Ab Interno Canaloplasty in Open-angle Glaucoma Patients Combined With In Vivo Trypan Blue Aqueous Venography

Gavin Docherty, MD, FRCS,* Derek Waldner, BSc, PhD,† Matt Schlenker, MD, MSc,‡ Andrew Crichton, MD, FRCS,* Bryce Ford, MD, FRCS,* Iqbal I.K. Ahmed, MD, FRCS,§|| and Patrick Gooi, MD, FRCS*¶

Purpose: To demonstrate canalogram patterns observed when trypan blue tracer is combined with oculoviscoelastic device during ab interno canaloplasty, and discuss surgical results and potential implications for diagnosis, prognosis, and treatment.

Methods: This is a retrospective small case series study.

Results: The authors performed this procedure on 5 patients with informed consent with 4 to 18 months of follow-up. All procedures have been complication free. The average preoperative intraocular pressure was 21.4 mm Hg with an average number of topical medications used equaling 3.6. Postoperatively, the average intraocular pressure was 16.4 mm Hg with an average number of topical glaucoma medications being equal to 1.8.

Conclusions: Currently, there are limited practical options to evaluate the patency of the aqueous outflow system in our patients. The primary purpose of this paper is to describe canalogram patterns observed during ab interno canaloplasty with trypan blue. This technique may allow us to further our understanding of the aqueous outflow system and its role in the underlying pathophysiology of glaucoma. Further research is required to evaluate the prognostic and diagnostic significance of this technique.

Key Words: canaloplasty, minimally invasive glaucoma surgery, trypan blue, aqueous humor, canalogram

Glaucoma is the leading cause of irreversible blindness globally and affects 60.5 million people worldwide with predictions that this number will increase to over 110 million by 2040.1 Traditionally, the gold standard for glaucoma surgical intervention is the trabeculectomy, which is associated with a relatively high risk of complications and demanding follow-up regime.2 More recently, interest has arisen in minimally invasive glaucoma surgery (MIGS), particularly canaloplasty (ab interno and ab externo) as a method of reducing intraocular pressure (IOP) with less risk and follow-up demands compared with trabeculectomy.3,–11 Ab interno canaloplasty (ABIC) is an angle-based MIGS described by Khaimi and colleagues’ group10–13 that does not disturb the conjunctiva. Canaloplasty is associated with a significant reduction of IOP and IOP lowering medications after surgery.3,–13 Brusini6 described 3-year follow-up of ab externo canaloplasty and achieved IOP lowering without medical therapy to a level <21 mm Hg in 86.2% of patients.3 There are also recent developments that may help simplify and make canaloplasty results more reproducible.14,15

There are very few studies utilizing dye tracers during glaucoma surgery to visualize the outflow system. Zeppa et al16 demonstrated that simultaneous injection of indocyanine green (ICG) during canaloplasty combined with fluorescence imaging allowed visualization of the downstream collector channels and flow following the intervention. Grieshaber et al17 also demonstrated fluorescein venography during canaloplasty and found venous egress predictive of postoperative IOP outcomes. Although this was a novel technique it has several drawbacks. Primarily it required the OPMI PENTERO 900 microscope to allow visualization of the fluorescent activity of the ICG. Furthermore, it is an ab externo approach, which may disrupt conjunctiva and sclera for further surgeries. In the Grieshaber et al17 paper, it seems that fluorescein filling was directly evaluated without a fluorescent filter. Larocco et al18 describe the use of trypan blue combined with Kahook dual blade to visualize the aqueous outflow system.

We present a technique utilizing trypan blue mixed with an oculoviscoelastic device (OVD) during canaloplasty allowing for simultaneous surgical intervention and direct observation of downstream flow without the need for specialized tracers, such as ICG, or infrared video recording equipment. This combined procedure has not been described in the literature previously. It provides the advantage of immediate therapeutic treatment and visualization of downstream aqueous flow through collector channels without any additional surgical equipment than what would be required for conventional venography.

METHODS

The surgical procedure was performed at the Southern Alberta Eye Care Centre, Calgary, Alberta, Canada by one surgeon (P.G.). Informed consent was obtained following a detailed description of the procedure. The study was approved for publication May 6, 2020; accepted August 22, 2020.

From the *Department of Surgery; †Cumming School of Medicine; ‡Cloudbreak Eyecare, University of Calgary, Calgary, AB; ††Credit Valley Eyecare, Mississauga; †‡Department of Ophthalmology, Faculty of Medicine; and †¶Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada.

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Reprints: Gavin Docherty, MD, FRCSC, University of Calgary, 315-5340 SW 1st Street, Calgary, AB, Canada T2H 0C8 (e-mail: gavdoch@gmail.com).

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CASE REPORT/SMALL CASE SERIES

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by local institutional ethics and conformed to the tenets of the Declaration of Helsinki.

Trypan Blue Ophthalmic Solution
Under sterile conditions, trypan vision blue was mixed with an ophthalmic viscosurgical device (Healon GV; Advanced Medical Optics, Santa Ana, CA) using 1-inch 25-G needle (Fig. 1). Using a 1-inch needle allows the trypan blue to be mixed into the ophthalmic viscosurgical device at various levels providing a more homogenous mixture.

Microcatheter
The microcatheter used (iTrack 250 A; iScience Interventional, Menlo Park, CA) consists of 3 parts. An optical fiber allows for direct visualization of the procession through Schlemm canal, a support wire provides strength to progress the wire with pushing technique, finally a lumen allows fluid delivery. A screw-driven syringe connected to the proximal end of the microcatheter allows delivery of the trypan blue and OVD mixture directly into Schlemm canal. One-eighth turn of the injection knob equals ~150 μL volume of solution injected.10

Canaloplasty
A temporal 2.2 mm wound was established to allow for goniotomy and anterior chamber delivery of OVD. A superior 1.2 mm paracentesis wound was made to allow the delivery of the iTack microcatheter. A small goniotomy was made using a 25 gauge needle. The iTrack was then inserted into the goniotomy site. For each clock hour of advancement, a one-eighth turn of the screw syringe allowed the advancement of the OVD-trypan blue mixture into Schlemm canal. Figure 2 demonstrates diffuse filling at 6 and 11 o’clock.

RESULTS
The authors have performed this procedure on 5 patients with informed consent. Details can be seen in Table 1. All procedures have been complication free. The average preoperative IOP was 16.4 with an average number of topical glaucoma medications being equal to 3.6. Two patients were on acetazolamide. Postoperatively, the average IOP for the group was reduced to 13 mm Hg with a concurrent drop in the average number of topical medications (M = 1.8). No patients were on acetazolamide after the procedure. The authors are evaluating the safety and efficacy of this technique and data collection is ongoing. IOP was lowered by 21% and topical medications were reduced by 50%. Although the reduction in IOP was not statistically significant, the reduction in topical medications was statistically significant.

Several canalogram patterns of episcleral venous flow were observed after injection of OVD-trypan mixture. The flow was described as diffuse (Fig. 2), reticular (Fig. 3), minimal (Fig. 4), or none. The authors also observed areas of trypan blue staining or a “blue blush” sign potentially indicating both intrascleral and episcleral flow. An episcleral fluid wave, previously described, along with blanching could also be seen in some cases.15

DISCUSSION
ABiC with OVD-trypan blue venography is a variation on an established technique that allows therapeutic intervention and evaluation of canalogram patterns downstream to the trabecular meshwork. This technique may treat resistance both at the trabecular meshwork (when combined with Schlemm canal unroofing or gonioscopy-assisted transluminal trabeculotomy) and the post-trabecular outflow system, which is felt to contribute up to 50% of resistance to outflow. Viscodilation of the collector channels and episcleral veins may reduce resistance by releasing adhesions of channels that have collapsed, opening valves that may have fibrosed closed, and also physically clearing cellular debris obstructing the channels. In cases where there was a diffuse trypan blue venographic pattern, there was also a prominent episcleral venous fluid wave.19 Both these signs are felt to be good prognostic factors. The absence of a prominent trypan blue pattern may be because of a number of factors. Extensive fibrosis may prevent recanalization of the channel, the injection pressure may be inadequate to release the adhesions, or the pattern may be the patient’s anatomic variant. These patients may eventually benefit from filtering surgery. In

FIGURE 1. Trypan blue is injected into oculoviscoelastic device using a 1-inch 25-G needle.

FIGURE 2. A, Diffuse episcleral venous filling at 6 and 11 o’clock. B, Large episcleral veins.
addition, future therapeutics could target and enzymatically release adhesions in the post-trabecular outflow system, and our technique could then be used to confirm a therapeutic endpoint.

This procedure is versatile as it may be performed with or without cataract surgery. Moreover, this technique can be tailored to a particular patient. The extent of goniotomy can be varied from 90 degrees to the full 360 degrees. If the patient is on multiple anticoagulants, and there is a concern for postoperative hyphema, one may perform a full canaloplasty with minimal goniotomy, and place trabecular microbypass stents (iStent; Glaukos, San Clemente, CA). Furthermore, this procedure is conjunctival sparing, allowing for future subconjunctival filtration surgery.

Previously, Zeppa and colleagues described the use of ICG for a similar effect. Our method has the advantage of being an ab interno approach promoting the preservation of conjunctiva and sclera for future filtering surgeries.

| TABLE 1. Individual Case Demographics, Preoperative, and Postoperative Information |
| Case | Age | Diagnosis | Previous Surgery | Postoperative Medications | No. Glaucoma Medications | Average Daily Dose of Diamox | Postoperative Dose of Diamox | IOP (mm of Follow-up) | Postoperative Daily Dose of Diamox | Postoperative Meds | Postoperative IOP (mo of Follow-up) |
|------|-----|-----------|-------------------|---------------------------|-------------------------|-----------------------------|-----------------------------|----------------------|-------------------------------|------------------|-------------------------------|
| 1    | 64  | Pseudoexfoliation glaucoma | SLT, LPI, CEIOL | SLT, LPI | 4 | 24 | 12 | 12 (5) |
| 2    | 53  | Pigment dispersion glaucoma | SLT, MLT | SLT, MLT | 4 | 17 | 0 | 13 (15) |
| 3    | 74  | Primary open-angle glaucoma | MLT | MLT | 3 | 12 | 0 | 11 (18) |
| 4    | 62  | Pseudoexfoliation glaucoma | CEIOL | MLT | 3 | 14 | 0 | 14 (8) |
| 5    | 61  | Pigment dispersion glaucoma | MLT | MLT | 4 | 15 | 1000 | 15 (4) |

CEIOL indicates cataract extraction and intraocular lens implantation, F, female; IOP, intraocular pressure; LPI, laser peripheral iridotomy; M, male; MLT, micropulse laser trabeculoplasty; SLT, selective laser trabeculoplasty.

FIGURE 3. Reticular episcleral filling between 9 and 12 o’clock.

FIGURE 4. Minimal episcleral venous filling.
Grieshaber et al\textsuperscript{17} also previously described fluorescein venography during canaloplasty. Our technique does not require the need for additional or expensive surgical microscopes as trypan blue can be directly visualized without a fluorescence filter. Furthermore, the visualization of trypan blue is more likely to be superior to that of fluorescein without a fluorescent filter making direct observation easier and more practical for combination with surgical intervention. Another novel aspect of our study is the observation of the “Blue Blush” phenomenon, which may be a method to investigate the patency and contribution of a patient’s intrascleral drainage pathway. A particular patient’s canalogram pattern may guide the degree of goniotomy that is required, and prognosticate the long-term success of this particular procedure. Moreover, this procedure and canalogram classification may identify which patients would benefit most from various glaucoma procedures and provide some insight to the nature of glaucoma pathophysiology. Utilizing approaches where tracer is placed in the anterior chamber\textsuperscript{20} to evaluate trabecular meshwork outflow may be complimentary to our technique in that it predominantly evaluates flow downstream to the trabecular meshwork. Furthermore, our pilot study indicates there is a fair amount of heterogeneity in canalogram patterns between patients than previously described.\textsuperscript{19} This may be because of the supraphysiological pressures and OVD utilization during canaloplasty with resultant modulation of outflow patterns seen in these canalograms.

Our results were not statistically significant. However, the primary purpose of this paper was to share a new technique that may aid in our understanding of aqueous outflow and possibly improve our ability to select MIGS procedures. With regards to our results, there are several reasons that the results may not have reached the criteria for statistical significance. Primarily, we have a low sample size, making a type II error more probable. Second, our patients had relatively low preoperative IOP ($M = 16.4$ mm Hg) with the primary reason for the operation being the inability to tolerate maximal medical therapy. Despite this, we still saw a 15% IOP reduction, which is impressive given relatively lower IOP preoperatively and considering that it is difficult to achieve significant reductions as one approaches the level of episcleral venous pressure. In addition, topical medications were reduced from a mean of 3.6 to a mean of 1.6. Although not statistically significant this is still clinically relevant as this shows the procedure was successful at obtaining lower IOP with less topical medications and discontinuation of acetazolamide.

Further evaluation is required but the authors feel that initial results suggest that patients with more advanced disease tended to have a less prominent trypan blue venographic pattern. It may be because of the severity of the disease, but another factor may be an aqueous steal from the conventional outflow pathway.\textsuperscript{19} This is when prostaglandin analogs direct more flow through the unconventional pathway, leaving less flow through the conventional outflow pathway, which subsequently becomes atrophic. Aqueous suppression with glaucoma drops compounds this problem. Thus, being on glaucoma drops for many years may predispose patients toward poor outcomes after Schlemm canal procedures (iStent, GATT, KDB, etc.), including our described technique.\textsuperscript{16}

Although this method provides 360 degrees in vivo aqueous venography, there are some limitations. The OVD-trypan blue mixture is not standardized, and thus may not be completely homogenous, and its viscosity and molecular weight are unknown. This technique provides a qualitative analysis of venography under conditions that are likely supraphysiological. It may provide information on whether the post trabecular outflow system is patent, but it does not reveal any potential dysfunction of the aqueous pumps or valves.\textsuperscript{21}

\textbf{CONCLUSIONS}

Our modified ABIC with in vivo trypan blue aqueous venography is a cost-effective method to map and treat a patient’s post trabecular outflow system, whereas significantly reducing the need for topical IOP lowering medications. Further study may help identify the optimal glaucoma surgery for a particular patient, and the surgical plan may be augmented immediately depending on the venographic pattern. On a larger scale, this technique may help to increase our understanding of the physiology of the post trabecular outflow system, which may assist in developing new glaucoma surgeries and therapeutics.

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