A comparison of intraocular pressure changes throughout general anesthesia in infants and children undergoing intravitreal chemotherapy injections: a pilot study.

Ana Mavarez, MD; Benjamin Pruden, MD; Luis Rodriguez, MD; Caroline Ripat, MD, MPH ;Daniel Baux, BS; Linda Cernichiaro-Espinosa, MD; William Harbour, MD; Audina Berrocal, MD; Jacqueline Tutiven, MD; Alecia Stein, MD

Department of Anesthesiology, Perioperative and Pain Medicine, Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, Miami, Florida

Introduction

- Retinoblastoma (Rb) is the most common primary intraocular malignancy in children, goals in treatment are to eradicate tumor load while preserving as much vision as possible.
- Treatment options include systemic and intra-arterial chemotherapy via the ophthalmic artery, radiation, laser therapy and eventually, enucleation.
- In addition to intra-arterial chemo reduction via the ophthalmic artery, adjuvant intravitreal injection of chemotherapeutic agents (iViC), such as mephalan or topotecan target vitreous seeding as an effort to delay eye enucleation.[1]
- iViC treatments are indicated in other retinal pathologies and used in noncancerous eyes.
- iViC treatment carries an associated risk of extraocular tumor spread from reflux of chamber contents following IOP increase and scleral pressure gradient changes.[2]
- Data on the effects of iViC on intraocular pressure (IOP) in anesthetized children is lacking.

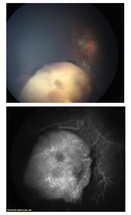
Objective

- The aim of the study was to compare temporal IOP changes in Rb and nonRb eyes receiving iViC at key points throughout an anesthetic.
- We hypothesized that Rb group would have higher IOPs than non-Rb eyes after iViC, due to increase intraocular contents.
- Pending results, would examine effects of noninvasive anesthetic maneuvers to reduce IOP.

Methods

- IRB approved retrospective study of 30 children (<18 y/o); 46 eyes, over a 2 years and 10 months period, from February 2015 to November 2017.
- General anesthesia was induced and maintained via inhaled sevoflurane/O_2/air combination; the airway secured a supraglottic airway, after IV access had been obtained and propofol /glycopyrrolate given.
- IOP measurement were obtained via tonometry (Tono-pen, Reichert, Inc. Buffalo, NY) at four peri-anesthetic times: Post-induction, Pre-iViC, Post-iViC and Pre-emergence.
- IViC agents and dosing concentrations: bevacizumab (1.25mg/0.05ml), melphalan (20µg/0.05ml) and topotecan (6.5µg/0.015ml)
- Continuous variables were compared with student's two sample t-test and Pearson's chi-square test. Fisher's exact test for categorical variables.

Measurement of IOP with Tono-pen Pre-iViC in a 2 month old infant. Bascom Palmer Eye Institute



Retinal pigment epithelial alterations in retinoblastoma with vitreous seeding (upper figure) and enhancement on fluorescein angiography (lower figure)

Results

- Patient demographics were distributed evenly in sex and eye laterality. Control group was older than Rb group, mean age 2.6 vs 5.3 years, p=0.009 (Table 1).
- The control group received iViC for retinal disease and pathology including: Coat's disease, Incontinentia Pigmenta, intraocular hemorrhage, hemangiomas, and other various retinopathies.
- All IOP measures showed a post induction drop followed by an overall increase post-iViC (Graph 1).
- The non-Rb group had greater IOPs at all four data-points compared to the the Rb group (Graph 3 & 4). The Rb had a mean IOP increase of 16.7 mmHg compared to 28.1 mmHg in control patients, p<0.001 (Table 2).

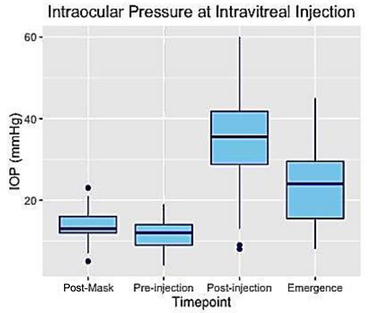
Table 1. Patient and disease characteristics

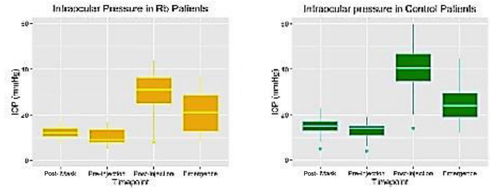
	Total (n=46)	Rb (n=20)	Control (n=26)	p-value
Mean age, y	4.1 ± 3.6	2.6 ± 3.0	5.3 ± 3.7	0.009
Male sex	25 (54%)	9 (45%)	16 (62%)	0.414
Ocular pathology				
Retinoblastoma		20 (100%)	0	
Coat's disease		0	13 (50%)	
Incontinentia pigmenti		0	3 (11%)	
ROP		0	2 (8%)	
Intraocular hemorrhage		0	2 (8%)	
Hemangioma		0	2 (8%)	
Other retinopathies		0	4 (15%)	
Intravitreal chemotherapy				<0.01
bevacizumab	29	3	26	
melphalan	12	12	0	
topotecan	5	5	0	
OD	23 (50%)	10 (50%)	13 (50%)	1.000
OS	23 (50%)	10 (50%)	13 (50%)	1.000
Mean IOP (mmHg)				
Post mask	13.7 ± 3.6	12.3 ± 2.7	14.8 ± 3.9	0.019
Pre-injection	11.8 ± 4.3	10.2 ± 3.4	12.4 ± 4.6	0.086
Post-injection	35.2 ± 12.6	28.6 ± 10.5	40.3 ± 11.8	0.001
Emergence	22.8 ± 9.3	21.2 ± 9.4	24.5 ± 9.2	0.236

Rb, retinoblastoma; y, years; ROP, retinopathy of prematurity, OD, right eye, OS, left eye; IOP, intraocular pressure; Post mask, measured before laryngeal mask airway placement; pre-injection, measured before injection of intraocular chemotherapeutic agent; post-injection, measured after injection of intraocular chemotherapeutic agent.
Data expressed as N (%) or as mean ± standard deviation unless otherwise specified.

Table 2. Mean Increase in Intraocular Pressure, Pre-injection to Post-injection

	mmHg	95% CI	p-value
All patients	23.8	19.7 – 28.0	<0.001
Retinoblastoma	16.7	11.1 – 22.3	<0.001
Control	28.1	22.9 – 33.4	<0.001



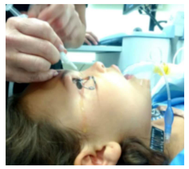


Discussion

- In this study we sought to capture IOP at various time-points of an anesthetic to help stratify risk of extraocular spread from iViC of intravitreal Rb. Elevations in IOP are a risk factor for post-injection reflux. [1]
- As a pilot study, understanding the IOP fluctuation throughout an anesthetic was necessary prior to future efforts to investigate maneuvers by which we may reduce IOP during iViC injection.
- In both groups, iViC was, as expected, associated with transient elevation in IOP and subsequent decrease (which remained above baseline). However, the Rb group was not significantly higher compared to the control group which displayed higher measured IOP at all time-points.
- The relative older age of the control group may account for the higher overall pressures in the non-Rb group. Ocular size and posterior chamber volume capacity increases rapidly early in life: the average axial length of 17.02 mm at birth increases to 22.07 mm by age 3; mean IOP in < 1 year old is 8±3 mmHg, whereas it's 15±3mmHg for children aged 11-12 years. [2]
- Aspects of an anesthetic, such as head-up positioning, ocular massage, supraglottic airway use, and mild hyperventilation (ETCO2 30-35mmHg) reduces cerebral blood flow and venous congestion. Maneuvers including; intravenous propofol bolus immediately before iViC to lower venous pressure has been described to decrease IOP.[3]

Conclusion

- There is a significant acute increase in IOP following iViC which does not immediately return to baseline.
- Further studies to determine if noninvasive anesthetic techniques might attenuate IOP increase and decrease risk of tumor spread. Efforts will be made to eliminate bias by controlling for age and injectate volume variability.
- Considering the level of concern from ophthalmologist colleagues with regard to iViC, future understanding of the mechanism and use of preventative maneuvers will be a significant medical contribution.



Intravitreal injection of bevacizumab in a 4 year old for non-Rb pathology. Bascom Palmer Eye Institute

References

1. Munier et al. IViC for vitreous seeding in retinoblastoma. Saudi J Ophthal 2013;27,147-150
2. Karl et al. IOP changes following intravitreal melphalan and topotecan for the treatment of retinoblastoma with vitreous seeding. J Pediatr Ophthal Strab 2017;54,185-190
3. Murgatroyd et al; IOP, Anaesthesia Critical Care & Pain, 2008; 8, 100–103