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Intraocular Pressure Variations after Intravitreal Injections Measured with an Implanted Suprachoroidal Telemetry Sensor

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Abstract

Purpose: Intravitreal injections (IVI) may create transient intraocular pressure (IOP) elevation. This report describes continuous IOP fluctuations following multiple IVI measured with a permanent implantable sensor.

Patient and methods: We report the case of a 49-year-old Caucasian glaucomatous male with refractory macular edema secondary to central retinal vein occlusion in his left eye who underwent deep sclerectomy combined with the implantation of a suprachoroidal tonometry sensor. Serial IOP measurements were performed immediately before and after each IVI over a one-year period.

Results: During the first 7 months following deep sclerectomy, IOP remained below 10 mmHg. During this period, mean IOP before each injection was 2.1 ± 2.6 mmHg, and each IVI caused a reduction of 1.2 ± 0.8 mmHg on average, with a maximum reduction of 2.7 mmHg, before IOP normalized within 50 minutes to 24 hours. From 7 months post-operatively, mean IOP increased to the low teens. During this period, mean IOP before each injection was 9.9 ± 1.8 mmHg, and each IVI caused an increase of 15.8 ± 11.7 mmHg on average, with a maximum increase of 44.8 mmHg, before IOP normalized within 20 minutes to 4 hours.

Conclusions: During the initial post-operative phase, IVI may cause acute reduction in IOP, either through subconjunctival leaks or increased filtration secondary to increased fluid pressure. Several months after surgery, this effect subsides and IOP spikes sharply immediately after each IVI, suggesting the resolution of the initial mechanism, most likely through scarring and fibrosis.

Key words: Glaucoma; Continuous; 24h; IOP; IVT; Aflibercept; VEGF; intravitreal injections; eyemate

Introduction

Glaucoma is a group of progressive optic neuropathies characterized by degeneration of the retinal ganglion cells. While the exact pathophysiology of glaucoma remains a subject of debate, intraocular pressure (IOP) was identified as a key risk factor for the disease. Thus, reduction of IOP is the cornerstone of glaucoma management.[1] Yet, IOP monitoring and resulting therapeutic decisions often rely on single or infrequent in-office measurements, and transient IOP variations occurring outside regular clinic hours have long been ignored.[2] The recent advent of implantable tonometry sensors has made continuous out-of-office IOP monitoring both possible and practical. Moreover, these devices were shown to be safe and effective in determining in-vivo IOP fluctuations in various scenarios.[3,4,5] Anti-vascular endothelial growth factors (anti-VEGF) agents are routinely used for the treatment of intraocular neovascular disorders. They are most commonly used as series of intravitreal injections (IVI) that, despite a favorable safety profile, were shown to cause short-term and, in some cases, sustained IOP elevation.[6]

This report, written with the patient's informed consent, constitutes the first in-vivo description of IOP fluctuations following multiple anti-VEGF injections measured with an implanted suprachoroidal telemetry sensor.

Case Report

Case Presentation

A 49-year-old Caucasian male with long-standing primary open-angle glaucoma and refractory macular edema secondary to central retinal vein occlusion in his left eye underwent deep sclerectomy combined with the implantation of a suprachoroidal tonometry sensor (eyemate-SC, Implandata Ophthalmic Products GmbH, Hannover, Germany) due to uncontrolled IOP of 27 mmHg. Prior to this, the patient had undergone the following procedures in his left eye: 2 panretinal photocoagulation laser sessions, 21 ranibizumab injections, 3 ozurdex implant injections and 68 aflibercept injections, a cataract surgery combined with XEN 45 gel stent implantation. **(Figure 4)**

Following the implantation of the suprachoroidal tonometry sensor, the patient received 13 additional aflibercept injections (2mg/50µl) over a 1-year and 3 months period. IOP was monitored with the implantable sensor throughout this period.

Eyemate-SC Sensor

The eyemate-SC suprachoroidal tonometry sensor is a wireless intraocular transducer (WIT) constituted of eight miniature pressure sensor cells, a temperature sensor, an identification encoder, an analog-to-digital encoder and a telemetry unit into a single microelectromechanical system (MEMS). The MEMS is attached to a gold circular 260 antenna and the entire device is encapsulated in implantation-grade silicone. A handheld reader unit, that in its current design resembles a television remote control, receives the digital data and visually displays the IOP values on its LED display. The reader and the intraocular transponder unit must be within 5 cm of each other before a button is pressed on the reader to activate the electromagnetic coupling sequence and the two units can correspond with each other. This is all the cooperation required from the patient. The sensor does not require a battery. The handheld reader is battery powered and supplies the WIT externally through electromagnetic inductive coupling at the time of communication. The sensor can conduct up to 10 IOP measurements per second.[2] The sensor was implanted perpendicularly to the limbus between the choroid and the superficial sclera during non-penetrating deep sclerectomy.

IVI Procedure

Before each injection, oxybuprocaine hydrochloride 0.4% was administered three times at 5 minutes interval in the left eye. After application of 10% povidone-iodine to eyelids and eyelashes and sterile draping, 5% povidone-iodine was applied to the conjunctival surface for at least 30 seconds. The injection was performed in the infero-temporal sector at 7 o'clock, 4 mm from the corneal limbus. Gross visual acuity was assessed immediately after injection by hand movement. In case of IOP spike recorded with eyemate-SC, IOP was confirmed with Goldmann applanation tonometer (GAT) and surveillance was maintained for 30 minutes after which a new measurement was performed with the eyemate-SC. When a reduction in IOP was observed, no additional medications were administered. Over the reported period, no additional IOP lowering agents were required to control IOP spikes. Moreover, even when pre-injection IOP was low, no changes to the injecting protocol were required and no difficulties were observed.

IOP Measurements

During the reported year, a total of 2,382 IOP readings were recorded by the sensor both in and out of clinic **(Figure 1)**. In clinic, IOP was measured by the treating ophthalmologist using the eyemate-SC sensor's reader unit immediately before and after each injection. The pre-injection reading was performed a few seconds before the eye was draped, and the post-injection reading was performed immediately after the drape

was removed. All other eyemate-SC measurements were performed by the patient himself, and automatically transferred wirelessly from the device to his medical notes. On 8 occasions (4 pre-injection and 4 post-injection), the treating ophthalmologist confirmed the sensor readings with GAT. The comparison between these measurements and that obtained with the eyemate-SC is presented in **Table 1**. Paired t-tests were used to compare the IOP measurements both before and after IVI, and between GAT and eyemate-SC. Statistical analysis was performed with a commercially available software (QuickCalcs, version Prism 8, GraphPads, San Diego, California, USA). No statistically significant difference between GAT and eyemate-SC IOP measurements were demonstrated before injection (1.72 ± 1.53 mmHg; $p < 0.539$) or after injection (2.16 ± 1.39 mmHg; $p < 0.750$).

Interestingly, when it comes to the effect of IVI on IOP, two distinct stages were observed. In the first 7 months post-operatively, IOP mostly remained below 10 mmHg with a mean of 5.3 ± 2.3 mmHg (range: -1.4 to 18.5 mmHg; median: 5.2 mmHg) over a total of 1277 measurements. In clinic, a mean IOP of 2.1 ± 2.6 mmHg was measured before each injection. Through this initial period, most IVI were followed by a reduction in IOP. On average, IOP decreased by 1.2 ± 0.8 mmHg after each injection, with a maximum reduction of 2.7 mmHg within 15 minutes of each injection. Immediately after the needle was withdrawn, the IOP reduction was 0.1 ± 1.6 mmHg on average. Following each IVI, IOP normalized within 50 minutes to 24 hours.

From 7 months post-operatively, IOP gradually increased to the low teens, with a mean of 8.6 ± 3.8 mmHg (range: 1.2 to 44.6 mmHg; median: 7.9 mmHg) over a total of 1105 measurements. In clinic, a mean IOP of 9.9 ± 1.8 mmHg was measured before each injection. From this point, all IVIs were followed by an IOP spike. On average, IOP increased by 15.8 ± 11.7 mmHg, with a maximum increase of 44.6 mmHg within 15 minutes of each injection. Immediately after the needle was withdrawn, the IOP increase was 15.7 ± 10.9 mmHg on average. Following each IVI, IOP normalized within 20 minutes to 4 hours.

IOP Medications and Clinical Examinations

During the entire period reported, the patient did not use any anti-glaucoma medications. Uncorrected and best corrected decimal Snellen visual acuity remained stable at 0.3 and 0.6 respectively throughout the study period in the left eye. Slit lamp biomicroscopic examination was unremarkable throughout the follow-up period, with a quiet and formed anterior chamber, a diffuse filtration bleb, and a negative Seidel test. Gonioscopic examination was unremarkable, confirming an open iridocorneal angle and the presence of a well-positioned XEN tube in the superior quadrant. Trabeculo-Descemet's membrane was intact, and no sign of cyclodialysis or angle neovascularization were observed. **(Figure 2)**

Moreover, in order to assess for any displacement of the implanted telemetry sensor, anterior segment optical coherence tomography (AS-OCT) was performed at regular intervals during the measurement period. No significant movement of the device was observed throughout the study period. **(Figure 3)**

Discussion

This report uses on a permanent intraocular telemetry sensor to describe IOP fluctuations associated with anti-VEGF injections of aflibercept over a period of one year and three months following non-penetrating deep sclerectomy. Pre- and post-injection IOP monitoring with eyemate-SC sensor revealed a clear division between two post-operative stages. During the first 7 months IOP remained low, between 0 and 10 mmHg, and injections generated a profound drop in IOP which took up to 24 hours to resolve. We suspect this may be due to a subconjunctival leak through the injection track, to a microscopic bleb leak, or simply to increased filtration, secondary to increased fluid pressure following the injection. One previous publication reported a decrease in IOP after injection of ocriplasmin in a pseudophakic glaucoma patient implanted with an Ahmed glaucoma drainage device.[6] The authors speculated that the increased pressure and proteolytic properties of ocriplasmin improved aqueous flow through the drainage device. Similarly, Georgalas et al. described marked IOP reduction in a pseudophakic glaucomatous patient with patent trabeculectomy, following ranibizumab IVIs. In this case, the anti-VEGF agent caused a leak through the fine-walled filtrating bleb.[7]

The role of increased fluid pressure on recently operated ocular tissues is supported by the observation that, beyond the 7-month timepoint, mean IOP fluctuations behave differently, with marked increases following each injection. This suggests a resolution of the initial mechanism causing post-IVI hypotony, most likely through scarring and fibrosis. With regards to this late post-operative stage, several mechanisms described in the literature may account for these transient pressure spikes: 1) the increased intraocular fluid volume from the IVI may no longer be compensated by the initially speculated overflow mechanism, due to fibrosis of the bleb, trabeculo-Descemet's membrane or scleral tracks,[8] 2) obstruction of the conventional outflow pathway by protein aggregates or foreign particles,[9] 3) damage to the outflow pathway by local inflammation,[10] 4) mechanical trauma,[11] 5) transient angle closure,[12] 6) toxicity following repeated injections[13], 7) or reduced aqueous outflow facility.[14] Finally, the negative values occasionally recorded by the sensor are a known occurrence that were previously explained by an initial offset in device calibration or difficulties in orthostatic adaptation of the eyemate-SC sensor.[3,4] Yet, while GAT was not performed to confirm every sensor reading, the observed discrepancy between GAT measurements and the implantable sensor's (mean: 1.72 mmHg; range: 0.33-4.24 pre injection and mean: 2.16 mmHg; range: 0.75-4.26 post-injection) were within the range generally accepted by clinicians. More research is warranted to confirm these anecdotal observations and clarify the clinical relevance of post-operative stages of fibrosis with regards to IVI and IOP management.

Figure Legends

Figure 1. Intraocular pressures measured with the eyemate-SC sensor over the entire study period. Red vertical lines represent intravitreal injections moments. Blue line represents all measurements taken by both the treating ophthalmologist before and after injection together with the ones assessed by the patient (IOP: intraocular pressure, mmHg: millimeters of mercury).

Figures 2. Biomicroscopic photograph of the filtration bleb prior to an intravitreal injection.

Figure 3. Anterior segment optical coherence tomography pictures of the eyemate-SC implanted telemetry sensor. A and A1 show vertical and horizontal cross sections respectively, at 9 months post-surgery. B and B1 show vertical and horizontal cross sections respectively, at 1 month after surgery.

Figure 4. Timeline showing all procedure the patient underwent before and after eyemate-SC implantation. IVI: intravitreal injection, CRVO: central retinal vein occlusion, PRP: panretinal photocoagulation.

References:

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014 May 14;311(18):1901-11. doi: 10.1001/jama.2014.3192. PMID: 24825645; PMCID: PMC4523637.
2. Gillmann K, Bravetti GE, Niegowski LJ, Mansouri K. Using sensors to estimate intraocular pressure: a review of intraocular pressure telemetry in clinical practice, Expert Review of Ophthalmology, 2019; 14:6, 263-276, DOI: 10.1080/17469899.2019.1681264
3. Choritz L, Mansouri K, van den Bosch J, Weigel M, Dick HB, Wagner M, Thieme H; ARGOS study group. Telemetric Measurement of Intraocular Pressure via an Implantable Pressure Sensor-12-Month Results from the ARGOS-02 Trial. Am J Ophthalmol. 2020 Jan;209:187-196. doi: 10.1016/j.ajo.2019.09.011. Epub 2019 Sep 20. PMID: 31545953.
4. Mansouri K, Rao HL, Weinreb RN; ARGOS-02 Study Group. Short-Term and Long-Term Variability of Intraocular Pressure Measured with an Intraocular Telemetry Sensor in Patients with Glaucoma. Ophthalmology. 2020 Jul 12:S0161-6420(20)30678-3. doi: 10.1016/j.ophtha.2020.07.016. Epub ahead of print. PMID: 32663530.
5. Mansouri K, Gillmann K, Rao HL, Weinreb RN; ARGOS–2 Study Group. Weekly and seasonal changes of intraocular pressure measured with an implanted intraocular telemetry sensor. Br J Ophthalmol. 2020 Jun 4:bjophthalmol-2020-315970. doi: 10.1136/bjophthalmol-2020-315970. Epub ahead of print. PMID: 32499329.
6. Singh RS, Kim JE. Ocular hypertension following intravitreal anti-vascular endothelial growth factor agents. Drugs Aging. 2012 Dec;29(12):949-56. doi: 10.1007/s40266-012-0031-2. PMID: 23179897.
7. McClintock M, MacCumber MW. Lowered intraocular pressure in a glaucoma patient after intravitreal injection of ocriplasmin. *Clin Ophthalmol*. 2015;9:1995-1998. Published 2015 Oct 23. doi:10.2147/OPTH.S85509.
8. Tao X, Sigireddi RR, Westenskow PD, Channa R, Frankfort BJ. Single transient intraocular pressure elevations cause prolonged retinal ganglion cell dysfunction and retinal capillary abnormalities in mice. Exp Eye Res. 2020 Oct 8;201:108296.
9. Georgalas I, Papaconstantinou D, Tservakis I, Koutsandrea C, Ladas I. Severe hypotony and filtering bleb leak after intravitreal injection of ranibizumab. *Ther Clin Risk Manag*. 2009;5(1):17-19.

10. Liu L, Ammar DA, Ross LA, Mandava N, Kahook MY, Carpenter JF. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. *Invest Ophthalmol Vis Sci*. 2011; 52: 1023–1034.

11. Yannuzzi NA, Patel SN, Bhavsar KV, Sugiguchi F, Freund KB. Predictors of sustained intraocular pressure elevation in eyes receiving intravitreal anti-vascular endothelial growth factor therapy. *Am J Ophthalmol*. 2014; 158: 319–327.e2.

12. Wen JC, Cousins SW, Schuman SG, Allingham RR. Dynamic changes of the anterior chamber angle produced by intravitreal anti-vascular growth factor injections. *Retina*. 2016.

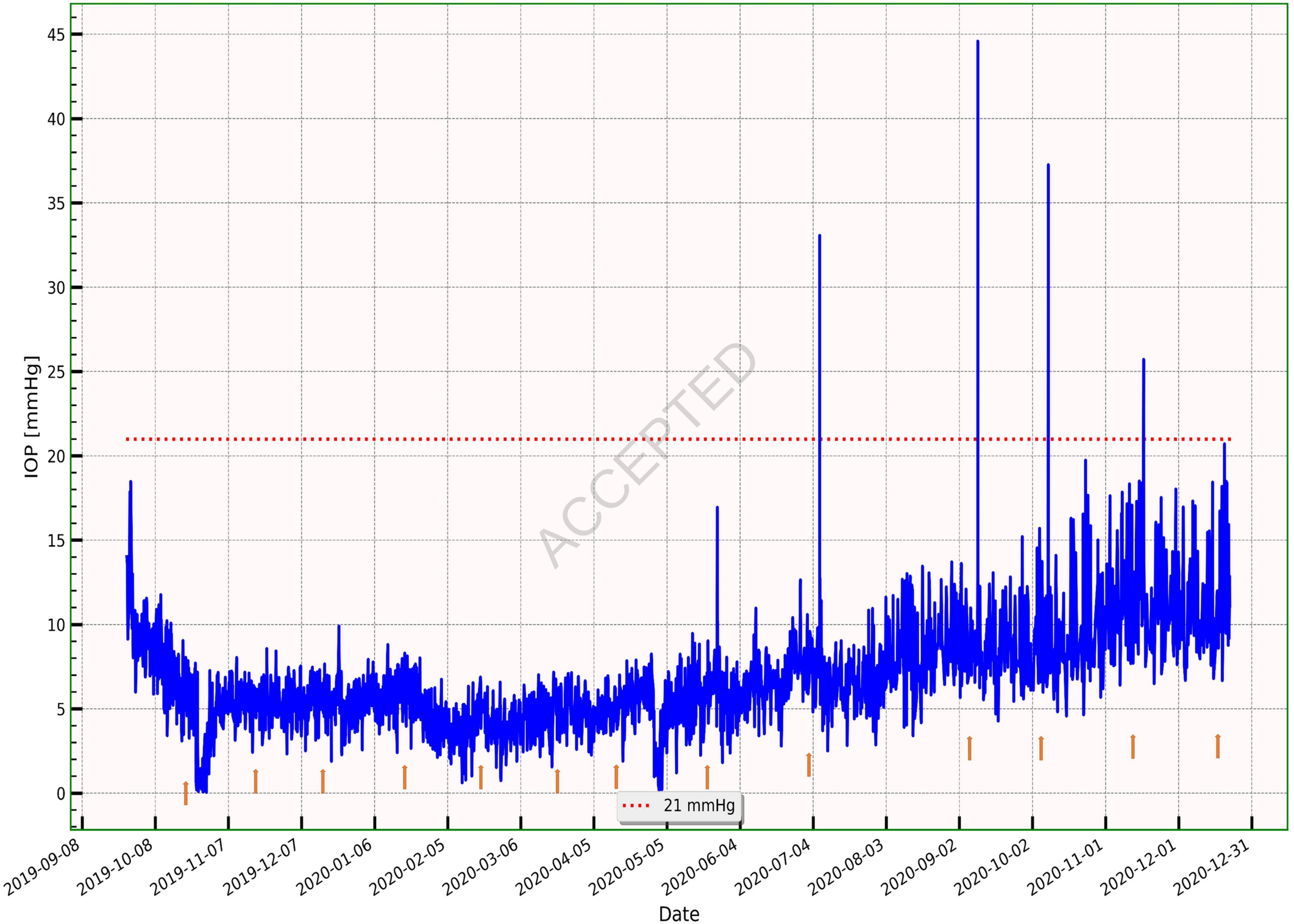
13. Kahook MY, Ammar DA. In vitro effects of antivascular endothelial growth factors on cultured human trabecular meshwork cells. *J Glaucoma*. 2010; 19: 437–441.

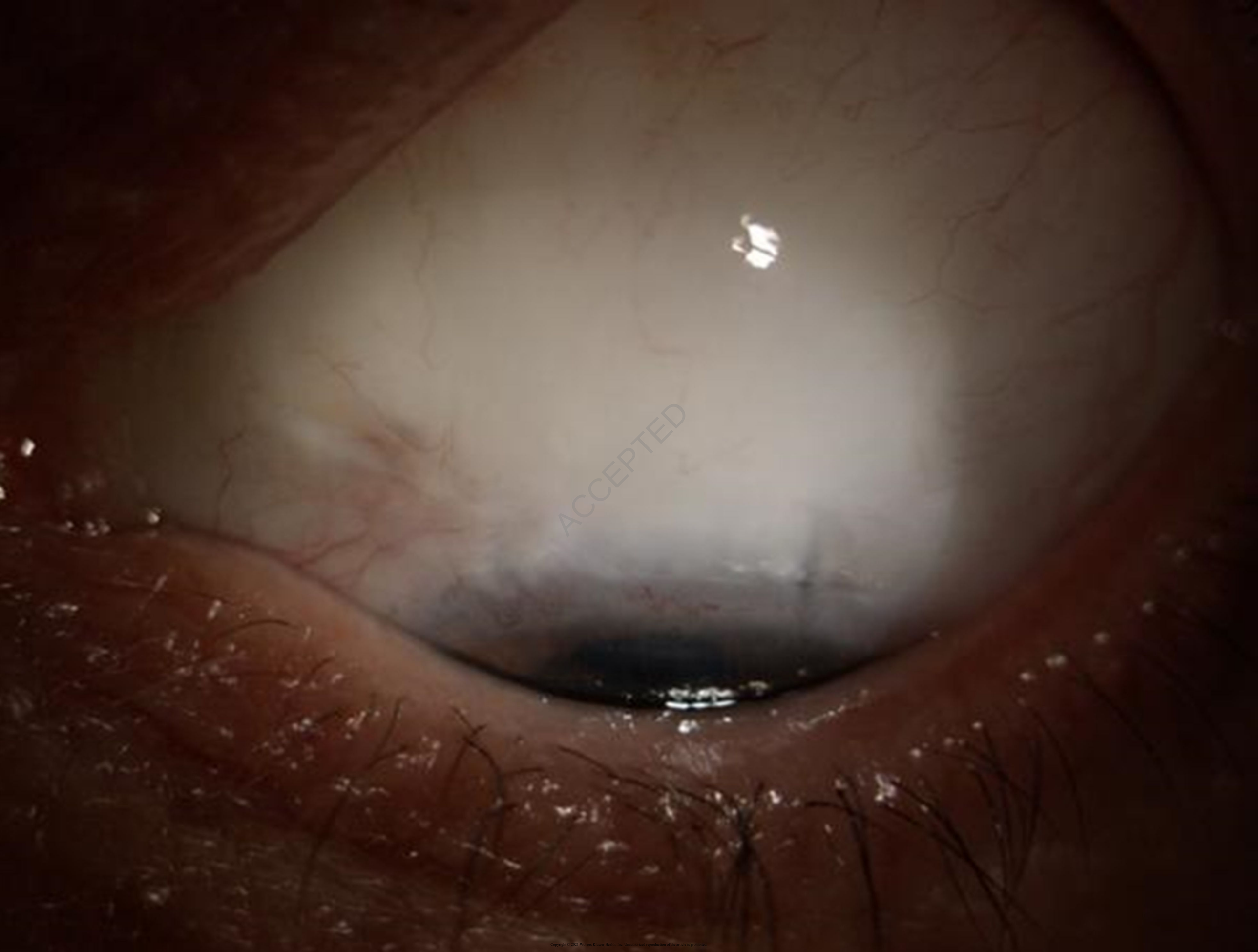
14. Joanne C. Wen, Ester Reina-Torres, Joseph M. Sherwood, Pratap Challa, Katy C. Liu, Guorong Li, Jason Y. H. Chang, Scott W. Cousins, Stefanie G. Schuman, Priyatham S. Mettu, W. Daniel Stamer, Darryl R. Overby, R. Rand Allingham; Intravitreal Anti-VEGF Injections Reduce Aqueous Outflow Facility in Patients With Neovascular Age-Related Macular Degeneration. *Invest. Ophthalmol. Vis. Sci*. 2017;58(3):1893-1898. doi: https://doi.org/10.1167/iovs.16-20786.

	Pre-injection IOP			Post-injection IOP		
Dates dd/mm/yyyy	GAT mmHg	Δ GAT-eyemate-SC mmHg	eyemate-SC mmHg	eyemate-SC mmHg	Δ GAT-eyemate-SC mmHg	GAT mmHg
24/10/2019	4	4.24	-0.24	-1.26	-4.26	4
23/12/2019	4	0.64	3.36	2.47		
24/01/2020	4	-1.68	5.68	6.11		
26/02/2020			-0.06	-0.62		
26/03/2020			4.09	7.14		
29/04/2020			-0.01	-1.4		
25/05/2020			9.32	16.75		
06/07/2020	8	0.33	7.67	33.06	1.06	32
11/08/2020			9.54	12.17		
09/09/2020			13.33	44.58	2.58	42
08/10/2020			9.8	37.25	-0.75	38
26/11/2020			10.84	19.32		
21/12/2020			8.77	15.92		
Average	5.00 ± 1.73	1.72 ± 1.53	6.31 ± 4.36	14.73 ± 14.68	2.16 ± 1.39	28.75 ± 15.29
p value	0.539			0.750		

GAT: Goldmann Applanation Tonometer, IOP: Intraocular Pressure, d: day, m: month, y: year, Δ: difference, mmHg: millimeters of mercury. p value < 0.05 was considered statistically significant. p value was assessed via paired t-test.

Table 1. IOP measurments with both GAT and eyemate-SC by the examining ophtalmologist.





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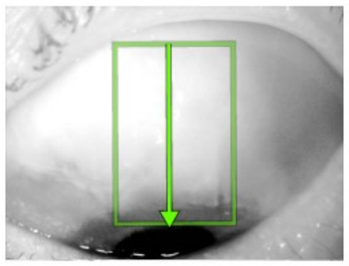

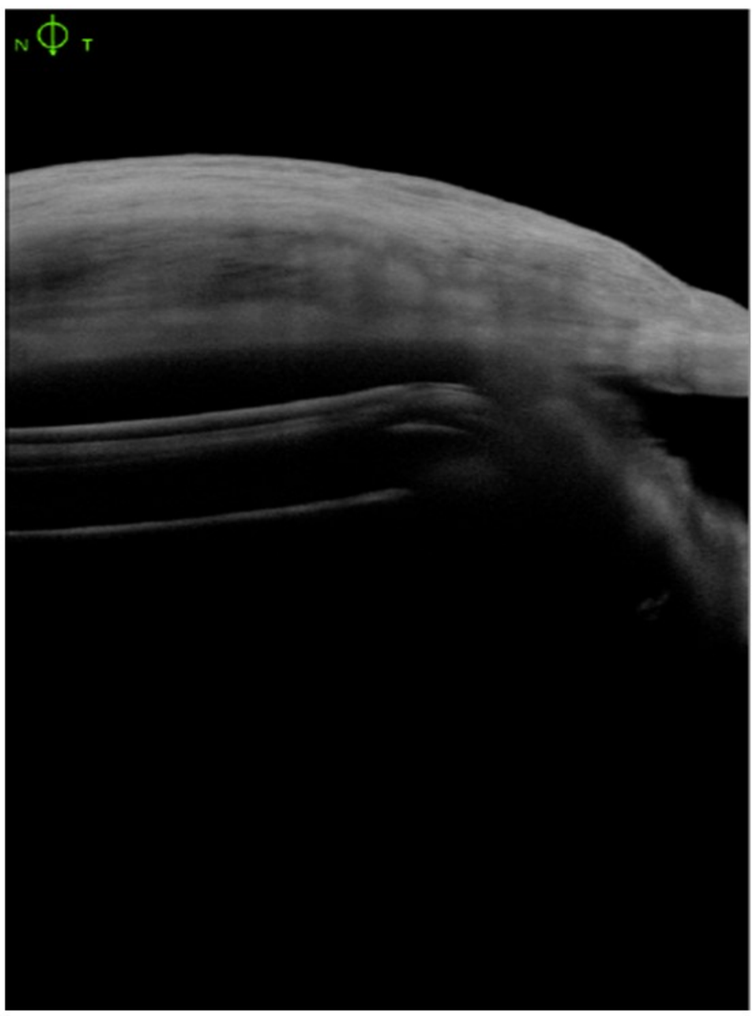

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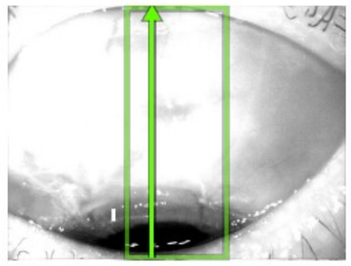

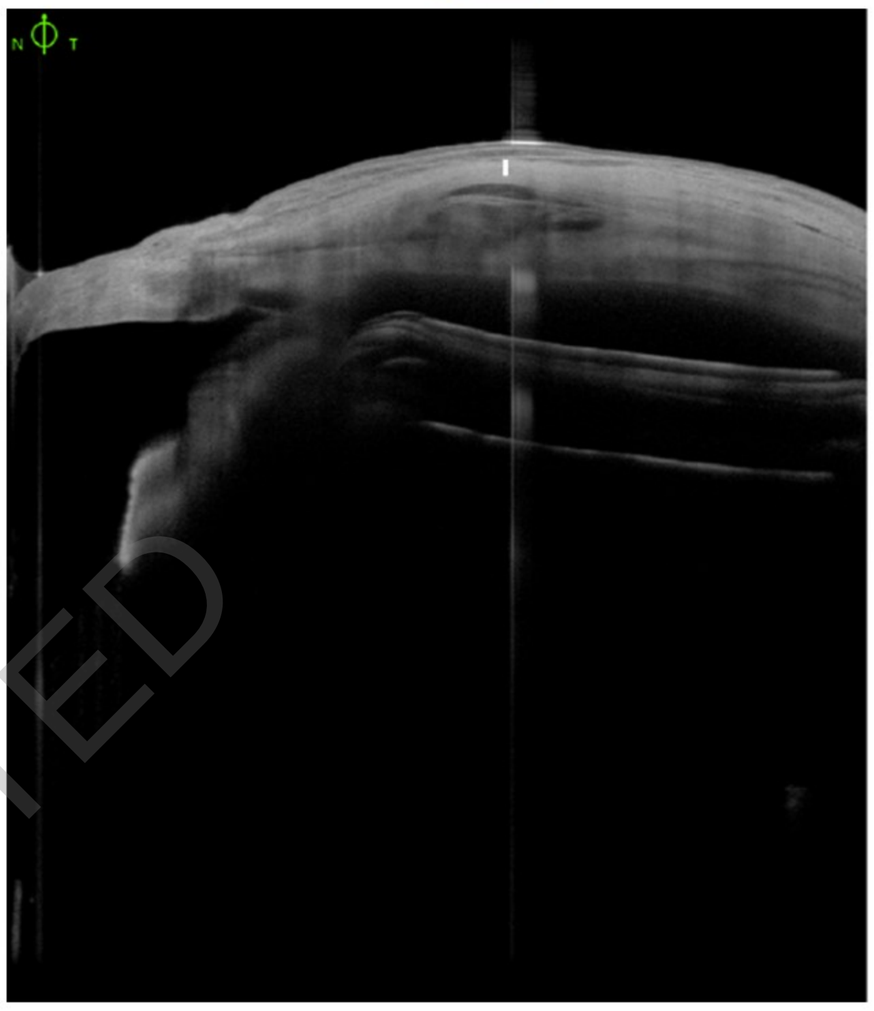

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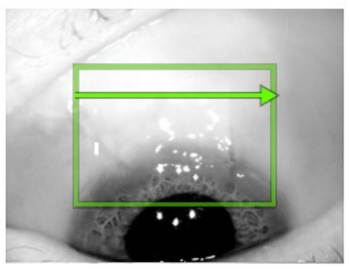

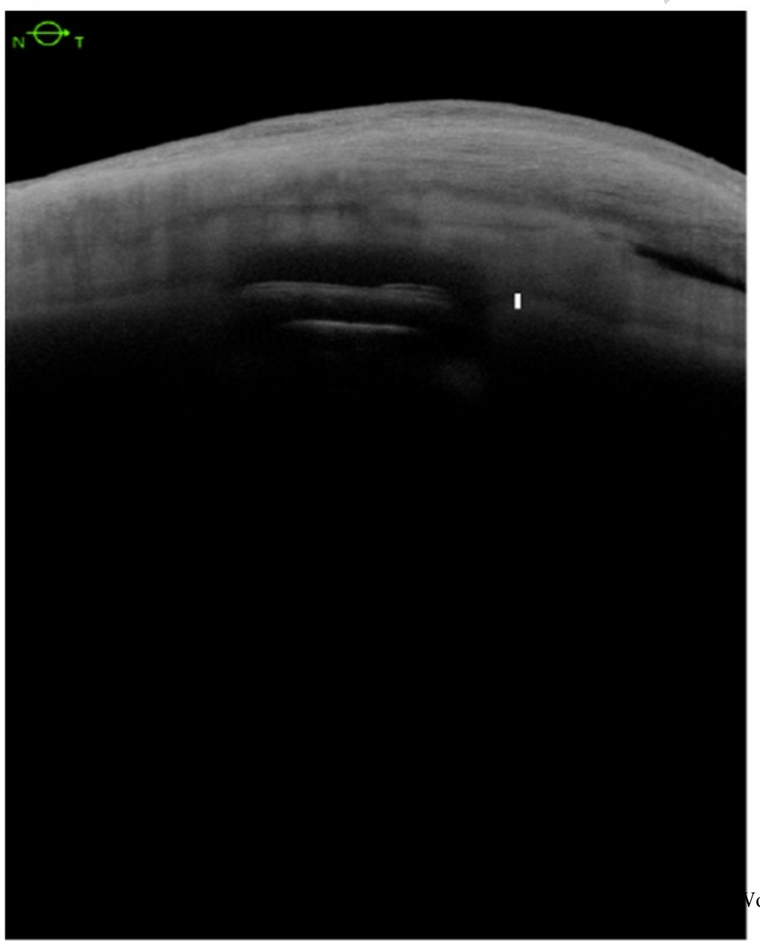

B1