicians at our institution have anecdotally adapted elements for the protocol to facilitate this procedure, using an IV opioid and benzodiazepine infusion along with at least 1 dose of an IV neuromuscular blocker agent to keep the patient comfortable and still and to avoid the need for general anesthesia in the operating room.

Only 2 studies^{7,8} have specifically evaluated pain and/or sedation in infants undergoing bevacizumab

intravitreal injections. Castellanos et al⁷ evaluated the Premature Infant Pain Profile scores in 9 infants receiving intravitreal bevacizumab under topical anesthesia with 1 drop of tetracaine hydrochloride 0.5 g/mL. All patients completed the study, and the mean total pain score was 8.7 ± 2.4 (range, 5–14), indicating mild to significant pain was observed. However, the investigators noted 7 infants (77.8%) cried throughout most of the procedure. Our protocol includes the use of both topical anesthetics and mydriatics. However, these agents alone are insufficient to prevent adequate analgesia and undesired patient movement and tear production associated with crying. Both movement and tear production have the potential to affect the accuracy of the needle during the injection. It is difficult to compare these pain scores with our own data because we used a different scoring tool to assess comfort during the procedure. The SRS scores documented in the procedure illustrated that our patients had an appropriate level of sedation with the median minimum and maximal scores between 1 and 2.

Another study by Tokgoz and et al⁸ evaluated the use

Table 4. Vital Sign Changes (N = 15)

Vital Signs	Baseline Median (IQR)	Lowest Median (IQR)	Percentage Change (IQR)
Heart rate, beats/min	145 (138.5–151)	124 (110–146)	13.1 (3.6–17.1)
Respiratory rate, breaths/min	44.0 (40–49)	40.0 (32–43)	9.1 (0–31)
Oxygen saturation, %	94.0 (92.5–95)	92.0 (90.5–94.5)	2.1 (-1.1–5.8)
Systolic blood pressure, mm Hg	63.0 (59.5–68.5)	59.0 (55–61.5)	6.3 (1.7–18.5)
Diastolic blood pressure, mm Hg	37.0 (33–43)	30.0 (27–32)	13.5 (0–36)
MAP, mm Hg	45.0 (42–50)	41.0 (38–42.5)	7.7 (2.5–20.9)

MAP, mean arterial pressure

of general anesthesia with sevoflurane in 33 infants receiving intravitreal bevacizumab injections. Anesthesia was received for a total mean duration of 10.2 ± 1.7 minutes during the first intravitreal injection. All procedures were successfully completed with no adverse effects; however, no pain scores were reported. The concern with inhaled anesthesia is the need for an operating room and anesthetic management, resulting in higher expenses, as well as the poor neurodevelopmental effects associated with general anesthetics. Ing et al¹¹ performed a case-control analysis of children born between 1989 and 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 many clinicians to explore suitable alternatives for analgesia and sedation for ROP procedures.

No other studies have evaluated the use of an IV analgesic plus sedation regimen to facilitate bedside intravitreal bevacizumab injections. All infants received a fentanyl or morphine infusion, and most (80%) received a midazolam infusion. In addition, all infants received at least 1 dose of an IV neuromuscular blocker. Two prior studies^{10,12} have described the use of an IV opioid and benzodiazepine regimen for ROP laser photocoagulation. Overall, approximately 60% of infants in these reports successfully completed the procedure without termination or interventions, compared to 86.7% in the present study. Our success rate in this study may have been higher given that the procedure lasted a median of 15 minutes, which is significantly shorter than laser photocoagulation (1–2 hours). This may have also been due to the fact that all infants received at least 1 dose of vecuronium or rocuronium just prior to intravitreal bevacizumab.

Since an IV neuromuscular blocker agent was administered, all infants were required to be intubated and placed on mechanical ventilation for the procedure. Eight infants (53.3%) had to be intubated for the procedure. There may be concern about the use of sedation, analgesia, and neuromuscular blockade because of the need for intubation and mechanical ventilation for this procedure as there are inherent risks with intubation. However, topical anesthesia alone seems inadequate

at providing an appropriate level of pain control and provides no sedation. In addition, all infants who receive general anesthesia would have to be intubated as well. The median time to extubation in this study was 33.5 hours. Most (75.0%) were extubated within 48 hours of the procedure. Considering that the median gestational age was 25.5 weeks, this delay in extubation may have been due to complications with bronchopulmonary dysplasia rather than the sedative and analgesic regimens themselves. It is possible that these same infants may have had a delay in extubation had they undergone general anesthesia for the procedure.

Five infants (33.3%) had at least 1 cardiopulmonary AE. Owing to the small sample size, it is very difficult to determine what factors put a patient at greater risk of cardiopulmonary AEs. It is difficult to compare these findings to those of Tokgoz et al,⁸ as they did not provide definitions for their cardiopulmonary AEs. Despite this, only 1 patient required an intervention with a dose of naloxone for oxygen desaturation, not responding to conventional therapy. Only 1 infant had a delay in the procedure; this infant had hypotension, bradycardia, and oxygen desaturation. It was noted in the EMR that the ETT was obstructed, and that these cardiopulmonary AEs were not associated with the analgesics and sedatives. The ETT was changed, and the infant successfully completed the procedure.

There are limitations to this study that must be noted. First, this study included a small sample size. 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 versus general anesthesia for their intravitreal bevacizumab injections. In addition, we were unable to compare the outcomes associated with different opioid and benzodiazepine doses. Third, based on the retrospective design, it is difficult to determine if the cardiopulmonary AEs were directly attributed to the opioid and benzodiazepine agents. Despite this, all patients successfully completed the procedure, and a significant delay was noted only in 1 infant.

Further work needs to be conducted to determine the best approach for analgesia and sedation for bevacizumab intravitreal injections. This may include comparison of opioids $\pm$ sedatives administered via

Table 5. Reasons for Procedure Failure and Cardiopulmonary Adverse Events (N = 15)

Reason	Number (%)
Termination of procedure	0
Delay of procedure	1 (6.7)
Requiring an intervention	
Naloxone	1 (6.7)
Atropine	0
Cardiopulmonary adverse effects (n = 5)	
Bradycardia	2 (13.3)
Desaturations	3 (20.0)
Hypotension	4 (26.7)

continuous infusions versus intermittent IV dosing or alternative routes of administration (e.g., intranasal, buccal). In addition, future studies should be conducted to determine whether administration of neuromuscular blocker agents is required to keep the baby still and ensure safety during the procedure. It is possible that this could be achieved with analgesia and sedation alone and may remove the requirement for elective intubation for the procedure. In a previous study from our institution, evaluating an IV opioid and benzodiazepine infusion protocol for laser photocoagulation, we noted that approximately 40% of patients not on mechanical ventilation were intubated during the procedure.¹⁰ Until future studies can be conducted, clinicians wishing to implement an IV analgesia and sedation regimen for intravitreal bevacizumab injections may implement our general dosing recommendations based on the median doses found in this report. We propose that fentanyl could be initiated at 2 mcg/kg/hr, titrated up or down by 0.5 mcg/kg/hr, to a maximum of 4 mcg/kg/hr. For midazolam, we recommend an initial midazolam dose of 0.06 mg/kg/hr, titrated up or down by 0.02 mg/kg/hr, to a maximum of 0.1 mg/kg/hr. Additionally, we recommend 1 dose of IV vecuronium 0.1 mg/kg be administered approximately 5 to 10 minutes before the bevacizumab injection.

Conclusion

Most infants in this study received fentanyl and midazolam infusions with a dose of vecuronium just prior to the bedside intravitreal bevacizumab injection. Thirteen (86.7%) met the criteria for procedure success. One-third experienced a cardiopulmonary AE, but only 1 patient required an intervention. Physicians could complete the procedure in all patients. This case series suggests the need for standardization of analgesia/sedation for intravitreal injections of bevacizumab.

ARTICLE INFORMATION

Affiliations Department of Pharmacy (JLM, PNJ), Clinical and Administrative Sciences at the University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma, The Children's Hospital at OU Medical Center (KH), Oklahoma City, Oklahoma, and Department of Ophthalmology/Dean McGee Eye Institute (RMS), University of Oklahoma College of Medicine, Oklahoma City, Oklahoma

Correspondence Jamie L. Miller, PharmD;
jamie-miller@ouhsc.edu

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