Topical Lidocaine Gel With and Without Subconjunctival Lidocaine Injection for Intravitreal Injection: A Within-Patient Study

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BACKGROUND AND OBJECTIVE: To determine whether patients prefer topical anesthesia or subconjunctival anesthesia for intravitreal injection.

PATIENTS AND METHODS: Consecutive patients receiving bilateral simultaneous injections of anti-vascular endothelial growth factor agents were asked to participate in this within-patient, prospective, single-blinded, randomized, factorial study. Fifty-seven patients completed the study. Both eyes were treated with topical anesthesia. One eye was also injected with subconjunctival lidocaine. Anesthesia for the next treatment visit was based on patient preference at the conclusion of the study visit and at a 4-hour and 24-hour follow-up telephone call. Patients were allowed to change their anesthesia preference during the next three visits. The final endpoint for the study was anesthesia preference for ongoing intravitreal injections.

RESULTS: Fifty patients (88%) preferred subconjunctival anesthesia and seven patients (12%) preferred topical anesthesia for ongoing treatments. (P = .0003)

CONCLUSION: Given the choice, most patients prefer subconjunctival anesthesia to topical anesthesia for intravitreal injections.

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INTRODUCTION

Intravitreal injections of anti–vascular endothelial growth factor antibodies are in widespread use for the treatment of vision loss associated with wet age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion.

The optimal anesthesia for intravitreal injections has yet to be determined.[1] In 2009, the last time the Procedures and Trends Survey conducted by the American Society of Retina Specialists asked about anesthesia for administering intravitreal injections, 75% of respondents favored topical anesthesia and 24% favored subconjunctival anesthesia.[2]

There are several reasons it is difficult to determine the optimal anesthesia for intravitreal injections. Pain sensation is highly variable[3-5] and can be affected by age, gender, anxiety, depression, treatment expectation, medications, genetic makeup, and social history.[6-10] In addition, there is no objective measurable index of pain. Furthermore, the same patient receiving the same anesthesia on different visits might have no reaction at some treatment visits and a severe reaction at other treatment visits.[11] Finally, the pain from the anesthesia, the pain from the intravitreal injection, and the pain from the subsequent reactive chemical conjunctivitis all need to be considered as part of the overall experience.

This study addresses these challenges. First, because of the subjectivity and high variability of pain perception, a within-patient, masked, randomized study design was used. Patients receiving simultaneous bilateral intravitreal injections underwent a treatment visit in which one eye received subconjunctival

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anesthesia and the other eye received topical anesthesia only. Second, patient preference rather than a pain score was used as the primary study endpoint. Third, because of varied experiences at different treatment visits, patients were allowed to change their anesthesia preference up to three visits after the initial study visit.

The goal of this study was to determine which type of anesthesia patients prefer for intravitreal injection, topical anesthesia or subconjunctival anesthesia.

PATIENTS AND METHODS

Consecutive patients receiving bilateral simultaneous injections for wet AMD, retinal vein occlusion macular edema, or diabetic macular edema were asked to participate in the study. Patients were excluded if they reported pain greater than a score of 1 on a 10-point scale prior to any drops being placed in the eye. To be included in the final analysis, patients had to complete at least three follow-up treatment visits after the study visit. This study was approved by the University of South Florida institutional review board and complied with the tenets of the Declaration of Helsinki.

After enrolling in the study, the Wong-Baker faces pain scale was both shown to the patient on a large card and explained using the accompanying script.[12,13]

The patient was unaware which anesthesia was used in each eye. Patients with an even medical record number received subconjunctival anesthesia in the right eye; patients with an odd medical record number received subconjunctival anesthesia in the left eye. The right eye was always treated before the left eye, but both eyes were treated as nearly simultaneously as possible. The left eye received an intravitreal injection within 30 seconds of the right eye.

Based on methods in recently published studies, we combined tetracaine gel with proparacaine drops in an effort to use the most effective topical anesthesia.[14,15]

Initially, one drop of proparacaine 0.5% and one drop brimonidine 0.2%[16] were instilled into each eye, followed by 0.25 inches of tetracaine gel 0.5%. Patients were then asked to keep their eyes mostly closed throughout the study visit to avoid exposure keratitis. Three minutes later, another 0.25 inches of tetracaine gel 0.5% was administered to both eyes. Three minutes later, another drop of proparacaine 0.5% and another 0.25 inches of tetracaine gel 0.5% were administered inferonasally to both eyes. One eye was injected with 0.2 cc of subconjunctival lidocaine, 20 mg/mL through a 27-gauge needle inferonasally, and the fellow eye was given a sham injection using a syringe with no needle and some pressure on the eye inferonasally. Three minutes later, another 0.25 inches of tetracaine gel 0.5% was administered inferonasally to both eyes. Three minutes later, a drop of proparacaine 0.5% was administered inferonasally to both eyes. Each eye was prepared with a drop of povidone iodine 5% solution. Then, using a sterile lid speculum, each eye (right then left) was injected through the pars plana, 3 mm posterior to the corneal scleral limbus, using a 30-gauge needle with the antivascular endothelial growth factor agent. The eyes were irrigated with sterile eye rinse, and a drop of ketorolac tromethamine ophthalmic solution 0.45% was instilled into both eyes.

TABLE 1
Patient Anesthesia Method Preference After Intravitreal Injection

	Study Visit (n)	4 Hours Later (n)	24 Hours Later (n)
Strongly prefer topical anesthetic	0	2	3
Somewhat prefer topical anesthetic	1	3	1
No preference	7	16	19
Somewhat prefer subconjunctival anesthetic	30	17	14
Strongly prefer subconjunctival anesthetic	19	19	20

Patients were asked to keep their eyes mostly closed for 1 hour after the injection, to use artificial tears hourly for 4 hours, and to not rub their eyes.

Pain was rated in two ways: a 5-point scale comparing the two eyes and a 10-point standardized pain scale. Pain was rated at six time points: prior to any treatment, after the first drop of proparacaine, after subconjunctival anesthesia injection and sham injection, after intravitreal injection, 4 hours later by telephone, and 24 hours later by telephone.

At each of these times, patients were asked to rate pain in each eye from 0 to 10 based on the standardized Wong-Baker pain scale. They were then asked whether they were experiencing much more pain in the right eye, a little more pain in the right eye, no difference, a little more pain in the left eye, or much more pain in the left eye. At the end of the study visit and the two telephone calls, they were also asked

TABLE 2

Baker-Wong Pain Level Scores at Different Time Points

	Initial Proparacaine Drop (n)		Subconjunctival Lidocaine Injection (n)		Intravitreal Injection (n)		4 Hours Later (n)		24 Hours Later (n)	
Pain Level	SA	TA	SA	TA	SA	TA	SA	TA	SA	TA
0	48	45	38	55	41	6	43	38	47	54
1	4	5	4	1	2	6	6	5	4	0
2	3	4	9	1	6	10	4	9	3	2
3	1	1	3	0	4	12	0	0	0	0
4	1	2	3	0	3	5	1	2	0	0
5	0	0	0	0	1	3	1	0	0	1
6	0	0	0	0	0	5	1	2	0	0
7	0	0	0	0	0	2	0	0	2	0
8	0	0	0	0	0	2	1	1	0	0
9	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	6	0	0	1	0

SA = subconjunctival anesthesia; TA = topical anesthesia.

which anesthesia method they preferred, that administered in the right eye or in the left eye.

When determining which treatment to use at the first post-study visit, we used the preference cited immediately after injection for all patients who continued to have that preference or who later switched to no preference. If their anesthesia preference changed from the study visit to the follow-up telephone calls, we used the anesthesia preference they expressed at the time of their follow-up telephone call. Patients were also allowed to change their preference based on their overall assessment of the experience during the next three visits. The final endpoint for the study was anesthesia preference for ongoing intravitreal injections.

RESULTS

Sixteen patients declined enrollment in the study, and three patients who were enrolled in the study were excluded because of inadequate follow-up.

Fifty-seven patients completed the study. The average patient age was 82 ± 11 years (SD). Thirty-seven were women and 20 were men. The reason for injections was wet AMD in 51 patients, diabetic macular edema in five patients, and central retinal vein occlusion with macular edema in one patient. Eyes treated with subconjunctival anesthesia were injected with bevacizumab (n = 21), ranibizumab (n = 31), and aflibercept (n = 5). Eyes treated with topical anesthesia were injected with bevacizumab (n = 22), ranibizumab (n = 30), and aflibercept (n = 5). Three patients were treated with different medications in each eye. Subconjunctival lidocaine was administered to the right eye in 28 patients and the left eye in 29 patients.

At the end of the study visit, there was a strong preference for subconjunctival anesthesia (Table 1, page 307). Seven patients had no anesthesia preference after the treatment visit. At the hour 4 telephone call, 16 patients had no anesthesia preference, and at the hour 24 telephone call, 19 patients had no anesthesia preference. Only one patient went from no anesthesia preference at the treatment visit to subconjunctival anesthesia preference at 24 hours. That patient was treated with subconjunctival anesthesia on subsequent visits (and continued to vacillate). The other six patients with no initial preference were treated with topical anesthesia at subsequent visits. Fifteen patients switched their anesthesia preference at least once during subsequent visits. After three post-study visits, 50 patients preferred subconjunctival anesthesia and seven preferred topical anesthesia ($P = .0003$, chi-squared test).[17]

During the subconjunctival anesthesia injection, a pain score of 0 to 4 was reported by all patients in each eye (Table 2). When asked to compare the two eyes, there was more discomfort in the eye treated with subconjunctival anesthesia (Table 3). During intravitreal injection, in the eye that received subconjunctival lidocaine, one patient reported a pain

TABLE 3
Pain Comparison Between Fellow Eyes at Different Time Points

	Proparicaine Drop (n)	Suconjunctival Lidocaine (n)	Intravitreal Injection (n)	4 Hours Later (n)	24 Hours Later (n)
Topically anesthetized eye hurts much more	0	0	19	2	0
Topically anesthetized eye hurts a little more	2	0	30	10	0
Pain level equal for both eyes	53	38	7	40	49
Subconjunctivally anesthetized eye hurts a little more	2	17	1	3	6
Subconjunctivally anesthetized eye hurts much more	0	2	0	2	2

score of 5; all other patients reported scores of 0 to 4. During intravitreal injection, in the eye treated with topical proparacaine and tetracaine gel, six patients reported a pain score of 10, two reported scores of 8 to 9, 10 reported scores of 5 to 7, and 34 reported scores of 0 to 4 (Table 2).

The average of the pain scores from the subconjunctival anesthesia and intravitreal injection is sometimes used to compare subconjunctival lidocaine to topical anesthesia.[18,19] The mean pain score of 0.75 for the lidocaine injection and the intravitreal injection was significantly lower than the mean pain score of 1.93 for the sham lidocaine injection and the intravitreal injection ($P = .001$, paired t-test).

Reported pain at 4 hours did not differ for the two treatment methods. However, 24 hours after treatment, three patients (5%) reported experiencing severe pain in the eye treated with subconjunctival lidocaine (Table 2).

There was a trend toward more subconjunctival hemorrhage in the subconjunctival anesthesia group. At the end of the study visit, 28% of eyes (16 of 57) receiving subconjunctival anesthesia experienced a subconjunctival hemorrhage: 14 involved one quadrant, one involved two quadrants, and one involved three quadrants. Sixteen percent of eyes (nine of 57) receiving topical anesthesia had a subconjunctival hemorrhage: eight involved one quadrant, one involved two quadrants, and none involved three quadrants ($P = .16$, chi-squared).[17]

DISCUSSION

Retinal specialists usually (75% of the time) use topical anesthesia for intravitreal injections.[2] Our study suggests that most (88%) of the time, patients prefer subconjunctival anesthesia.

Several published studies comparing subconjunctival lidocaine anesthesia to topical anesthesia concluded that topical anesthesia was superior.[18-21] A within-patient study of 28 patients comparing topical to subconjunctival anesthesia for intravitreal steroid injections concluded that the two modes of anesthesia were nearly equivalent, and the added burden of subconjunctival hemorrhage that occurred with subconjunctival anesthesia made topical anesthesia preferable. Interestingly, this study showed better pain control with subconjunctival anesthesia. Our study found that patients overwhelmingly prefer subconjunctival anesthesia despite the increased incidence of subconjunctival hemorrhage.

Three studies compared subconjunctival lidocaine anesthesia to topical anesthesia and found no difference in pain scores between patients treated with the two different types of anesthesia.[19-21] These three studies allowed at most 30 seconds, 1 minute, or 1 to 2 minutes for the subconjunctival lidocaine to take effect prior to intravitreal injection. In the current study, we allowed at least 6 minutes for subconjunctival lidocaine to take effect. Although we know of no studies measuring the time of onset of anesthesia from subconjunctival lidocaine, a study of 2% lidocaine for dental procedures shows that the onset of anesthesia is 3.3 ± 1.5 minutes (average ± SD).[22] It is likely that the reason these three studies found no difference in reported pain scores following intravitreal injection with topical anesthesia compared to subconjunctival lidocaine was that they did not allow adequate time for the subconjunctival lidocaine to take effect.

Because all of our patients were receiving ongoing intravitreal injection therapy, we planned our study to include these ongoing visits after the study visit.

This enabled us to use patient preference over a series of treatments as a study endpoint. The patients were unaware which eye was treated with which anesthesia. As described above, we used their preferences stated during and after the study visit to determine their likely preferred choice for anesthesia going forward with subsequent treatment. That preference determined which anesthesia technique was used in both eyes at the first post-study visit. At the end of the first post-study visit, patients were asked how that treatment felt compared to prior treatments. If they felt the treatment was more unpleasant than they recalled prior treatments to be, we offered to change the anesthesia on the following visit. This was done at each of the three post-study visits until the patients settled on a final anesthesia preference.

Fifteen patients (26%) vacillated on anesthesia preference during their three post-study visits, changing their anesthesia preference at least once. There are a number of reasons why preferences could have changed. Unpleasant side effects of topical anesthesia, such as inadequate anesthesia, are not necessarily evident at every treatment visit. Similarly, unpleasant side effects of subconjunctival anesthesia, such as chemosis, chemical conjunctivitis, and subconjunctival hemorrhage, are also not evident at or after every treatment visit. In addition, our patients are elderly, and their memory of their prior treatments and experiences from visit to visit was not always perfect. By allowing the patients to base their preference on an initial comparative test and then their experience with subsequent treatment visits, we were trying to select the optimal anesthesia method for them.

In conclusion, most patients prefer subconjunctival anesthesia to topical anesthesia for intravitreal injections. The likely reason why our results differ from those of previous studies is that we allowed adequate time for the subconjunctival lidocaine to take effect and we used patient preference as a study endpoint. The minimum total time for anesthesia in this study was 12 minutes per eye: 6 minutes for topical anesthesia and then an additional 6 minutes for subconjunctival anesthesia. Physicians may need to modify this time schedule because it may not be practical in all clinic settings. We have found that the more time allowed for subconjunctival anesthetic to take effect, the less discomfort the patients experience up to about 20 minutes.

Our study suggests that there is not one optimal anesthesia for intravitreal injections. If one believes that the optimal anesthesia is the one that patients prefer, then for most patients subconjunctival lidocaine is the optimal anesthesia for intravitreal injections. Because intravitreal injection therapy is usually ongoing, treating physicians can allow patients to try different anesthesia methods and decide what type of anesthesia they prefer.

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