PROS VERSUS CONS OF PRESERVING TRABECULAR MESHWORK IN THE TREATMENT OF GLAUCOMA: PART 1

In the first installment of a two-part debate, a panel of glaucoma specialists explore the rationale for preserving the trabecular tissue when necessary and discuss when it may be prudent to favor removal.

One of the prominent issues that continues to percolate in our field is whether it is better to preserve the trabecular meshwork (TM) tissue—several lines of research have revealed new insights on the TM tissue and its role in regulating IOP—or whether we should favor TM removal. It is, in essence, diseased tissue and potentially an obstacle to physiologic aqueous flow dynamics.

To begin to explore this debate, I participated in a roundtable discussion with an esteemed panel of glaucoma experts (See Figure; Scan the QR code on the next page to watch a video of the discussion). In the first installment below, Shamil Patel, MD, MBA, and Mahmoud A. Khaimi, MD, take the "pro-spare" side, offering their rationale for why they favor saving the TM tissue wherever possible. While it may seem obvious, it is worth noting that in the following we are speaking in generalities, and patient-specific factors appropriately steer our decision-making in the clinic. Indeed, even Drs. Khaimi and Patel acknowledge there are instances where removal of TM is warranted to help gain control of the glaucoma.

To spare or tear the TM? That is the question.

— Iqbal Ike K. Ahmed, MD, FRCSC

Iqbal Ike K. Ahmed, MD, FRCSC: What do we know about the TM tissue and its role in physiologic outflow?

Shamil Patel, MD, MBA: Our understanding of the TM and its role in regulating pressure has evolved. We used to think that in healthy eyes it was a passive filter and that in eyes with glaucoma it was an obstacle. While it is true that the TM filters debris and chemical activators from the aqueous, thereby removing their potential to obstruct downstream structures in the aqueous pathway, we now properly think of the TM as an active filter—and what that really means is that the TM has a role in responding to pressure spikes.[1] The evidence for that comes from studies showing that TM endothelial cells regulate hyaluronic acid (HA) levels within the outflow pathway.[2] HA interacts with cell surface receptors in the Schlemm canal (SC) to promote cell motility, adhesion, and proliferation.[3] As well, HA activates matrix metalloproteinases 2 and 9 to clear the deposition of extracellular matrix (ECM) in the TM,[4,5] whereas in the absence of HA, its receptor alters into sCD44 and becomes cytotoxic to TM cells.[6] Taken together, there is strong evidence that the TM is dynamic and important for regulating pressure. We also realize that we do not have the full picture yet. For example, Murray Johnstone, MD, from the Swedish Medical Center in Seattle, continues to research a demonstrated 'pump' function to the system that requires the inner wall of the TM. The early, but rapid, growth of our understanding of the dynamic nature of the TM—from stem cells to mechanoreceptors—justifies its preservation to allow for the application of the growing knowledge base.

Dr. Ahmed: We know that the TM has a lot of interactions with the ECM, and that the ECM, particularly in the juxtacanalicular region and from the inner wall basement membrane of the SC, is a prominent source of resistance.[7]

Dr. Patel: Yes. There is evidence that IOP regulation is a function of the TM's ability to regulate and maintain the homeostasis of the ECM and preserve the flow of aqueous through

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the conventional outflow system. An example is the decrease in HA in glaucomatous eyes. While we still don't know if the decrease is part of the cause or the result of the disease, the dysregulation of this protein within the space has been identified as a treatment target.

Dr. Ahmed: If the TM is, in essence, diseased tissue, why not strip it out?

Dr. Patel: If the TM were truly non-functional and contributing to glaucoma pathology, there is a case to be made for removing it. However, because of its important role in regulating pressure, it makes sense to see if we can restore its function first. That is what makes canaloplasty with iTrack (Nova Eye Medical) so interesting—microcatheterization breaks herniations in the SC and restores patency; introduction of high molecular weight ophthalmic viscosurgical device (OVD) further flushes the canal, the TM, and the collector channels, which are frequently clogged in eyes with primary open-angle glaucoma; and OVD also delivers HA to the TM tissue.[8-11] Due to the favorable safety profile associated with canaloplasty, you start by trying to rejuvenate the TM, and if it is unsuccessful, you still have options, but if you start by removing the TM, you have somewhat limited what you can do next. There are going to be other MIGS options on the horizon that will have standalone indications to provide patients another treatment option should rejuvenation alone not be adequate. But, if the TM is not spared initially, such an option would not exist.

Mahmoud A. Khaimi, MD: What if we get to a point where a pharmaceutical, stem cell, or gene therapy that targets the TM proves viable? What do we tell patients who had their TM removed? Canaloplasty is an option that preserves the anatomy and leaves future options viable. That includes innovations we are following in the developmental pipeline, as well as options that target the TM with stents or stripping procedures. We should keep in mind, though, that not all canaloplasty procedures are the same. With iTrack, we are performing the procedure for the complete 360° of the conventional outflow pathway, so we are addressing all the structures of the conventional pathway, and we are addressing them around the full circumference of the canal. Outflow is segmental and pulsatile, and the most likely explanation for that is the distribution of collector channels. If we place a stent, it is a focal bypass at one location. Then, the iTrack viscoinjector uses a pressurized mechanism to deliver OVD.

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DURABILITY

Dr. Ahmed: When OVD is introduced to the eye via pressurized viscodilation, it has the effect of flushing the entire system. Do we have any evidence for how long that effect lasts?

Dr. Patel: The viscoelastic remains in the eye for a couple of days postoperatively before it is eliminated. I don't think that is disputed. Yet, the point of pressurized viscodilation is to clear the herniations in the canal and beyond so that physiologic flow can occur, and that is how patency is maintained. The surgeon does not need to keep repeating the viscodilation and continually rejuvenate the system to maintain patency. It is only in the context of some sort of obstruction that reduced flow occurs.

Dr. Ahmed: If you release the obstructions, you are restoring the flow. At the level of the TM, viscodilation also stretches the TM beams to increase the effective filtration area. Is that a permanent effect?

Dr. Khaimi: There is some evidence that pressurized viscodilation creates small fractures in the trabecular beams, so the procedure may not just be expanding the effective filtration area, but also creating some new ones. That is what contributes to the longevity of the procedure. How long does that effect truly last? We don't have the answer to that, but there is no glaucoma procedure that we know of that lasts forever. The beauty of canaloplasty, and not tearing the TM, is that it can be offered again if there is a subsequent elevation in IOP. We know from various published data sets that a reduction in IOP and medication burden following canaloplasty can be sustained for periods of 36 months or greater.[12-14]

Dr. Ahmed: Have you had success repeating canaloplasty with iTrack? Or do you just move on to another procedure?

Dr. Khaimi: It is something we have repeated in selected cases. But when you get a subsequent pressure elevation after an iTrack, you have to question where the resistance is occurring. It may be time to start thinking about a subconjunctival drainage procedure. You could argue that in more difficult cases it might be prudent to start with a procedure that removes the TM, even if you think you might have to go to subconjunctival drainage down the line. In my experience, though, there is a higher chance of a rebleed in that secondary procedure after TM removal. To me, that is just another piece of evidence that at least trying canaloplasty as a first option is a better option than TM removal.

SURGICAL TECHNIQUE

Dr. Ahmed: How much OVD do you typically deliver during an iTrack procedure, and are you introducing OVD as you advance the microcatheter or as you are withdrawing it?

Dr. Khaimi: I typically use between four to five clicks per clock hour (2.8 µL per click). I prefer to viscodilate as I

am retracting the microcatheter. There is some speculation that viscodilating as you are backing out is associated with a higher risk for detaching the Descemet membrane. What I do to counteract that is to keep the patient's head tilted away, and I press down lightly on the gonioprism to ensure the anterior chamber is pressurized. That technique has allowed me to safely use more clicks to titrate the delivery in a tight canal without risking a Descemet detachment.

Figure. Shown from left to right, Drs. Patel, Khaimi, and Ahmed, along with Georges M. Durr, MD, FRCSC, and I. Paul Singh, MD, who take the "pro-tear" side in the upcoming Part 2 article, discuss iTrack at the Interventional Glaucoma Congress in Chicago in 2021.

Dr. Ahmed: Does the type of viscoelastic make a difference? I use Healon GV (Johnson & Johnson Vision) because it has a higher viscosity and molecular weight, which might have a better ability to create space. Or is the volume of OVD the more important consideration?

Dr. Patel: I also use Healon GV. There was a brief period of time when Healon GV was not available, and I had to switch to Healon Pro (Johnson & Johnson Vision). Our outcomes were no different (unpublished data). From my view, though, volume of OVD is more consequential than type. When I started with iTrack, I was using, on average, three clicks per clock hour, i.e., approximately 100 µL over the full 360° of the canal. Over time, I increased the number of clicks and started doing them going forward and backward, and I was getting close to 100 around the whole 360°. I did not see any Descemet detachment while doing that.

Dr. Ahmed: The concern about Descemet detachment comes from old studies with external canaloplasty showing a higher risk when introducing OVD while advancing compared to when the catheter is being retracted. My sense is that if you are moving the microcatheter, you are reducing the risk of a Descemet detachment. And I think you make a good point about keeping the anterior chamber filled and pressurized against the cornea, which is additional protection against a Descemet detachment. Still, I don't get the sense that either of you think this is a particularly difficult procedure associated with a long learning curve?

Dr. Khaimi: Canaloplasty is not technically challenging, and the learning curve with iTrack is relatively short in my opinion. This is a procedure we routinely teach to second-year residents who are still learning the finer points of ocular surgery, and they have no problem with it. There are some crucial steps and maneuvers to learn, but it is easy to incorporate into one's armamentarium.

PATIENT SELECTION

Dr. Ahmed: Are there any situations in which you think removing the TM tissue is beneficial or even preferable? Or have you completely moved away from those procedures?

Dr. Patel: The good thing about having a variety of MIGS options is that we have a better chance of finding the right procedure for the individual patient. I will favor removing the TM when there is clear TM pathology, but the system still has potential. Some examples include juvenile glaucoma, a young patient with pigmentary glaucoma, a younger patient with pseudoexfoliative glaucoma, a patient with uveitic glaucoma that's quiet and where the iris is far enough away, and a patient with ocular hypertension after a steroid response. Another example is uncontrolled pressure after receiving an intravitreal anti-VEGF injection, which also tends to involve the trabecular tissue. But this is still an individualized decision, and several factors come into my consideration. For instance, a higher pressure, younger age, and if there is something in the workup that suggests the pathology is localized to the TM, I may consider removal of some TM tissue to improve outflow.

Dr. Khaimi: I am more limited in my use of TM removing procedures. My concern with TM removal in a uveitic eye is the risk for inducing an inflammatory response. Generally, I only perform TM tearing maneuvers in congenital and juvenile open-angle glaucoma, although I think there is a role for canaloplasty in those cases, as well. If we think about pressurized viscodilation, we are creating small tears in the TM. It is not a gross tear out of the tissue, but rather a more controlled tearing. I have had some good success with juvenile open-angle glaucoma.

Dr. Ahmed: It sounds like the etiology of the glaucoma may be a factor, but the surgeon should still evaluate and think about some patient characteristics, as well. Stage and severity of disease have a role, as does

the number of medications a patient is using—and whether they are motivated to try and reduce medication dependence.[12] For eyes with controlled disease on drops where we are trying to get drop reduction or a moderate amount of IOP lowering, canaloplasty could be ideal. Another scenario is the patient who is eligible for cataract surgery; stents are an option, but if you want to impact multiple parts of the anatomy, and treat for 360°, iTrack provides this. With all that said, these kinds of preference questions depend a lot on the surgeon's patient population.

FINAL THOUGHTS

Dr. Ahmed: Within glaucoma circles, there is a debate about whether it is better to tear or spare the TM. I think this debate is not so much about which side is right or wrong, but more so about when each approach makes sense. It's really a matter of patient selection and choosing the right approach for the right patient. We have several factors to consider, including disease severity, the patient's history of and current medication use, and underlying mechanism of glaucoma. Ultimately, while glaucoma management is changing because of MIGS, where procedural options are being favored earlier in the continuum, an important underlying principle has not changed: We treat glaucoma in a continuum, and we want to go from less invasive, less risky options and move to invasive and riskier options as needed. With that in mind, canaloplasty with iTrack, which is associated with a favorable safety profile and has proven effective, is a good consideration earlier in the disease, especially because it leaves later lines of intervention viable. It is also important to acknowledge that intervening earlier means considering MIGS in standalone procedures. We do not have to wait for patients to need cataract surgery with a procedure like iTrack. We don't need to wait for progression, either. We can intervene to help address quality of life issues around medication use and improve compliance issues by intervening for these patients at an earlier disease stage. ■

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