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Automated Subretinal Injection: Greater Accuracy, Precision, and Reliability

Improving delivery of subretinal injections will take on greater importance as more gene and cell therapies become available for retina patients.

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Manual techniques for administering subretinal injections during vitreoretinal surgery are associated with a number of challenges. Fundamentally, placing the subretinal injection cannula tip into the subretinal space and maintaining its placement without opening a larger retinotomy requires a good degree of fine motor skill. Even the best surgeons with the steadiest of hands struggle with accuracy in this setting, to say nothing of the additional challenge of depressing the syringe plunger while keeping the attached subretinal cannula in place.

One potential solution is for the surgeon to hold the cannula while an assistant injects the drug. However, even if the surgeon works with the same team during every surgery (which is not always the case), there is no good way to tell how hard the assistant is pushing on the plunger. A lack of reliability and consistency in dose delivery dynamics undermines the ability to know if enough drug has been delivered to achieve a therapeutic benefit, not to mention the risks of transretinal pigment epithelium (RPE) injection and damage from excessive jet pressure at the tip of the cannula.

As gene and cell therapies delivered via subretinal injection move closer to regulatory approval, these concerns become more important. We need to know exactly what dose is being delivered and that it is being delivered safely. If we can't demonstrate that therapeutic modalities are safely delivered in a precise, accurate manner, it may compromise regulatory approval. Furthermore, manual delivery techniques may yield a substantial amount of drug efflux through the retinotomy with some estimates of between 40% and 60% of the delivered product escaping to the vitreous cavity.^{1,2} A number of concerning questions arise from



Figure. The MicroDose Injector set up with subretinal cannula and VFI tubing.

this reality: What happens to the live viral vector containing the therapeutic product? Does it percolate into the aqueous and/or transfect the trabecular meshwork? Does it reach the systemic circulation and transfect extraocular structures? If so, what if there is a need to turn off the biologic activity of the gene or stem cell therapy if the product has already reached the bloodstream? We need more confidence in our subretinal injections.

AUTOMATED INJECTION DELIVERY

A recently introduced automated injection system may solve several problems with subretinal drug delivery. The MicroDose Injector (MedOne; Figure), a pneumatic powered syringe which received 510(k) clearance from the US Food and Drug Administration earlier this year for low volume ophthalmic injections into the subretinal space, is connected to a vitrectomy machine to allow actuation of the syringe stopper via surgeon foot pedal control. It is fully compatible with most of the currently available vitrectomy platforms, including the CONSTELLATION (Alcon), Stellaris (Bausch + Lomb), and EVA (DORC) platforms. The MicroDose also results in less dead

space and related drug wastage because the tubing between the cannula and the injection syringe (held by the assistant) is eliminated.

The MicroDose is easy to set up, simple to use, has almost no learning curve, and results in predictable, reliable, precise, and accurate drug delivery into the subretinal space. Because a surgical assistant is not involved in the drug injection, the surgeon's hands concentrate on subretinal cannula placement, and foot pedal control injects the drug. I have used the device to inject tissue plasminogen activator mixed with an anti-VEGF agent to treat subretinal hemorrhage secondary to age-related macular degeneration and as part of the protocol in some of the gene therapy studies in which I have participated. Although I have not yet used it in any applications related to subretinal cell therapy, I have been involved in trials with the cell therapies where presumed cell efflux into the vitreous was associated with epiretinal membrane formation.

SET-UP, USE, AND IMPACT ON EFFICIENCY

The MicroDose Injector is simple to use and easy to integrate into one's routine with improved efficiency. The filling process, which takes about 20 seconds, can be completed in one of three ways:

- Inject from a second syringe into the tip of MicroDose syringe whose plunger has been withdrawn;
- Utilize a draw needle from a vial and use aspiration from a vitrectomy machine; or
- If the injectable is in a vial with a luer adapter, screw it onto the syringe and withdraw directly using aspiration from the vitrectomy machine.

The injector is then primed to evacuate any air. Giving the syringe a firm shake drives the injection drug against the syringe plunger and air toward the subretinal injection cannula where it is expelled using a low pressure setting on the vitrectomy machine. Try to avoid creating a constant stream of injectable from the subretinal injection cannula tip to reduce the chance of jet pressure-related damage to the RPE or injection into the choroid. Depending on the viscosity of the drug being delivered, the pressure setting will need to be adjusted. I typically start at 10 psi and adjust until I see a slow drip—about 1 to 2 drips per second.

During the actual injection, the rate of delivery can be adjusted via the foot pedal. In most cases, I set my maximum injection pressure at 14 to 16 psi, but most of the drug injection is delivered at a lower pressure. I use more pressure (closer to the max limit)

until a bleb starts to form and then back off the pressure (to the 4 to 6 psi range) while gently pulling the cannula away from the RPE, maintaining it in the subretinal space. I use NGENUITY (Alcon) for all my surgeries, and the heads-up display settings are of great benefit in making real-time dynamic foot pedal-based adjustments to injection pressures in response to changing bleb geometry as the subretinal bleb forms.

CONCLUSION

Automating the plunger depression for subretinal delivery of drugs has several benefits, including improved predictability, reliability, precision, and accuracy. It is also associated with an improved safety profile, less drug wastage due to lower dead space, and a smaller retinotomy, which may reduce drug efflux into the vitreous cavity. As more patients receive precious and expensive gene and cell therapies, better, safer, and more precise drug delivery with less wastage will only become more important. ■

1. Hsu ST, Gabr H, Viehland C, et al. Volumetric measurement of subretinal blebs using microscope-integrated optical coherence tomography. *Transl Vis Sci Technol*. 2018;7(2):19.

2. Sastry A, Li JD, Raynor W, et al. Microscope-integrated OCT-guided volumetric measurements of subretinal blebs created by a suprachoroidal approach. *Transl Vis Sci Technol*. 2021;10(7):24.

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