Intravitreal (IVT) injection is the most common procedure performed by retina specialists, with estimates of more than 6 million injections performed in the United States annually. That number is only expected to increase as new therapeutics are developed for expanding indications.

Due to the large volume of IVT injections in the retina clinic, significant efforts have been focused on making the workflow for performing IVT injections as efficient as possible and improving the patient experience.

**CURRENT TRENDS**

Despite the safety and efficacy of IVT injections, patients can experience significant anxiety and discomfort while undergoing a procedure. Indeed, in a survey of patients undergoing IVT injections, the step most associated with significant discomfort was the injection itself, as opposed to the preparation or waiting. Another study found that needle penetration was one of the highest points of concern for patients during IVT injection. These findings suggest that improving anesthesia may improve the patient experience for IVT injection.

Current methods of anesthesia for IVT injection include the application of topical anesthetic drops, a pledget soaked with lidocaine, topical lidocaine gel, and subconjunctival lidocaine injection. All of these methods have benefits and tradeoffs in terms of patient comfort and time of onset of anesthesia, and there is no consensus choice for anesthetic use in IVT injections. This is reflected in the most recent American Society of Retina Specialists (ASRS) Preferences & Trends (PAT) survey, which found that 23% of responding retina specialists used topical drops, 18% used pledgets soaked with lidocaine, 25% used lidocaine gel, and 34% used...
subconjunctival lidocaine injection (Figure). These numbers are similar to those in other surveys of IVT anesthesia preference by retina specialists.

Prospective studies comparing the efficacy of different methods of anesthesia have been mixed; one study suggested that subconjunctival lidocaine is more efficacious than lidocaine gel or topical anesthesia, whereas others found no difference in pain scores among those three methods. Systematic reviews of IVT injection anesthesia have also not identified superiority of one type of anesthesia over another in pain scores.

Considerations for anesthesia for retina specialists include the efficiency of the procedure, the comfort of the patient, and the best utilization of resources and costs. An alternative method of anesthesia that is fast, tolerable to patients, and has minimal adverse events could help to improve both the patient experience and the workflow of retinal physicians.

**A COOLER APPROACH**

Cooling anesthesia is a form of nonpharmacologic anesthesia that has shown promising results in clinical studies. We define cooling anesthesia as the local application of temperatures slightly below freezing (usually between -10° and -20° C) as an anesthetic agent. This temperature is much warmer than temperatures that have been shown to cause tissue damage to the eye.

Using low temperature to anesthetize human tissue is not a new idea, and this approach is sometimes used as anesthesia for injection of dermal fillers. The mechanisms by which anesthesia using low temperature works include decreasing nerve conduction, which inhibits the firing of pain receptors, and the release of endorphins.

Recent publications have suggested that cooling the surface of the eye, in lieu of pharmacologic agents, might provide effective anesthesia for IVT injections. A case report demonstrated that ice in a glove, applied to the conjunctiva and sclera for 2 minutes, was sufficient to effectively anesthetize the eye for a patient with a lidocaine allergy. A clinical study with a prototype cooling device demonstrated that, as measured by a visual analog scale (VAS), cooling anesthesia was well tolerated and that pain with cooling anesthesia was not significantly different from pain with lidocaine gel use.

Recently, results of a longitudinal study with a clinical-grade device manufactured by RecensMedical were presented at the 2020 ASRS Meeting.

**COOL-2 DESIGN AND RESULTS**

The COOL-2 trial (NCT03956797), sponsored by RecensMedical, was an open-label longitudinal study assessing the safety of cooling anesthesia over a series of six injections. Pain scores as measured by a VAS and data from a patient preference instrument were collected. Participants had received at
least three IVT injections before enrolling in the study. In the study, for six consecutive injections, participants received cooling anesthesia at either -15°C for 10 seconds or -15°C for 15 seconds.

The study has been fully enrolled, and 39 patients have finished the study. For these patients, pain as measured by VAS was not different from standard of care histories controls in previous studies, and VAS scores from cooling anesthesia did not change over the course of the study. Cooling anesthesia was well tolerated, and there were no ocular serious adverse events or adverse events unrelated to the injection or the device. The average injection time from start of anesthesia to injection was less than 2 minutes.

Interestingly, more than 80% of patients who received cooling anesthesia at -15°C for 10 seconds preferred that over their previous form of anesthesia. (All patients had previously received subconjunctival lidocaine as anesthesia.)

A multicenter masked randomized trial comparing cooling anesthesia to standard of care is planned to start in the near future.

**DISCUSSION AND CONCLUSION**

These studies demonstrate the proof of concept and safety of using cooling anesthesia for IVT injections. The rapid, nonpharmacologic nature of this anesthesia may improve the patient experience, decrease toxicity to the ocular surface, and facilitate a more rapid workflow and improved time and space efficiency for retina specialists.

Cooling anesthesia is an alternative, rapid, nonpharmacologic form of anesthesia that may have differentiating characteristics that make it attractive to patients and physicians alike for IVT injections. We look forward to the emergence of additional data on cooling anesthesia and its potential for the safety and comfort of our patients in the future.

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