

# Pain assessment in premature infants treated with intravitreal antiangiogenic therapy for retinopathy of prematurity under topical anesthesia

Maria Ana Martínez Castellanos · Shulamit Schwartz ·  
Ricardo Leal · Robison Vernon Paul Chan ·  
Hugo Quiroz-Mercado

Received: 20 February 2012 / Revised: 1 May 2012 / Accepted: 3 May 2012 / Published online: 18 May 2012  
© Springer-Verlag 2012

## Abstract

**Purpose** To evaluate the physiological and behavioral pain response in premature infants receiving intravitreal bevacizumab injection (IVB) for retinopathy of prematurity (ROP) under topical anesthesia.

**Methods** A prospective interventional non-comparative case series. Premature infants with high-risk prethreshold or threshold ROP received IVB using topical anesthesia with tetracaine eye drops. A Premature Infant Pain Profile was used to assess the pain response during the procedure.

**Results** Nine premature infants requiring bilateral IVB therapy were included in the study. Mean gestational age was  $28.7 \pm 1.3$  weeks, and birth weight was  $1,200 \pm 194$  grams. The mean total pain score was found to be  $8.7 \pm 2.4$  (range 5–14), indicating generally mild pain during the procedure. Eye squeeze was the most prominent indicator of pain. Most changes occurred at the beginning, with the insertion of the lid speculum and were hardly noted during the rest of the procedure including the injection itself.

**Conclusion** Topical anesthesia with tetracaine is an effective method for the relief of pain associated with intravitreal injections in premature infants with ROP.

**Keywords** Retinopathy of prematurity · Intravitreal injections · Bevacizumab · Local anesthesia

The authors have full control of all primary data, and they agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data upon request.

Authors have no financial relationship with the manufacturer of any product discussed in this manuscript.

Clinical Trials Registration Number: NCT00346814

M. A. M. Castellanos · R. Leal  
Retina Service Asociación para Evitar la Ceguera en México,  
Hospital "Luis Sanchez Bulnes" I.A.P.,  
Mexico City, Mexico

M. A. M. Castellanos  
Early Detection of Retinopathy of Prematurity Program,  
Hospital de Especialidades "Belisario Domínguez"  
Gobierno del Distrito Federal,  
Mexico City, Mexico

S. Schwartz (✉) · H. Quiroz-Mercado  
Ophthalmology Department, Denver Health Medical Center,  
University of Colorado Denver,  
777 Bannock St.,  
Denver, CO 80204, USA  
e-mail: schwartz330@gmail.com

R. V. P. Chan  
New York-Presbyterian Hospital, Will Cornell Medical College,  
New York, NY, USA

## Introduction

Retinopathy of prematurity (ROP) is a neovascular retinal disorder, affecting premature infants of low birth weight. It represents one of the leading causes of childhood blindness in the United States and worldwide.

Since the 1980s, peripheral retina ablation is the gold standard of care. It has recently been understood that vascular endothelial growth factor (VEGF) plays an important role in its multifactorial pathogenesis. Beginning in 2008, several reports presented promising experience with off-label use of intravitreal bevacizumab (IVB) in infants with progressive ROP [1, 2].

Anesthesia is an important component of the injection process. The four commonly used topical anesthetic techniques for intravitreal injections in adults are: drops, viscous gels, anesthetics administered on pledget or cotton tip, and

**Table 1** The Premature Infant Pain Profile (PIPP) scoring system\*

Process	Indicator	0	1	2	3	score
Chart	Gestational age	36 weeks and more	32–35 weeks, 6 days	28–31 weeks, 6 days	Less than 28 weeks	
Observe infant 15 s	Behavioral state	Active/ awake Eyes open facial movements	Quiet/ awake Eyes open No facial movements	Active/ sleep Eyes closed facial movements	Quiet/ sleep Eyes closed No facial movements	
Observe infant 30 s to determine maximum reading	Heart rate max	0-4 beats/min increase	5-14 beats/min increase	15-24 beats/min increase	25 beats/min or more increase	
	Oxygen saturation min	0–2.4 % decrease	2.5–4.9 % decrease	5.0–7.4 % decrease	7.5 % or more decrease	
	Brow bulge	None: 0–9 % of time	Minimum: 10–39 % of time	Moderate: 40–69 % of time	Maximum: 70 % of time or more	
	Eye squeeze	None: 0–9 % of time	Minimum: 10–39 % of time	Moderate: 40–69 % of time	Maximum: 70 % of time or more	
	Nasolabial furrow	None: 0–9 % of time	Minimum: 10–39 % of time	Moderate: 40–69 % of time	Maximum: 70 % of time or more	Total score

\*Stevens et al. [6]

subconjunctival injections [3]. A few small studies have attempted to address adult patient perceptions of pain and discomfort associated with various methods of anesthesia [4]. All concluded that with proper anesthetic technique, intravitreal injections can be almost painless.

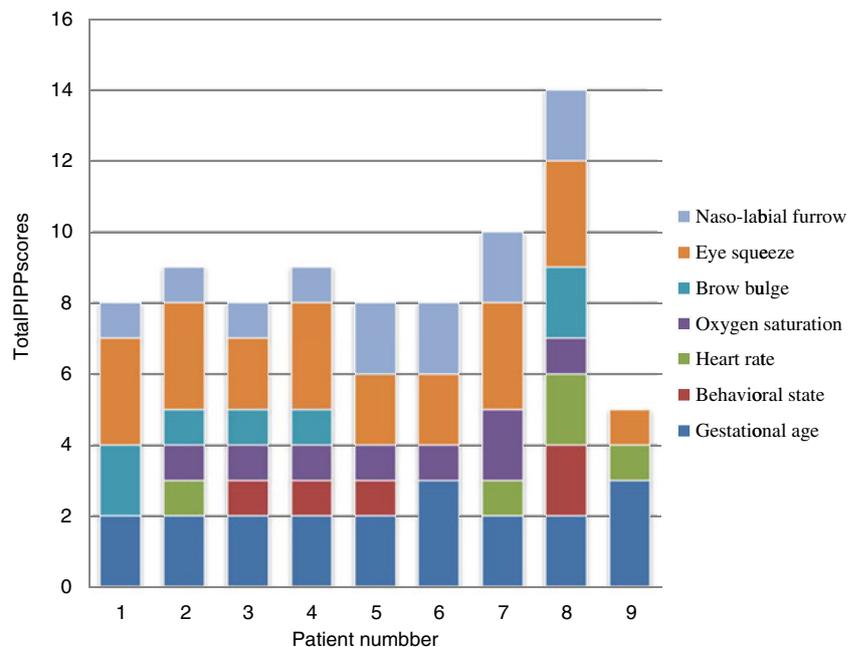
Sedation and general anesthesia are common practice in ablation therapy [5]. They are less favorable in premature infants, and can result in perioperative systemic complications. The appropriate anesthesia for intravitreal drug therapy in premature infants is one of the issues that were not addressed yet.

The aim of our study was to evaluate the pain response in premature infants receiving IVB for ROP under topical anesthesia.

## Methods

We conducted a prospective interventional non-comparative trial in Mexico City in 2009, approved by the IRB and performed in accordance with the ethical standards of the Declaration of Helsinki. Premature infants with high-risk prethreshold (Type 1) or threshold ROP were included in the study. Exclusion criteria were: acute illness, mechanical ventilation, treatment with inotropic drugs, major congenital anomalies, neurological deficits, or hypersensitivity to anesthetic drugs or bevacizumab. Parents provided written informed consent for all enrolled participants. All received bilateral IVB by a single retina specialist. Treatment technique included skin

**Fig. 1** Graph showing comparison of PIPP scores for each patient



and eyes preparation with 5 % povidone–iodine, local anesthesia with one drop of topical tetracaine hydrochloride 0.5 g/ml (Ponti Ofteno, Laboratorios Sophia S. A. de C.V.), insertion of a premature lid speculum followed by intravitreal injection of bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA) 0.625 mg/0.025 ml using a 30-gauge needle, 1 mm from the limbus.

Pain was assessed, immediately after the application of the anesthetic eye drops, by a single neonatologist. We used the Premature Infant Pain Profile (PIPP) scoring system (Table 1) developed and validated by Stevens et al. for assessment of pain in premature infants undergoing painful procedures [6]. The maximum attainable total score is 21–18, depending on GA; the youngest GA infant has the highest possible score. For all age groups, PIPP scores <7 indicate no pain, 7 to 12 mild pain and >12 significant pain.

## Results

Nine consecutive premature infants (five females and four males) were included in the study. The mean GA was  $28.7 \pm 1.3$  weeks (range: 27–31), birth weight was  $1200 \pm 194$  grams (range: 940–1,460) and age at the time of injection was  $33.5 \pm 2.4$  weeks (range: 31–38.4). The mean total pain score recorded during the whole procedure was  $8.7 \pm 2.4$  (range 5–14). Seven infants (77.8 %) experienced only mild pain (PIPP score of 7–12). Eight infants were awake during the injections, 62.5 % of them actively crying the majority of the time. Fig. 1 shows that eye squeeze was the most prominent indicator of pain, noticed at least 40 % of the time. Most changes occurred during the insertion of the lid speculum, and were hardly noted during the rest of the procedure including the injection itself. None of the infants required additional local or systemic anesthesia. No systemic or ocular side-effects related to anesthesia or IVB were observed.

## Discussion

Antiangiogenic intravitreal therapy is an emerging modality for the treatment of ROP that may lead to a shift in the present standard of care. It is a short procedure that doesn't require special equipment, and can be carried out with short-acting topical anesthesia.

Proparacaine, tetracaine, lidocaine, and benoxinate are the most commonly used topical ophthalmic anesthetics today [7]. All exhibit a rapid onset of action and a short to intermediate duration of efficacy. They are generally safe and well-tolerated, but can be toxic when abused. The risk

of systemic effects is very low, since little if any of the drops is absorbed into the blood.

Premature infants are difficult to assess, especially when they are very young or critically ill. We used the PIPP scoring system, which provides a more accurate pain assessment and proved to be a useful clinical tool.

We found a mean PIPP score of 8.7, which reflects a limited discomfort and pain. Our results cannot be compared to any other studies since all were performed in adults, using different scoring systems and mainly based on patient's experience.

The ophthalmological examination for ROP itself can be painful and distressing. Most studies support the use of topical proparacaine 0.5 %, which marginally decreased pain without any side effects [8]. Similar to our findings, the insertion of a lid speculum is the most uncomfortable aspect of the examination. Recently, Cagen et al. reported PIPP scores of 10.4 and 8.8 for artificial tears and topical anesthetic groups respectively ( $p=0.17$ ) for ROP examinations [9]. We found similar results, showing that intravitreal injections are probably less painful than the routine ophthalmic screening examination. Up to 77.8 % of our patients experienced only mild pain during the whole procedure.

A limitation of the study was the need to measure a total score for a short procedure lasting less than 5 minutes. Mehta et al. compared the effect of saline vs proparacaine drops on PIPP scores at 1 and 5 minutes after ROP examination [10]. Proparacaine lowered discomfort in the immediate post-examination period, with no significant difference 5 minutes after.

In conclusion, topical anesthesia with a short-acting agent such as tetracaine is an effective method for pain relief, associated with intravitreal injections in premature infants with ROP. It is of special concern in premature infants with other co-morbidities, who often cannot undergo longer procedures with general anesthesia.

## References

- Quiroz-Mercado H, Ustariz-González O, Martínez-Castellanos MA, Covarrubias P, Domínguez F, Sánchez-Huerta V (2007) Our experience after 1765 intravitreal injections of bevacizumab: the importance of being part of a developing story. *Semin Ophthalmol* 22(2):109–125
- Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group (2011) Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 364(7):603–615
- Prenner J (2011) Anesthesia for Intravitreal injection. *Retina* 31(3):433–434
- Blaha G, Tilton E, Barouch F, Marx J (2011) Randomized trial of anesthetic methods for intravitreal injections. *Retina* 31:535–539
- Chen SD, Sundaram V, Wilkinson A, Patel CK (2007) Variation in anaesthesia for the laser treatment of retinopathy of prematurity—a survey of ophthalmologists in the UK. *Eye* 21(8):1033–1036
- Stevens B, Johnson C, Taddio A (1996) Premature Infant Pain Profile: development and initial validation. *Clin J Pain* 12:13–22

7. McGee HT, Fraunfelder FW (2007) Toxicities of topical ophthalmic anesthetics. *Expert Opin Drug Saf* 6(6):637–640
8. Kandasamy Y, Smith R, Wright I, Hartley L (2011) Pain relief for premature infants during ophthalmology assessment. *J AAPOS* 15(3):276–280
9. Cogen M, Parker J, Sleep T, Elsas F, Metz T, McGwing G (2011) Masked trial of topical anesthesia for retinopathy of prematurity eye examinations. *J AAPOS* 15(1):45–48
10. Mehta M, Mansfield T, Vander Veen DK (2010) Effect of topical anesthesia and age on pain scores during retinopathy of prematurity screening. *J Perinatol* 30(11):731–735