Anesthesia maneuvers to decrease intraocular pressure rise after intravitreal injection of chemotherapy in children with Retinoblastoma

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Introduction

- Retinoblastoma (Rb) is the most common primary intraocular malignancy in children[1].
- Treatment of this disease was revolutionized with the initiation of intravitreal injection of chemotherapy (IViC) which improved outcomes due to its increased ocular penetration.
- However, this intervention contains some theoretical risk. IViC volume placed intra-vitreously is associated with significant acute increases in intraocular pressure (IOP)[2].
- These fluctuations may cause injury to the optic nerve, retinal artery and most significantly led to speculation of extravasation of vitreal Rb cells to the extraocular space following needle penetration[3].
- We sought to investigate whether known, non-invasive anesthesia maneuvers which reduce IOP, such as hyperventilation or increased depth of anesthesia may diminish or blunt the acute IOP spike following IViC and compare the results of these interventions with the control groups.
- We review here the preliminary results of this ongoing study.

Objectives

- To compare changes in IOPs with anesthetic interventions to historic controls.
- To compare the effect of various anesthesia interventions in IOP following IVIC. The three anesthetic interventions used in this study are as follows:
  1. Propofol bolus injection of 1mg/kg given 1 minute prior to IViC.
  2. Hyperventilation to ETCO2 of 30-35 mmHg started approximately 5 minutes before iViC.
  3. Both, propofol bolus injection as per above and hyperventilation as per above.

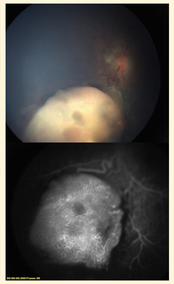


Image 1 (left): Measurement of IOP with Tono-pen Pre-iViC in a 2-month-old infant. Bascom Palmer Eye Institute.

Image 2 (right): Retinal pigment epithelial alterations in Rb with vitreous seeding (*upper*) and enhancement on fluorescein angiography (*lower*).

Methods

- Following institutional IRB approval, children scheduled to undergo exams under anesthesia (EUA) with IViC at Bascom Palmer Eye Institute were enrolled and randomized into 3 groups:
  - Group 1: 1mg/kg bolus of propofol, 1-minute prior to IViC.
  - Group 2: Hyperventilation titrated to ETCO2 of 30-35 mmHg prior IViC.
  - Group 3: Both interventions.
- General anesthesia was maintained via inhaled sevoflurane/O2/air. Airway was secured with laryngeal mask airway (LMA).
- IOP measurements were obtained via tonometry (Tono-pen, Reichert, Inc. Buffalo, NY) at five times points: post-induction of anesthesia, after LMA placement, pre-iViC, post-iViC and after LMA removal.
- IViC agents were melphalan (20µg/0.05ml) and topotecan (6.5µg/0.015ml).
- Continuous variables were compared with Mann-Withney-U (Wilcoxon) test and Fisher's exact test was used for categorical variables.

Results

- To date, we have recorded a total of 20 IViC that underwent anesthesia interventions randomized into 3 groups (Table 1). Patient demographics were distributed evenly in age, weight, sex and laterality. These patients were compared to a total of 20 control IViC who followed standard of care general anesthesia (Table 3).
- A majority of children in the 3 treatment groups had undergone previous IViC (n=19; 95%). Most of the eyes (15 eyes, 75%) received the chemotherapy melphalan + topotecan (see Table 1).
- Pre-injection to post-injection IOP mean changes were as follows: group 1: 21 mmHg (-4 to 41), for group 2: 23 mmHg (-1 to 43) and for group 3: 2 mmHg (-17 to 73) (Table 2). With the lowest increase in IOPs in group 3 (both interventions)
- When comparing the 3 interventions groups overall with the control group, the mean increase in IOP was 14 mmHg (-17 to 73) for the intervention groups compared to 18 mmHg of the control group (-1 to 35) (P value = 0.66)

Table 1. Patient eye and clinical characteristics

	Total (n=20)	Group 1 (n=7)	Group 2 (n=5)	Group 3 (n=8)
Median age, m	14 (4-18)	13 (7-15)	11 (4-14)	16 (7-18)
Median weight, kg	11 (5.8-12.4)	10.9 (9.2-12)	7.2 (5.8-10.9)	11.2 (6.4-12.4)
Hx prior IVIC	19 (95%)	7 (100%)	5 (100%)	7 (88%)
Hx prior IAC	20 (100%)	7 (100%)	5 (100%)	8 (100%)
Hx systemic chemo	5 (25%)	3 (43%)	0 (0%)	2 (25%)
ASA				
II	14 (70%)	5 (71%)	1 (20%)	8 (100%)
III	6 (30%)	2 (29%)	4 (80%)	0 (0%)
OD	7 (35%)	2 (29%)	2 (40%)	3 (38%)
OS	13 (65%)	5 (71%)	3 (60%)	5 (62%)
IVIC administered				
Melphalan only	1 (5%)	1 (14%)	0 (0%)	0 (0%)
Topotecan only	4 (20%)	2 (29%)	1 (20%)	1 (12%)
Melphalan + Topotecan	15 (75%)	4 (57%)	4 (80%)	7 (88%)
Median IVIC volume, mL	0.09 (0.05-0.16)	0.09 (0.05-0.13)	0.09 (0.06-0.16)	0.10 (0.07-0.12)
Median Sevoflurane %	3.3 (2.3-4.4)	3.6 (2.5-4.4)	3.9 (3.1-3.9)	3.3 (2.3-3.5)
Median MAC	1.2 (0.9-2.0)	1.5 (0.9-2.0)	1.2 (1.2-1.8)	1.2 (1.0-1.3)
Median ETCO2, mmHg				
Pre-injection	43 (26-50)	46 (26-50)	41 (41-45)	45 (31-49)
Post-injection	40 (32-52)	44 (40-52)	33 (32-42)	36 (35-51)
Median MAP, mmHg				
Pre-injection	48 (43-87)	54 (46-62)	56 (46-87)	45 (43-56)
Post-injection	48 (44-66)	48 (44-65)	54 (48-66)	48 (45-52)
Median IOP, mmHg				
Pre-induction	9 (4-23)	6 (4-13)	16 (7-23)	9 (6-11)
Post-LMA	8.5 (5-19)	8 (5-11)	9 (8-18)	12 (8-19)
Pre-injection	9 (4-24)	8 (4-24)	9 (6-16)	10.5 (5-23)
Post-injection	19 (4-83)	32 (4-52)	39 (5-57)	13 (5-83)
Emergence	10 (1-34)	12 (5-20)	23 (5-34)	9 (1-21)

Data consists of median (range) for continuous variables and count (percentage) for categorical variables.
Group 1, Propofol 1mg/kg IV bolus administered 1 minute prior to intravitreal chemotherapy injection; Group 2, hyperventilation with goal ETCO2 30-35mmHg prior to intravitreal chemotherapy injection; Group 3, combination of 1+2 Propofol 1mg/kg and hyperventilation ETCO2 30-35 mmHg prior to injection.
M, months; kg, kilograms; hx, history; IVIC, intravitreal chemotherapy; IAC, intra-arterial chemotherapy; chemo, chemotherapy; ASA, American Society of Anesthesiology physical status classification; OD, right eye; OS, left eye; mL, milliliters; MAC, minimum alveolar concentration; ETCO2, end tidal carbon dioxide level; mmHg, millimeters of mercury; MAP, mean arterial pressure; IOP, intraocular pressure; LMA, laryngeal mask airway.

Table 2. Median Increase in Intraocular pressure, Pre-injection to Post-injection

	IOP increase in mmHg
All patients	14 (-17 to 73)
Group 1	21 (-4 to 41)
Group 2	23 (-1 to 43)
Group 3	2 (-17 to 73)

Table 3. Comparison of Intervention and Control patient characteristics

	Intervention (n=20)	Control (n=20)	P
Age, m			
median (range)	14 (4-18)	17 (8 – 132)	
mean ± SD	12.3 ± 4.5	31.4 ± 36.5	0.036^
Laterality			0.523
OD	7 (35%)	10 (50%)	
OS	13 (65%)	10 (50%)	
IVIC administered			0.299
Melphalan ± Topotecan	16 (80%)	14 (70%)	
Topotecan only	4 (20%)	3 (15%)	
Avastin	0 (0%)	3 (15%)	
IOP, mmHg			
Pre-induction	9.0 (4-23)	---	---
Post-LMA	8.5 (5-19)	12.0 (7-17)	0.044
Pre-injection			
median (range)	9.0 (4-24)	9.0 (5-17)	
mean ± SD	10.8 ± 5.8	10.2 ± 3.41	0.814^
Post-injection			
median (range)	19.0 (4-83)	31.0 (8-44)	
mean ± SD	28.6 ± 10.2	27.0 ± 21.4	0.570^
Emergence			
median (range)	10.0 (1-34)	21.0 (8-37)	
mean ± SD	12.7 ± 8.3	21.2 ± 9.4	0.004^
Median Increase in IOP (Pre- to Post-injection)	14 (-17 to 73)	18 (-1 to 35)	0.664

Intervention group consists of the composite of: Group 1, Propofol 1mg/kg IV bolus administered 1 minute prior to intravitreal chemotherapy injection; Group 2, hyperventilation with goal ETCO2 30-35mmHg prior to intravitreal chemotherapy injection; Group 3, combination of 1+2 Propofol 1mg/kg and hyperventilation ETCO2 30-35 mmHg prior to injection.
Control group consists of historical control patients who did not receive an intervention designed to decrease IOP.
M, months; kg, OD, right eye; OS, left eye; mmHg, millimeters of mercury; IOP, intraocular pressure; LMA, laryngeal mask airway.
^ Mann-Whitney U test computed mean ranks rather than median due to dissimilar distributions of data.

Figure 1: IOP relative to IViC in historic controls.

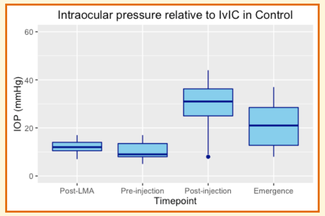


Figure 2.1: IOP relative to IViC in intervention group 1.

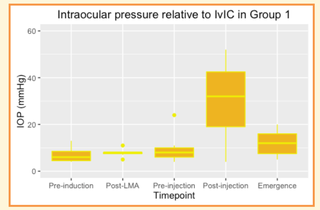


Figure 2.2: IOP relative to IViC in intervention group 2.

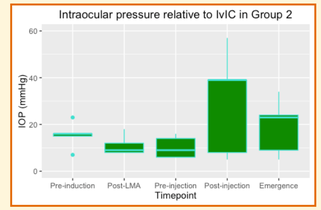
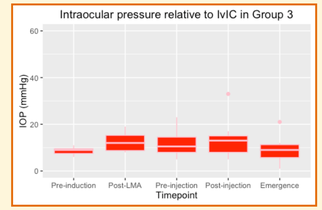


Figure 2.3: IOP relative to IViC in intervention group 3.



Discussion

- Increases in IOP are a known factor for post intraocular injection reflux following IViC.[1] In this ongoing study, the IOPs of children with diagnosed Rb being treated with IViC were measured at five specific time-points during general anesthesia. Mean change in IOP was calculated between pre-injection and post-injection of intravitreal chemotherapy.
- Well known neuroanesthesia interventions are used in clinical practice to lower intracranial pressure as well as IOP. These maneuvers had been described, including head elevation, mild hyperventilation and administration of IV anesthetic boluses like propofol. Children with active Rb with IViC-related IOP fluctuations cannot undergo alternative measures known to reduce IOP, such as anterior chamber paracentesis or ocular massage since it can increase the risk of external tumor seeding.
- These preliminary results demonstrate a reduction in IOP increase compared to the control group in all 3 intervention groups, suggesting that these non-invasive anesthesia maneuvers are a successful intervention in blunting the IViC associated rise in IOP in Rb children, and by so, reducing the risk of tumor seeding. The mean IOP difference in increase of the 3 groups was impacted by anesthesia interventions, with a minimal increase in IOP elevation (2mmHg) when administering propofol bolus combined with hyperventilation minutes before the intravitreal injection, followed by an increase in 21 mmHg when using propofol bolus alone and 23 mmHg when using hyperventilation alone.
- This current study is still ongoing, but thus far, data is promising that one or more of these three groups will show statistically significant in reducing/blunting the IOP increase after IViC. Further data will be collected to demonstrate significance on these results.

Conclusion

With standard-of-care anesthesia interventions employed often in clinical practice, early results indicate that the acute IOP fluctuations during IViC treatment for Rb may be blunted, reducing the risk of reflux and possible tumor seeding, increasing survival of this children.

References

1. Munier FL et al. Intravitreal chemotherapy for vitreus seeding in retinoblastoma. *SaudiJofOph.* 2013:27,147-150
2. Grzybowski A et al. 2018 Update on Intravitreal Injections. *Ophtalmologica.* 2018:239(4),181-193
3. Karl MD et al. Intraocular Pressure Changes Following Intravitreal Melphalan and Topotecan for the Treatment of Retinoblastoma with Vitreous Seeding. *JPediatrOphtalmolStrabismus.* 2017:54(3),185-190