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ASSOCIATION BETWEEN NEEDLE SIZE, POSTINJECTION REFLUX, AND INTRAOCULAR PRESSURE SPIKES AFTER INTRAVITREAL INJECTIONS

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Purpose: To compare the effect of 30-gauge versus 32-gauge needle size on postinjection reflux and immediate postinjection intraocular pressure (IOP_{immed_post}) spikes in eyes injected with anti-vascular endothelial growth factor agents.

Methods: This was a prospective interventional case series of 65 eyes of 54 consecutive patients in a clinical practice setting who received intravitreal anti-vascular endothelial growth factor therapy. All eyes had preinjection IOP, IOP_{immed_post}, postinjection reflux, and axial lengths recorded.

Results: There was a higher incidence of postinjection reflux in eyes injected with 30-gauge (53%) compared with those injected with 32-gauge (13%, $P = 0.0007$). Among 34 eyes injected with 30-gauge, 16 eyes without appreciable postinjection reflux had mean IOP_{immed_post} of 44.3 ± 7.48 mmHg and mean IOP_{immed_post} elevation of 29.6 ± 2.10 mmHg, which was significantly higher than the 18 eyes with reflux (mean IOP_{immed_post} of 18.8 ± 7.15 mmHg and mean IOP_{immed_post} elevation of 4.5 ± 1.74 mmHg, $P < 0.0001$). Among 31 eyes injected with 32-gauge, 27 eyes without appreciable postinjection reflux had mean IOP_{immed_post} of 44.4 ± 10.82 mmHg and mean IOP_{immed_post} elevation of 29.5 ± 1.99 mmHg, which was significantly higher than the 4 eyes with reflux (mean IOP_{immed_post} of 21.3 ± 8.54 mmHg and mean IOP_{immed_post} elevation of 9.5 ± 4.05 mmHg, $P < 0.001$). The differences in reflux and IOP between the two groups were unrelated to axial lengths ($P = 0.451$).

Conclusion: Eyes receiving injections with 32-gauge needles had a lower incidence of postinjection reflux and higher mean IOP immediately after injection.

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The rapid growth in the use of intravitreal anti-vascular endothelial growth factor (VEGF) therapy for the treatment of a variety of retinal diseases has raised concerns regarding potential long-term effects on intraocular pressure (IOP) in eyes receiving repeated intravitreal injections.[1–8] In fact, a greater number of intravitreal anti-VEGF injections have been shown to be associated with an increased risk of sustained IOP elevation.[9] Although the mechanism by which sustained IOP elevation is induced in susceptible eyes is still unclear, several theories have been proposed including a pharmacologic effect of VEGF blockade, inflammatory trabeculitis, protein aggregates, or silicone droplet debris leading to impaired outflow and damage to the trabecular meshwork because of repeated trauma and/or immediate IOP spikes associated with the injection procedure.[1–5] Elevation in IOP immediately postinjection, although shown to be common and transient,[10–16] may remain a significant contributing factor to the development of sustained IOP elevation in the long term.

Physicians may have a tendency to favor smaller gauge needles because they are believed to induce less

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pain and reduce vitreous reflux, which avoids the potential lowering of drug concentration and efficacy. However, it has also been demonstrated that factors influencing the immediate postinjection IOP elevation include the presence or absence of vitreous reflux and needle bore size.[13,15,16] Benz et al[13] first showed that patients who experienced vitreous reflux had lower immediate postinjection IOP compared with those who did not. Kim et al[15] subsequently showed that significant IOP spikes were observed with a smaller needle bore size. This study aims to investigate the hypothesis that a smaller needle bore size results in a lower occurrence of vitreous reflux, which in turn is related to a higher postinjection IOP.

Methods

Institutional Review Board approval was obtained for this Health Insurance Portability and Accountability Act-compliant prospective study, and all research adhered to the tenets of the Declaration of Helsinki. Consecutive patients of two physicians (K.B.F. and J.A.S.) at a vitreoretinal referral practice located in New York City, NY, who received intravitreal injections of ranibizumab (0.5 mg/0.05 mL) or aflibercept (2 mg/0.05 mL) were included in this study. A 30-gauge needle was used by the first physician, and a 32-gauge needle was used by the second physician, as per their usual injection technique, respectively. All patients had immediate preinjection IOP (IOP_{pre}) and immediate postinjection IOP (IOP_{immed_post}) measurements recorded using Goldmann applanation tonometry by unmasked investigators (C.E.P. and S.M.), ensuring that IOP_{pre} and IOP_{immed_post} were measured by a single person for each eye. IOP_{immed_post} was consistently measured within 1 minute to 2 minutes after the intravitreal injection, and IOP_{immed_post} elevation was calculated as the difference between IOP_{pre} and IOP_{immed_post}. Immediate postinjection reflux was assessed by denoting no detectable reflux as "absence of reflux" and any reflux that was visible as "presence of reflux." All patients had axial lengths measured by IOLMaster (Carl Zeiss meditec, Inc, Dublin, OH).

All injections were performed under topical anesthesia. Before injection, eyes were treated with topical proparacaine hydrochloride (0.5%) and topical 5% povidone–iodine solution applied to the conjunctiva. There was no attempt to presoften the globe with ocular massage. Injections were performed 3.5 mm to 4.0 mm posterior to the limbus, in the inferotemporal quadrant, with the patient in an almost upright position with the head supported backwards. All ranibizumab (0.5 mg/0.05 mL) was drawn up at the time of injection from the single-use glass vials supplied by Genentech, Inc (Lucentis; Genentech, Inc, San Francisco, CA). All aflibercept (2.0 mg/0.05 mL) was drawn up similarly from the single-use glass vials supplied by Regeneron Pharmaceuticals, Inc (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, NY). Physician 1 (K.B.F.) used a 30-gauge needle (Precision Glide 30 G × 1/2 gauge; Becton Dickinson & Co, Franklin Lakes, NJ) and physician 2 (J.A.S.) used a 32-gauge needle (TSK STERIJECT 32 G × 1/2 gauge; Tochigi Seiko KK, 2-1-5 Hirayanagi-cho, Tochigi-shi, Tochigi-ken, Japan). Both physicians adopted similar injection techniques without the use of conjunctival displacement, cotton-tip tamponade, or tunneling of the needle. After treatment, all eyes were documented to have visual acuity of hand motion or better within several minutes of the injection procedure. No eyes received anterior chamber paracenteses.

Data analysis was performed using Graph Pad Prism version 6.0 software (GraphPad software, San Diego, CA). The presence of postinjection reflux in eyes injected with 30-gauge needles was compared with that seen with 32-gauge needles using Fisher's exact test. Immediate postinjection changes in IOP (IOP_{immed_post} elevation) between eyes with and without appreciable reflux and between 30-gauge and 32-gauge needles were compared by a 2-tailed *t*-test. Significance was accepted at $P < 0.05$.

Results

Sixty-five eyes of 54 patients with neovascular age-related macular degeneration, retinal vein occlusion, or diabetic macular edema, were studied. Thirty-four eyes received intravitreal anti-VEGF injections with 30-gauge needles by physician 1 and 31 eyes received injections with 32-gauge needles by a physician 2. In eyes receiving injections with 30-gauge needles, the mean age was 83 ± 7.8 years, mean axial length was 24.0 ± 1.41 mm, and mean immediate IOP_{pre} was 14.9 ± 2.08 mmHg. In eyes receiving injections with 32-gauge needles, the mean age was 81 ± 10.3 years, mean axial length was 23.8 ± 1.43 mm, and mean immediate IOP_{pre} was 14.5 ± 4.04 mmHg. Both groups were compared using independent sample *t*-test and were found to be matched by age ($P = 0.213$), axial lengths ($P = 0.451$), and IOP_{pre} ($P = 0.612$) (Table 1).

Fifty-three percent of eyes injected with 30-gauge needles had postinjection reflux, compared with only 13% of eyes injected with 32-gauge needles. There was a higher incidence of postinjection reflux in the eyes injected with 30-gauge needles compared with

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Table 1. Characteristics of Eyes Receiving Intravitreal Injections With 30-Gauge and 32-Gauge Needles

	30-Gauge Needle	32-Gauge Needle	2-Tailed *t*-test, *P*
No. eyes	34 eyes	31 eyes	
Mean age, years	83 ± 7.8	81 ± 10.3	0.213
Mean AL, mm	24.0 ± 1.41	23.8 ± 1.43	0.451
Mean preinjection IOP, mmHg	14.9 ± 2.08	14.5 ± 4.04	0.612

AL, axial length.

those injected with 32-gauge needles (Fisher's exact test, $P = 0.0007$) (Figure 1).

Immediate postinjection IOP was compared between the 2 needle gauge groups, and it was found that the incidence of an IOP_{immed_post} of 30 mmHg or higher was 71% in the eyes injected with 32-gauge needle compared with 55% in the eyes injected with 30-gauge needle ($P = 0.304$). The incidence of IOP_{immed_post} of 40 mmHg or higher was 55% in the eyes injected with 32-gauge needle compared with 32% in the eyes injected with 30-gauge needle ($P = 0.139$), whereas the incidence of IOP_{immed_post} of 50 mmHg or higher was 42% in the eyes injected with 32-gauge needle compared with 9% in the eyes injected with 30-gauge needle ($P = 0.003$) (Figure 2).

The mean IOP_{immed_post} was significantly higher in eyes injected with 32-gauge needles (41.4 ± 13.07 mmHg, n = 31) compared with eyes injected with 30-gauge needles (30.8 ± 14.78 mmHg, n = 34) with $P = 0.003$ (2-tailed *t*-test). Calculating the difference in the IOP_{pre} and IOP_{immed_post} revealed that the mean IOP_{immed_post} elevation was significantly higher in eyes injected with 32-gauge needle (26.9 ± 2.17 mmHg, n = 31) compared with eyes injected with 30-gauge needle (16.3 ± 2.56 mmHg, n = 34) with $P = 0.002$ (2-tailed *t*-test) (Figure 3).

Among 34 eyes injected with 30-gauge needles, 16 eyes without appreciable postinjection reflux had

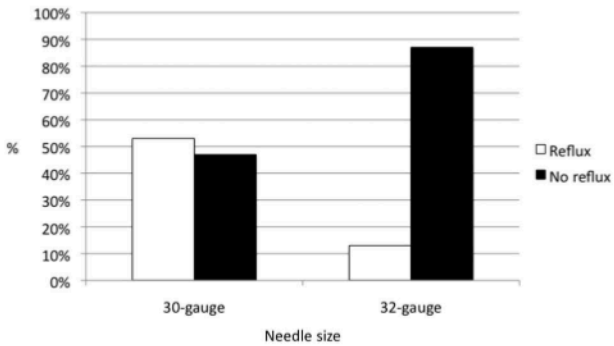

Fig. 1. Bar graphs showing the percentage of eyes with postinjection reflux after injection with 30-gauge and 32-gauge needles.

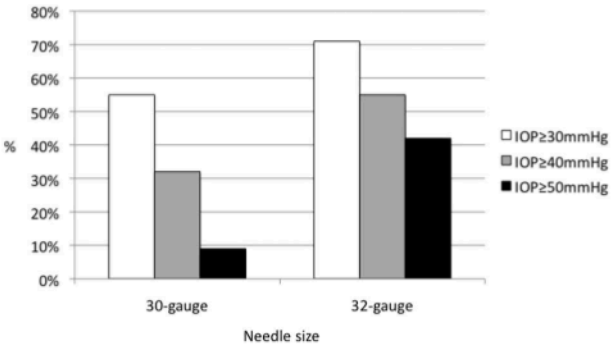

Fig. 2. Bar graphs showing the percentage of eyes with high postinjection IOP after injection with 30-gauge and 32-gauge needles.

a mean IOP_{immed_post} of 44.3 ± 7.48 mmHg and mean IOP_{immed_post} elevation of 29.6 ± 2.10 mmHg, which was significantly higher than the values in the 18 eyes with reflux (mean IOP_{immed_post} of 18.8 ± 7.15 mmHg and mean IOP_{immed_post} elevation of 4.5 ± 1.74 mmHg, $P < 0.0001$, 2-tailed *t*-test).

Among 31 eyes injected with 32-gauge needles, 27 eyes without appreciable postinjection reflux had a mean IOP_{immed_post} of 44.4 ± 10.82 mmHg and mean IOP_{immed_post} elevation of 29.5 ± 1.99 mmHg, which was significantly higher than the values in the 4 eyes with reflux (mean IOP_{immed_post} of 21.3 ± 8.54 mmHg and mean IOP_{immed_post} elevation of 9.5 ± 4.05 mmHg, $P = 0.0003$ and $P = 0.0009$, respectively, 2-tailed *t*-test) (Figure 4).

Of note, we found similar mean IOP_{immed_post} in the 2 groups of eyes without demonstrable vitreous reflux, injected by either 30-gauge or 32-gauge needles (44.3 ± 7.48 mmHg and 44.4 ± 10.82 mmHg, respectively, $P = 0.985$). The 2 groups of eyes with reflux also had similar mean IOP_{immed_post} whether injected by 30-gauge or 32-gauge needles (18.8 ± 7.15 mmHg and 21.3 ± 8.54 mmHg, respectively, $P = 0.895$). These results suggest good reproducibility of IOP measurements between the 30-gauge and 32-gauge needle groups.

Discussion

Despite the ubiquitous use of intravitreal anti-VEGF therapy, there is no current consensus or standardization in injection protocols among physicians. In fact, a recent survey performed among retina specialists with existing memberships to the American Society of Retina Specialists, the Macula Society, and the Retina Society revealed that there exists a wide variation in terms of needle gauge used, volume of medication injected, injection technique, use of anterior chamber paracentesis, use of cotton-tipped applicator to prevent

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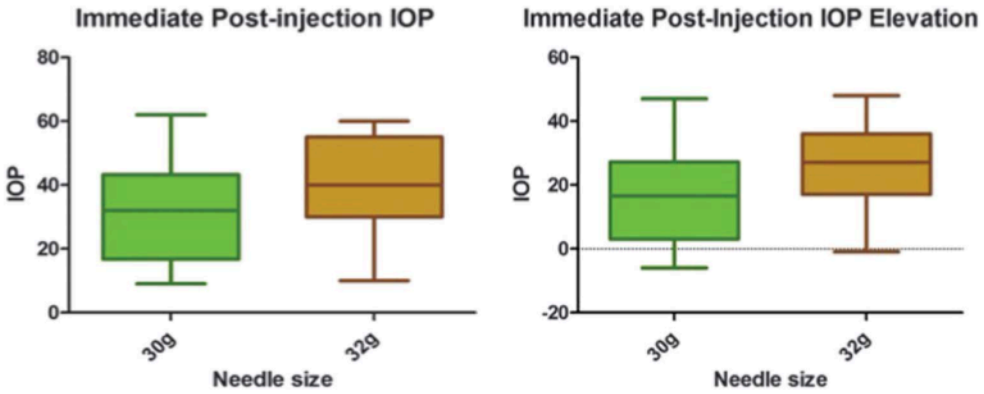

Fig. 3. Box Plots showing the immediate postinjection IOP and elevation after injection with the 30-gauge needle compared with the 32-gauge needles.

reflux, and IOP monitoring practices.[16] Based on previous observations that showed that the immediate IOP was higher in the absence of vitreous reflux[13,17] and with smaller bore needles,[15] this study was interested in exploring the significance of needle choice on the frequency of postinjection IOP spikes. We chose the 2 needle sizes that were used most frequently by the survey responders, 30-gauge needle and 32-gauge.[16] We anticipated that our results might be relevant for future recommendations on injection protocols.

Our study found strong evidence that the incidence of vitreous reflux was higher in eyes injected with larger 30-gauge needles compared with those injected with 32-gauge needles. Immediate postinjection IOP was also found to be significantly lower in eyes injected with 30-gauge needles compared with the smaller 32-gauge needles. Not surprisingly, eyes without appreciable postinjection reflux, regardless of the needle-gauge size used, had an IOP_{immed_post} elevation that was significantly higher than in eyes with appreciable postinjection reflux. This supports the hypothesis that a smaller needle bore size results in a lower occurrence of vitreous reflux, which in turn is related to a higher postinjection IOP.

Although it would seem that a shorter axial length and therefore smaller initial eye volume may predispose to a greater immediate IOP increase after

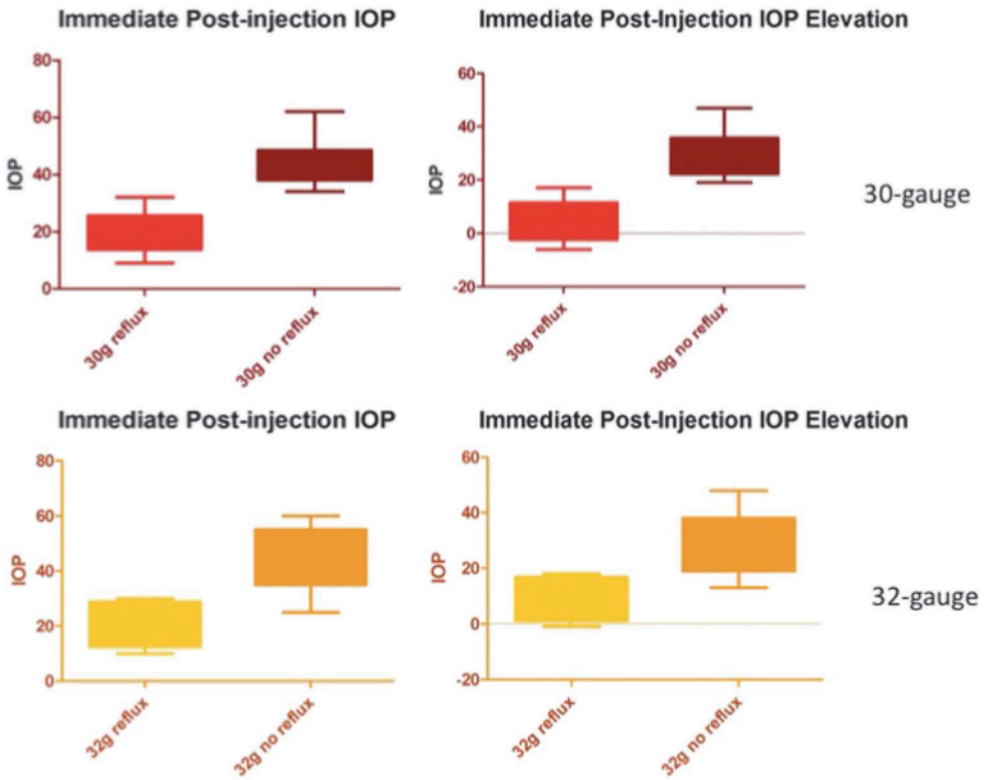

Fig. 4. Box Plots showing the immediate postinjection IOP and elevation in eyes with vitreous reflux compared with those without reflux, in both the 30-gauge and 32-gauge needle groups.

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injection, it was shown in a previous study[17] that axial length was not a predictor of subsequent transient or sustained IOP elevation. This study has taken into account that the axial length in both groups were comparable and hence not a significant confounder or related to immediate postinjection reflux or IOP.

The limitations of this study is the small sample size and the various variables that could not be controlled including physician and patient factors, such as injection technique, IOP measurement technique, status of vitreous, and number of prior injections. However, our study found strikingly similar mean postinjection IOP in eyes without demonstrable vitreous reflux injected by 30-gauge compared with those injected by 32-gauge needles and similar mean postinjection IOP in eyes with reflux injected by 30-gauge versus those injected by 32-gauge needles, demonstrating good reproducibility of IOP measurements between the 30-gauge and 32-gauge needle groups. This suggests that the differences in postinjection IOP are primarily attributed to the presence or absence of reflux and that any physician or patient variables that existed did not significantly alter the postinjection IOP outcomes.

In literature, the arguments surrounding the most appropriate needle size for intravitreal injections have been related to the patients' pain level during the injection. Studies have examined whether decreasing the needle-gauge size leads to an increase in patient comfort.[18–20] Although there was no objective measure of pain evaluated in this study, we did not detect any demonstrable subjective difference in the comfort level of patients who were injected with the 30-gauge needle compared with the 32-gauge needle. In fact, patients with high postinjection IOP often complain of a sensation of pressure or headache, hence the presence of reflux may be advantageous in preventing such discomfort to the patient.

Previously, it was thought that vitreous reflux during intravitreal injections should be avoided to maintain adequate drug concentration in the vitreous and promote optimum drug efficacy. Studies have recommended a tunneled scleral incision instead of a straight scleral incision to promote less vitreous reflux and less postinjection drug loss.[21,22] To the best of our knowledge, there have been no previous studies showing vitreous reflux relating to poorer visual outcomes. In fact, a recent study looking at the volume and composition of reflux after intravitreal injection in cadaveric human eyes showed that only a very small amount of injected therapeutic agent was lost in the reflux.[23] As the design of this study did not take into account treatment outcomes after injection, additional studies investigating whether reflux affects treatment efficacy may be useful.

In conclusion, immediate postinjection IOP was higher in eyes injected with the smaller 32-gauge needles compared with 30-gauge needles and this may be explained by the lower incidence of postinjection vitreous reflux. Based on these results and the theory that repeated injections with low reflux may cause mechanical expansile stress on the trabecular meshwork leading to sustained IOP elevation, we would advise caution regarding the use of excessively small-gauged needles in eyes with glaucoma, ocular hypertension, or when drug injection volumes are in excess of 0.05 mL.

Key words: intraocular pressure, intraocular pressure spikes, intravitreal injection, needle size, vitreous reflux, postinjection reflux.

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