A Novel Intravitreal Injection System

The Guarded Injection Device provides an extra layer of protection for injections without a lid speculum.

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The volume and frequency of intravitreal injections has grown at a great rate during the past decade, and this increase in utilization has put a burden on physicians, practices, patients, and the health care delivery system. With current projected volume now at or above 1 million intravitreal injections per year,[1] there is a need to make these procedures less burdensome and safer. Innovations that can lead to reduction in patient pain both during and after the injection, reduction in the time and resources needed for the injection, and safer injections, would be a boon to the profession and patients alike.

SIMPLIFY, SIMPLIFY

In the pivotal clinical trials evaluating ranibizumab for treatment of age-related macular degeneration (AMD), the list of required injection procedures was quite lengthy (Table 1; personal communication, Genentech, 2012), including several periods of waiting, the insertion and removal of a lid speculum, and other steps.[2]

A group of collaborators and I felt that the use of all these steps was making the procedure longer than necessary and increasing the amount of discomfort patients were experiencing. This was especially true after the injections, the period when patients most often complain of pain or discomfort. This led us to the question, "Are we doing too much?" We embarked on the development of a modified injection technique,[3] putting together steps that others have proposed and adding some of our own.

The first step in this simplification was elimination of the lid speculum. The rationale was to reduce the patient's irritation, with less chance of corneal abrasion and less corneal drying, and also to reduce the length of time needed for the injection for the patient and doctor. For staff, this also eliminated the need to sterilize and prepare the lid speculum.

We also switched to topical anesthetics, reasoning that this would reduce postinjection hemorrhage, reduce postinjection discomfort because of less tissue disruption, and allow staff to administer the anesthesia, saving physician time.

In changing from subconjunctival to topical anesthesia, however, patient blinking becomes an issue. It is hard to predict with topical anesthetics who will blink and who will not. In addition, in patients with concomitant glaucoma, an associated problem is the growing use of prostaglandin analogues, which along with beta-blockers are the most frequently prescribed first-line medications for glaucoma.[4] One of the side effects of this class of medications is eyelash growth.[5] Longer lashes increase the risk for contamination in association with excessive blinking, potentially resulting in endophthalmitis.

TABLE 1. INTRAVITREAL INJECTION TECHNIQUE USED IN PIVOTAL TRIALS

- 3 days of antimicrobial 4 times a day (oxyfloxacin, etc.)
- Draw up medication
- 2 drops topical anesthetics (0.5% proparacaine)
- 2 drops of antibiotics (as above)
- Periocular skin and eyelids scrubbed with 10% povidone-iodine swab
- Physicians gloved and sterile drape placed
- Insert sterile lid speculum
- 2 drops povidone-iodine 5.0% over injection site
- Wait 90 seconds
- Cotton-tip applicator saturated with 0.05% proparacaine HCl for 10 seconds to injection site
- Subconjunctival 1% lidocaine without epinephrine
- Sterile 4-by-4 used to absorb excess liquid
- Patient instructed to look away from injection site
- Injection of medication
- Remove lid speculum
- Instructions to patient

Postinjection infection after intravitreal injection is a significant concern. The incidence of infection after intravitreal injection has been estimated at approximately 1 in 2000.[6] Outcomes can be poor, especially with *Streptococcus* species, which are increasing in incidence.[7]

Endophthalmitis can result from contamination from local sources, such as the lids, lashes, tear film, and conjunctiva, or even from respiration or speech from the doctor or patient.[8-10] As a result of these concerns, 46% of international responders to the most recent Practices and Trends survey reported that they wear a mask and ask patients not to speak during the injection to try to reduce this risk. The most common causative organisms identified include *Staphylococcus epidermidis*, likely originating from the skin, lids, lashes, or conjunctiva, and *Streptococcus viridans* from the oral cavity or respiratory tract.[6,11]

GUARDED INJECTION DEVICE

As an alternative approach, we have developed a Guarded Injection Device (GID; Figure 1). This is a simple sleeve or protective cover that protects a 19-gauge needle as it is inserted into a vial to draw up the drug, and then is switched to a protected 33-gauge needle that is used for the intravitreal injection.

We evaluated the effectiveness of the GID to prevent infection. Eight vials of ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) were emptied and then filled with 2 mL of sterile thioglycollate medium, which promotes aerobic, anaerobic, and microanerophilic growth. Standard and GID-guarded 19-gauge and 33-gauge needles were then contaminated with saliva, and 2 needles were used from each group. Each needle was then inserted into a drug vial containing the thioglycollate medium, and once it was fully inserted the vial was swirled around to ensure contact of the needle with the medium. The vials were then incubated for 1 month at 33° to 35°C, and checked at 72 hours and at 1 month. One vial from each group that developed microbial growth was sent for microbial identification.

All vials injected with standard needles developed microbial growth within 72 hours. None of the vials injected with a GID showed any growth at 1 month. The organisms cultured were identified as *Streptococcus viridans* groups. We concluded from this study that the GID was effective at reducing the risk of needle contamination.

We then conducted an experiment to determine the amount of additional force required to insert a needle guarded by the GID, beyond the force required to insert an unguarded needle. Using a material similar in consistency to the human sclera, a force profile was determined for the amount of force needed to collapse 60% to 70% of the needle. The unguarded 19-gauge needle required 269.78 ±18.28 grams of force (gf), and the 19-gauge needle with GID required 266.26 ±15.54 gf, indicating that the force required to retract the sleeve was −3.52 gf. This difference may have been within the margin of error of our measurement ability; clearly, not much additional force was needed with the GID.

Figure 1. Guarded Injection Device (GID).

The unguarded 33-gauge needle required 59 ±3.0 gf, compared with 72.8 ±2.7 gf with the GID, indicating that the force needed to retract the sleeve was 13.8 gf. It has been estimated that, in cataract surgery, in order to detect a difference in force between 2 knives for creating a cataract incision, there must be a disparity of more than 15 gf between the knives (A.E.M., unpublished data). We concluded from this evaluation that the GID required minimal additional force and was ready for clinical trial.

GID CLINICAL TRIAL

The next step was to conduct a clinical trial to evaluate the speed and comfort of the GID compared with a standard injection procedure in patients receiving injections in both eyes.[3] We compared injection using a 33-gauge needle with GID with no lid speculum vs a

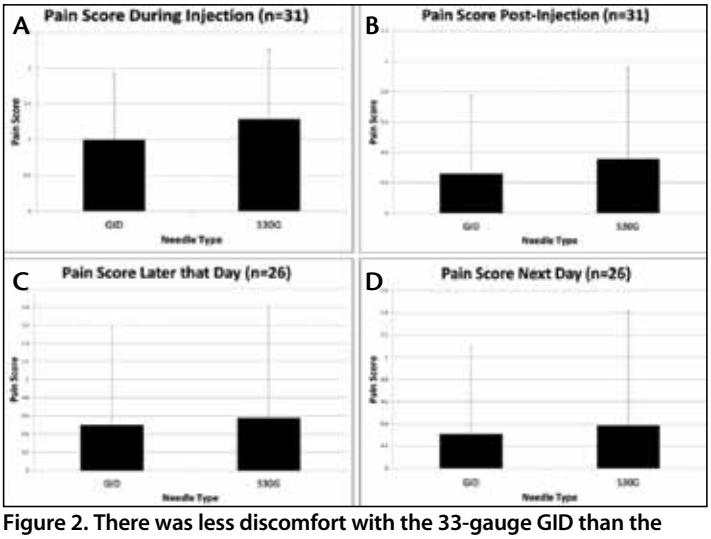

Figure 2. There was less discomfort with the 33-gauge GID than the standard 30-gauge injection at the time of injection, immediately after injection, and at the end of the day. There was still a difference in favor of the GID the next day, but it was not statistically significant.

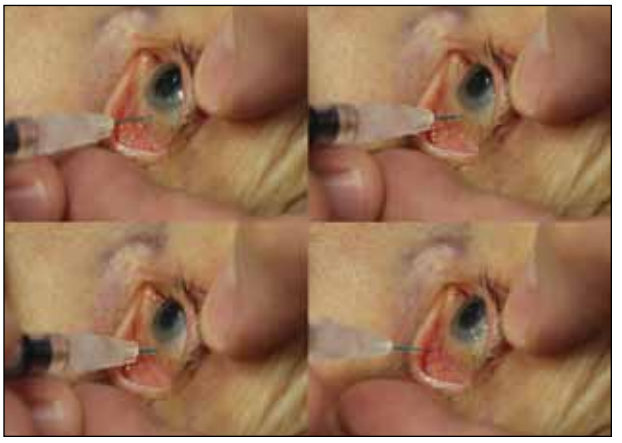

Figure 3. A routine injection procedure with the GID.

standard unguarded 30-gauge needle with lid speculum. Patients in this study received the same anesthesia in both eyes, either topical tetracaine HCl 0.5% (TetraVisc; Ocusoft) or subconjunctival lidocaine viscous 2.0%, and the same drug, either ranibizumab or aflibercept. The length of the procedure was timed, and comfort was evaluated at 4 time points: during injection, immediately after injection, later that day, and on postinjection day 1.

As of August 9, 31 patients were enrolled in the study, and 5 patients were lost to follow-up after the first 2 times points. Of the 31 patients, 26 received ranibizumab and 5 aflibercept.

Regarding pain, at the time of injection, there was less discomfort with the 33-gauge GID than the standard 30-gauge injection. Immediately after injection, and again at the end of the day, there was less discomfort with the GID. There was still a difference in favor of the GID the next day, but it was not statistically significant (Figure 2).

As for the time involved, for the investigator the GID injection took about 29 seconds, vs about 37 seconds for the unguarded 30-gauge needle with speculum. This was a statistically significant difference, and while it is not a large amount of time, it was done in a very controlled setting with research assistants, so the actual difference in practice might be greater.

For staff, the GID saved 5 minutes 8 seconds, which included the time to process the lid speculum and get it ready for the next patient. It did not include the time actually running the autoclave.

Videos were obtained for 30 of the first 31 injections done with the GID. In 4 videos, the sleeve can be seen coming in contact with the lids or conjunctiva, suggesting that the GID was providing a protective effect against infection, or at least protecting the needle from contamination.

All of the GIDs performed well in all the injections. Figure 3 shows an example of a routine injection. The sleeve collapses and does not re-cover the needle when the needle is removed.

CONCLUSIONS

Use of the GID is straightforward, and we believe it may provide an extra measure of caution and safety in the clinic. We all know from experience that a blink happens quickly, and when it happens, if an injection is being done without a speculum, there is always the question of whether there was contact or not. With the GID, it is a comfort to know there is a protective coating between the needle and the surrounding tissues.

In our investigations of the GID, the contamination studies showed a reduction in the risk of needle contamination using this device. Human studies demonstrated a reduction in the time needed for intravitreal injection time with the 33-gauge GID without lid speculum compared with standard 30-gauge needle with lid speculum. These studies also showed a trend toward more comfortable injections with the 33-gauge GID. Further studies will hopefully further clarify the benefits of this device for both the medical community and our patients. ■

This work was done in collaboration with Dyson Hickingbotham, BS; Dave Booth, MBA, BME; Robert L. Avery, MD; Hussein Wafapoor, MD; and Gabriel Gordon, PhD.

Alexander M. Eaton, MD, is the Founder and Director of the Retina Health Center in Fort Myers and Naples, FL. He may be reached at +1 239 337 3337 or +1 239 793 5200. The GID is an investigational device being investigated with institutional review board approval, and Dr. Eaton states that he has a financial interest in the device. He states that he receives support or research funding or has a financial interest in I Tech JV Development, IC Labs, EyeOScan, Alcon, Genentech, Neuron, Regeneron, and L Path.

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