WHITEPAPER

iTrack™ Canal-based Glaucoma Surgery: Evolution and Current Applications

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The landscape of glaucoma management has shifted considerably in the last decade with the introduction of minimally invasive glaucoma surgeries (MIGS). The result is a more scalable and nuanced approach to surgical decision-making for patients with glaucoma and decreased dependence on medications. More than 10 years ago, canaloplasty was introduced as a restorative, canal-based glaucoma surgery to improve aqueous egress through the conventional outflow system. However, despite good clinical efficacy, the technically challenging aspects of canaloplasty, an ab externo procedure, limited its uptake. More recently, surgeon-driven refinement has lowered the technical hurdles to canaloplasty using an ab interno approach, with gonioscopic visualization for intubation of Schlemm's canal, in what is referred to as iTrack™ canal-based MIGS. Presently, iTrack™ is the least invasive MIGS procedure available to reduce resistance to aqueous outflow in all segments of the conventional outflow system. As an added benefit, it can also be performed outside cataract surgery, as a standalone procedure.

Canaloplasty was originally conceived by Robert Stegmann, MD, Professor and Chairman of Ophthalmology at the Medical University of South Africa, as a procedure to treat open-angle glaucoma in a patient population with refractory disease, limited access to care, and sub-optimal conditions for penetrating filtration surgery. Following his earlier work in developing hyaluronic acid (HA)-based ophthalmic viscosurgical devices (OVDs), Professor Stegmann postulated that primary open-angle glaucoma (POAG) could be treated by OVD expansion of Schlemm's canal and the distal aqueous outflow system.[1] He thus began his pioneering work in viscocanalostomy leading to canaloplasty. Next, Professor Stegmann devised a microcatheter to facilitate canalization and pressurized viscodilation of the entire circumference of Schlemm's canal. It was designed with a 200-micron outer diameter coupled with an internal guide wire to provide adequate rigidity and flexibility to be reliably advanced.[1] A fiberoptic and illuminated tip provides visual confirmation that the microcatheter is in the correct anatomic space. The end of the microcatheter is bulbous to allow a suture to be attached, towed through Schlemm's canal and tied. This tensioning suture is thought to scaffold the trabecular meshwork and further improve aqueous outflow. A

specialized injector was developed to deliver precise microboluses of HA-based OVD during viscodilation. The number of microboluses delivered and therefore the amount of viscodilation could be varied by surgeon preference. Changing the speed of microinjector advancement and/or microcatheter withdrawal changed the total volume of HA-based OVD injected into Schlemm's canal and outflow channels.[1]

Canaloplasty Evolution

The microcatheter and surgical system were commercialized as the iTrack™ surgical system, and it subsequently underwent clinical trials in the United States, Europe, and South Africa. Canaloplasty was found to be clinically efficacious with long-lasting results.[2] It was also shown to have better clinical efficacy and lower risk of complications than viscocanalostomy. Studies with three-year follow-up, published as early as 2011, showed consistent and sustained lowering of intraocular pressure (IOP).[3-6]

At the three-year endpoint of a multicenter study by Lewis et al, all study eyes (N=157) had a mean IOP of 15.2 mm Hg ± 3.5 standard deviation compared with a baseline IOP of 23.8 ± 5.0 mmHg, a 36% reduction.[4] Glaucoma medication use was reduced from an average of 1.8 ± 0.9 to 0.8 ± 0.9 medications. Intraocular pressure and medication use in all eyes were significantly decreased from baseline at every timepoint ($P<.001$).[4] Four-year follow-up data from Brusini, published in 2014, showed a mean IOP reduction of 42.2%.[5] Moreover, canaloplasty has been shown to be equally effective in Asian and African patients.[6]

Despite good clinical efficacy, adoption of canaloplasty was limited by the long procedure time—typically 45 to 90 minutes—and the requirement for a higher degree of surgical skill in order to perform the scleral dissection and identify Schlemm's canal.

Canaloplasty via an Ab-Interno Approach

In an analysis of subgroups of canaloplasty patients over several years, it was noted that those patients in whom a tensioning suture could not be placed achieved similar reductions in IOP as compared to patients who had both viscodilation and placement of the suture.[7] Indeed, several published studies showed similar pressure reduction between sutured and sutureless canaloplasty.[8] This indicated that the procedure could possibly be simplified by

Mechanism of Action: Viscodilation Combined with 360-Degree Catheterization

Advancement of the iTrack™ microcatheter around the entirety of Schlemm's canal, followed by pressurized injection of high molecular weight HA-based OVD, is believed to produce increased aqueous outflow by three mechanisms; mechanical, hydraulic, and biochemical.[10-15]

1. Mechanical: The dimensions of the lumen of Schlemm's canal are smaller in glaucomatous eyes, and these changes correlate with outflow resistance.[16] Herniations of the inner wall and juxtacanalicular tissue into collector channels are more frequently observed in glaucomatous eyes than in age-matched, non-glaucomatous eyes.[11,17] The passage of the iTrack™ microcatheter mechanically breaks adhesions within Schlemm's canal and pushes herniations of trabecular meshwork out of collector channel ostia. This restores a more patent architecture to Schlemm's canal.

2. Hydraulic: Hydraulic pressure caused by injection of HA-based OVD stretches the trabecular meshwork, with possible creation of microperforations into the anterior chamber.[11] This dilates Schlemm's canal, ostia, and collector channels.[14] Visible blanching of aqueous veins suggests that dilation extends to the most distal portion of the collector channels.[10]

eliminating the ab externo scleral dissection and tensioning suture and, instead, accessing Schlemm's canal for viscodilation only via an ab interno approach. This surgical evolution of canaloplasty was conceived as gonioscopically performed MIGS, known as iTrack™ canal-based MIGS.

Assessing the Efficacy Outcomes of iTrack™

On average, iTrack™ canal-based MIGS achieves a reduction in IOP of 30% and a 50% reduction in medication dependence.[9] The procedure has been demonstrated to lower IOP and/or reduce the patient medication burden when performed as a standalone procedure, and in conjunction with cataract surgery.[9] It has also demonstrated efficacy in cases of controlled and uncontrolled glaucoma. In a consecutive case series by Gallardo et al, 84.9% of eyes experienced a reduction in IOP of more than 20%.[9] The case series also assessed the efficacy of iTrack™ when performed as a standalone procedure, and in combination with cataract surgery. At 12 months, mean IOP and medication use was reduced by 32.8% and 51.1% (P<0.001) respectively when performed as a standalone procedure (n=41). When performed in conjunction with cataract surgery (n=34), mean IOP and medication

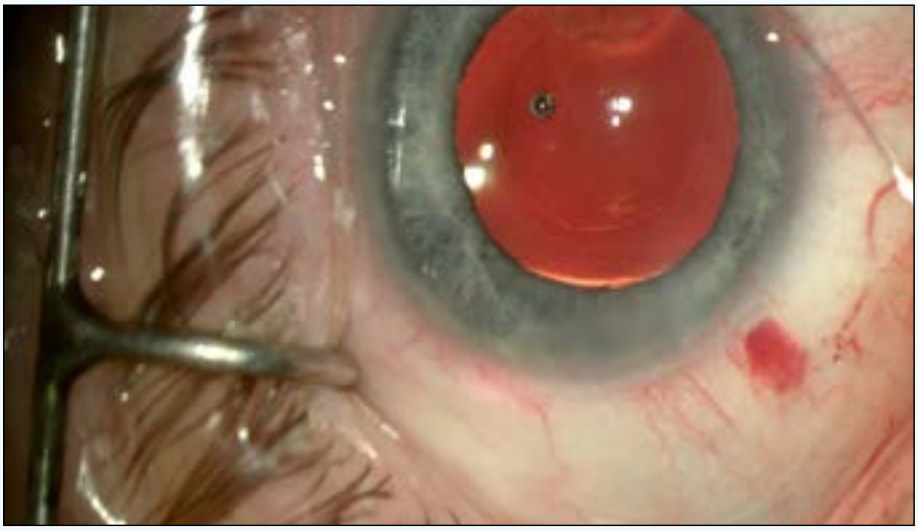

FIGURE 1: VISCODILATION WITH BLANCHING. Viscodilation is performed as the iTrack microcatheter is withdrawn. Progress is monitored by visualization of the illuminated tip in Schlemm's canal. Blanching of limbus is noted distal to tip of the iTrack microcatheter.

3. Biochemical: HA is a necessary substrate of the biophysiological architecture of a healthy aqueous outflow system. It is postulated that the pressurized injection of HA-based OVD into the outflow system during canaloplasty may cause beneficial biochemical changes that reduce resistance to aqueous outflow and thus lower IOP. This is based on the fact that a depletion of HA in patients' eyes may be associated with primary open-angle glaucoma.[13] A study by Knepper et al found that the amount of HA in the POAG trabecular meshwork was 77% less than that in the normal trabecular meshwork (P<.02), and HA was detected in only 4 of the 10 studied POAG trabecular meshworks.[12] High levels of matrix metalloproteinases (MMPs) have also been demonstrated to clear the deposition of extracellular matrix in the trabecular meshwork, thus facilitating the outflow of aqueous humor.[15] Decreased HA levels reduce the activity of MMP-2 and MMP-9.[18] It is thus hypothesized that in the trabecular meshwork cells of POAG patients, reduced HA can lead to down-regulation of MMPs, therefore contributing to the disruption of the extracellular matrix and, subsequently, development of POAG.[19] In the absence of high molecular weight HA its receptor, CD44, is cytotoxic to trabecular meshwork cells.[20] Viscodilation with a high molecular weight, HA-based OVD during canaloplasty (both ab-interno and ab-externo approaches) may cause binding with the CD44 receptor, reversing the cytotoxicity present in POAG - decreasing outflow resistance and thus reducing IOP.

use fell by 31.7% and 71.1% (both P<0.001) respectively. At 12 months, 30.8% of eyes treated with iTrack™ as a standalone procedure were medication-free. When performed in combination with cataract surgery, 50% of eyes treated with iTrack™ were medication-free.

iTrack™ in the Glaucoma Treatment Algorithm

A truly comprehensive procedure, iTrack™ canal-based glaucoma surgery lowers IOP by reducing resistance in all segments of the conventional outflow system, including the trabecular meshwork, Schlemm's canal, and proximal and distal collector channels.[7]

A restorative, tissue-sparing approach that can be performed outside of phacoemulsification, iTrack™ is a highly effective treatment option for moderate glaucoma. Specifically, it enables the treatment of early-stage moderate glaucoma patients in order to optimize patient outcomes whilst also preserving future treatment options. For example, in cases of controlled open-angle glaucoma, iTrack™ can be performed in patients with prior microtrabecular bypass surgery to reduce the medication burden, and to resolve symptomatic ocular surface disease (OSD). It can also be performed in cases of uncontrolled glaucoma, following microtrabecular bypass surgery, to lower IOP and to reduce the number of medications.

Canaloplasty was first conceived at a time when treatment options were limited. With a growing understanding of the biomechanics of glaucoma, iTrack™ canal-based MIGS is recognized as an efficacious and safe treatment for reducing IOP and/or medication dependence in open-angle glaucoma. Its inclusion in management algorithms can help reduce the need for medications and penetrating procedures without limiting use of future modalities. Ongoing study and understanding of its mechanisms of action will further help the science of glaucoma management.

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CONTRAINDICATIONS: The iTrack™ microcatheter is not intended to be used for catheterization and viscodilation of Schlemm's canal to reduce intraocular pressure in eyes of patients with the following conditions: neovascular glaucoma; angle closure glaucoma; and, previous surgery with resultant scarring of Schlemm's canal.

ADVERSE EVENTS: Possible adverse events with the use of the iTrack™ microcatheter include, but are not limited to: hyphema, elevated IOP, Descemet's membrane detachment, shallow or at anterior chamber, hypotony, trabecular meshwork rupture, choroidal effusion, Peripheral Anterior Synechiae (PAS) and iris prolapse.

WARNINGS: The iTrack™ microcatheter is intended for one time use only. DO NOT re-sterilize and/or reuse, as this can compromise device performance and increase the risk of cross contamination due to inappropriate reprocessing.

PRECAUTIONS: The iTrack™ microcatheter should be used only by physicians trained in ophthalmic surgery. Knowledge of surgical techniques, proper use of the surgical instruments, and post-operative patient management are considerations essential to a successful outcome.