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CLINICAL INVESTIGATION

Efficacy and safety of intravitreal drug injections using a short 34-gauge needle

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Abstract

Purpose To evaluate the efficacy and safety of intravitreal drug injections using a short 34-gauge needle.

Study design Retrospective study.

Methods This study included patients with age-related macular degeneration, diabetic macular edema, or macular edema associated with retinal vein occlusion. We reviewed the medical records of consecutive patients with one of those three diseases treated with antivascular endothelial growth factor (VEGF) agents using an 8-mm-long 34-gauge needle. Sustained intraocular pressure (IOP) elevations were defined as IOP exceeding 21 mmHg or 6-mmHg or higher increases from baseline on 2 consecutive visits at least 1 month apart. The main outcome measures were improved best-corrected visual acuity (BCVA), central retinal thickness (CRT), IOP changes, and incidence of complications related to the 34-gauge needle.

Results Six hundred ninety-eight injections were administered to 243 consecutive patients (mean age, 74.0 years) and reviewed. The mean follow-up time was 30.2 ± 15.9 weeks. The mean number of intravitreal injections/eye was 2.7 ± 1.8 (range, 1–9). The mean BCVA improved significantly ($P < .0001$), from 0.43 ± 0.4 logarithm of the minimum angle of resolution (logMAR) units at baseline to 0.36 ± 0.41 logMAR units at the last visit. The mean CRT decreased significantly ($P < .0001$), from 426.9 ± 168.5 microns at baseline to 297.6 ± 121.1 microns at the last visit. The mean IOP decreased significantly ($P < .0001$), from 13.6 ± 3.0 mmHg at baseline to 12.9 ± 3.1 mmHg at the visit after the first injection. A retinal tear occurred in 0.14%/injection (1/698). A sustained IOP elevation occurred in 1.29%/injection (9/698).

Conclusion Despite a few complications, the short 34-gauge needle was efficacious and safe for anti-VEGF intravitreal injections.

Keywords Intraocular pressure · Intravitreal injection · Short 34-gauge needle · Vascular endothelial growth factor

Introduction

Administration of intravitreal injections is an effective method to deliver drugs at therapeutic levels directly to the retina [1, 2]. Intravitreal injections of antivascular endothelial growth factor (VEGF) agents have achieved excellent results and become commonly used treatments for neovascular age-related macular degeneration (AMD) [3–6], diabetic macular edema (DME) [7, 8], and ME associated with retinal vein occlusion (RVO) [9, 10].

However, some ocular adverse effects related to the intravitreal injections themselves have been reported, including subconjunctival hemorrhage, traumatic lens injury, intraocular inflammation, vitreous hemorrhage, transient or sustained intraocular pressure (IOP) elevation, retinal tears and rhegmatogenous retinal detachment (RRD), and endophthalmitis [11–23].

Room for discussion remains about the appropriate needle size necessary to reduce these injection-related complications. Several studies have investigated the proper needle sizes and depths to which the needle tip descends into the vitreous cavity [24, 25]. Hubschman and colleagues [24] studied the amount of drug reflux and vitreous leakage with different needle sizes (27-, 30-, and 32-gauge) of the same length (12 mm) and different depths (8 or 4 mm) of

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needle-tip penetration into the vitreous cavity in porcine eyes and reported that 30-gauge needles and deep penetration (8 mm) of the needle tip into the vitreous may reduce reflux and vitreous incarceration. De Stefano and colleagues [25] also examined the scleral damage in porcine eyes using different needle sizes for intravitreal injections and reported that thinner needles had 2 advantages: less scleral damage and lower risk of complications. The effect of the needle length on the treatment efficacy must also be considered. Previous guidelines noted the necessity of inserting the needle into the vitreous cavity to a depth exceeding 6 mm [1]. Updated guidelines also reported that the needle length should be 18 mm or shorter but sufficiently long to facilitate complete penetration of the pars plana [26]. The drugs' intraocular pharmacokinetics might be affected by many factors such as the vitreous characteristics (presence or absence of a posterior vitreous detachment), previous vitrectomy, and axial length (high myopia). As described previously, no consensus has been reached regarding the most suitable needle size for intravitreal injections. Thus, investigating the ideal needle size is an important issue for intravitreal injections.

We previously evaluated the usefulness of a short 34-gauge needle for intravitreal injections as compared with a 30-gauge needle and reported that the former significantly reduced patients' perceived pain during the intravitreal injection and that the lower incidence of reflux after the injection was comparable to that of the 30-gauge needle [27]. Peer review of that study recommended evaluating the efficacy and safety of drug administration using the short needle. Therefore, in the current study, we increased the sample size and evaluated the efficacy and preliminary safety of intravitreal drug injections using a short 34-gauge needle.

Patients and methods

Study design and patient population

The primary goal of this single-center, retrospective chart review was to evaluate the efficacy and preliminary safety of intravitreal drug injections using a short 34-gauge needle.

This study was conducted according to the tenets of the Declaration of Helsinki. The institutional review board for clinical research of Aichi Medical University Hospital approved the study (reference number, 2017-H361). All the patients provided written informed consent after they had received a detailed description of the injection procedure.

We reviewed the medical records of consecutive patients who had neovascular AMD, DME, or ME associated with RVO and who were aged 20 years or older and had been treated with intravitreal injections using a 34-gauge needle (8 mm long) between December 2016 and January 2018.

If a patient was treated bilaterally, both eyes were evaluated separately, ie, the best-corrected visual acuity (BCVA) and central retinal thickness (CRT) of the right and left eyes were evaluated at baseline and at the last visit, and the IOP was evaluated at baseline and at the visit after the first injection. Patients were excluded who had an active ocular infection or intraocular inflammation; had undergone surgeries such as phacoemulsification, vitrectomy, and laser photocoagulation during the current study; and had been treated with sub-Tenon capsule triamcinolone acetonide within 3 months before the first intravitreal injection and during the current study. Patients who could not be examined more than 28 days after the injection were also excluded.

A sustained IOP elevation was defined as either an IOP over 21 mmHg or an increase from baseline of 6 mmHg or more on 2 consecutive visits at least 1 month apart. The criterion for the sustained IOP elevations was selected on the basis of a previously published definition [18].

Ophthalmic examinations

During the follow-up time, the BCVA was measured using Landolt C acuity charts, and the IOP was measured with a noncontact tonometer (Tonoref II; Nidek). Slit-lamp fundus microscopy was performed to identify complications such as retinal detachment or endophthalmitis. The CRT was measured by optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec).

The efficacy of anti-VEGF treatment using a short needle was evaluated on the basis of the improvement in the BCVA and decrease in the CRT in the spectral-domain OCT images at the last follow-up visit. The safety of the intravitreal injection with a short needle was evaluated by IOP measurement and slit-lamp examination before and after the injection at each follow-up visit.

Injection procedures

The patients were treated with an intravitreal injection of an anti-VEGF drug administered with a 34-gauge needle (0.18 × 8 mm, Pasny; Unisis). Either ranibizumab (Lucentis; Genentech) 0.05 mL (0.5 mg) or aflibercept (Eylea; Regeneron Pharmaceuticals) 0.05 mL (2 mg) was administered. A prefilled syringe was used for ranibizumab and a 1-mL syringe for aflibercept; these syringes were attached to a 34-gauge needle. Twenty surgeons administered the intravitreal injections at our outpatient office using aseptic techniques under topical anesthesia. Before the procedure, all the eyes were sterilized with 5% povidone iodine eye drops. The periocular skin, eyelid margins, and eye lashes were sterilized with 10% povidone iodine swabs, and 5% povidone iodine was instilled in the conjunctival cul-de-sac. A sterile lid speculum was inserted, and all the injections

were performed at a straight angle via the superotemporal or superonasal pars plana 3.5 to 4.0 mm posterior to the limbus if the patient was pseudophakic or phakic, respectively. The surgeons performed a similar injection technique using a sterile ophthalmic caliper and cotton-tip applicator to prevent reflux of the therapeutic agent and vitreous. Immediately after the injection, the surgeons checked the VA (hand motions or light perception). No anterior chamber paracentesis was created before or after the injection. After the procedure, the patients were instructed to use antibiotic drops 4 times daily for 3 days.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 software (SAS Institute). A statistician (K.M.) performed all the analyses. The decimal VA was converted to logarithm of the minimum angle of resolution (logMAR) units for the analyses. A paired *t* test was used for continuous variables, and the Fisher exact test, for categorical variables. Probability values of less than .05 were considered significant.

Results

Patient demographic data and characteristics

A total of 243 consecutive patients (mean age at baseline ± standard deviation [SD], 74.0 ± 11.3 years; range, 30–98 years) with neovascular AMD, DME, or RVO treated with a total of 698 injections met the inclusion criteria. Ten patients were treated bilaterally. Table 1 shows the baseline characteristics of the participants. The most common indications for the injection were AMD (59.2% [413/698]), and the intravitreal anti-VEGF agent injected most often was aflibercept (82.2% [574/698]). The mean number of injections/eye was 2.7 ± 1.8 (range, 1–9 injections). The mean follow-up time was 30.2 ± 15.9 weeks (range, 4–60.9 weeks).

BCVA

Overall, the mean logMAR BCVA improved significantly ($P < .0001$), from 0.43 ± 0.4 logMAR at baseline to 0.36 ± 0.41 logMAR at the last visit. Subgroup analysis showed the differences in the BCVA levels among the patients with AMD, DME, and RVO (Table 2). In the patients with AMD, the mean BCVA improved slightly, from 0.35 ± 0.37 logMAR units at baseline to 0.34 ± 0.35 logMAR units at the last visit, but the difference did not reach significance ($P = .34$). In the patients with DME and RVO, the mean respective BCVAs improved significantly ($P = .0013$ and $P < .0001$, respectively), from 0.39 ± 0.25 and 0.57 ± 0.45 logMAR units at baseline to 0.29 ± 0.24 and 0.42 ± 0.51 logMAR units at the last visit. In 10.8% (14/130), 20.0% (7/35), and 34.1% (30/88) of the eyes with AMD, DME, and RVO, respectively, the BCVA increased by 0.3 logMAR units or more at the last visit (Fig. 1), which is equivalent to a 3-line or greater increase on the Snellen chart or 15 letters on the Early Treatment Diabetic Retinopathy Study chart.

Table 1 Baseline demographics and characteristics

No. of patients		243
No. of injections		698
Age, y; mean ± SD		74.0 ± 11.3
Age range		30–98
Gender, no. (%)	Female	100 (41.2)
Eye, no. (%)	OD	370 (53.0)
Lens status, no. (%)	Phakic	422 (60.5)
	Pseudophakic	276 (39.5)
BCVA, logMAR; mean ± SD		0.43 ± 0.4
CRT, microns; mean ± SD		426.9 ± 168.5
IOP, mmHg; mean ± SD		13.6 ± 3.0
Indication for injection, no. (%)	AMD	413 (59.2)
	DME	73 (10.4)
	RVO	212 (30.4)
Drugs injected, no. (%)	Aflibercept	574 (82.2)
	Ranibizumab	124 (17.8)
No. injections/eye, mean ± SD		2.7 ± 1.8
Range		1–9
Follow-up, wk; mean ± SD		30.2 ± 15.9
Range		4–60.9

AMD age-related macular degeneration, *BCVA* best-corrected visual acuity, *CRT* central retinal thickness, *DME* diabetic macular edema, *IOP* intraocular pressure, *logMAR* logarithm of the minimum angle of resolution, *OD* right eye, *RVO* retinal vein occlusion

Table 2 Treatment effects of anti-VEGF drugs administered with a short 34-gauge needle

	Baseline	Last visit	*P* value*
BCVA, logMAR; mean ± SD			
Overall	0.43 ± 0.4	0.36 ± 0.41	< .0001
AMD	0.35 ± 0.37	0.34 ± 0.35	.34
DME	0.39 ± 0.25	0.29 ± 0.24	.0013
RVO	0.57 ± 0.45	0.42 ± 0.51	< .0001
CRT, microns; mean ± SD			
Overall	426.9 ± 168.5	297.6 ± 121.1	< .0001
AMD	278.3 ± 83.5	244.3 ± 62.3	.0034
DME	524.3 ± 141	398.8 ± 142.9	.018
RVO	506.9 ± 146.9	310.6 ± 128.6	< .0001

AMD age-related macular degeneration, *BCVA* best-corrected visual acuity, *CRT* central retinal thickness, *DME* diabetic macular edema, *logMAR* logarithm of the minimum angle of resolution, *RVO* retinal vein occlusion, *VEGF* vascular endothelial growth factor

*Paired *t* test

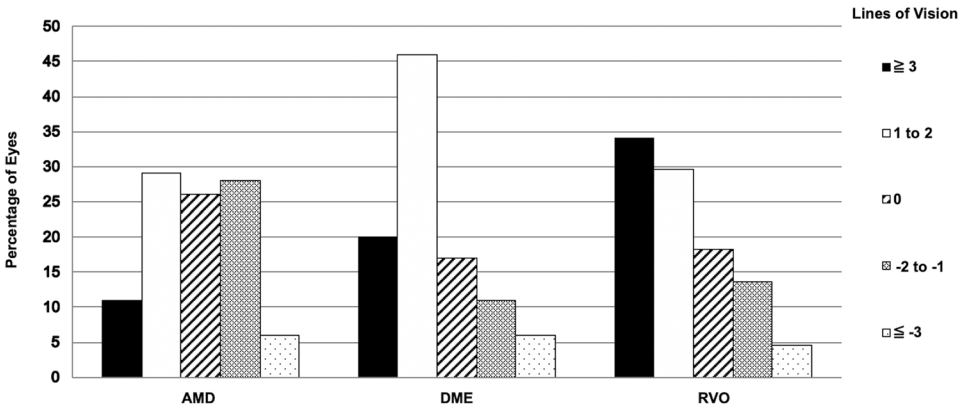

Fig. 1 Changes in visual acuity (VA) in age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO) from baseline to the last visit. The percentages of eyes with a VA improvement of 3 lines or more were 10.8%, 20.0%, and 34.1% in AMD, DME, and RVO, respectively. More eyes gained or maintained vision after injection of antivascular endothelial growth factor agents using the short 34-gauge needle

CRT and IOP

The mean CRT decreased significantly ($P < .0001$), from 426.9 ± 168.5 microns at baseline to 297.6 ± 121.1 microns at the last visit. The subgroup analysis showed that the CRT values differed among the patients with AMD, DME, and RVO (Table 2). In AMD, DME, and RVO, the mean CRT improved significantly ($P = .0034$, $P = .018$, and $P < .0001$, respectively), from 278.3 ± 83.5, 524.3 ± 141, and 506.9 ± 146.9 microns at baseline to 244.3 ± 62.3, 398.8 ± 142.9, and 310.6 ± 128.6 microns at the last visit, respectively.

The mean IOP decreased significantly ($P < .0001$), from 13.6 ± 3.0 mmHg at baseline to 12.9 ± 3.1 mmHg at 4.4 ± 2.9 weeks after the first injection. The subgroup analysis indicated that the IOPs differed among the patients with AMD, DME, and RVO. In those with AMD and RVO, the mean IOP decreased significantly ($P < .0001$ for both comparisons), from 13.2 ± 2.7 and 13.6 ± 2.9 mmHg at baseline to 12.5 ± 3.0 and 12.8 ± 2.7 mmHg at 4.5 ± 2.7 and 4.7 ± 3.2 weeks after the first injection, respectively. In those with DME, the mean IOP did not differ significantly ($P = .26$) between baseline (15.0 ± 3.6) and at 3.7 ± 2.2 weeks after the first injection (14.7 ± 3.4).

Complications

A retinal tear developed in 0.14%/injection (1/698). A sustained IOP elevation occurred in 1.29%/injection (9/698). In those 9 cases, the mean sustained IOP elevation was 22.1 ± 1.0 mmHg (range, 21.5–24.0) and the mean time of sustained IOP elevation was 6.2 ± 2.7 weeks (range, 4.3–12.9). No other serious complications occurred during the follow-up period (Table 3).

A case of a retinal tear

A 65-year-old man with ME associated with branch RVO in his left eye received 2 aflibercept injections. The injections were performed at a straight angle via the pars plana 4.0 mm posterior to the limbus in the superonasal quadrant. At the examination 1 month after his second injection, a small retinal tear was detected at the 2-o'clock position in the upper periphery. A Cirrus HD-OCT examination showed a foveal vitreous adhesion before the injection, but no posterior hyaloid was detected after the injection. Laser photocoagulation was applied around the retinal tear, and no RRD developed during the follow-up period. He was treated with 2 additional intravitreal aflibercept injections with the 34-gauge needle during the follow-up period, without further complications.

Table 3 Complications

	No. (%)
Retinal tear	1 (0.14)
RRD	0 (0)
Choroidal detachment	0 (0)
Traumatic lens injury	0 (0)
Uveitis	0 (0)
Endophthalmitis	0 (0)
Vitreous hemorrhage	0 (0)
Central retinal artery occlusion	0 (0)
Sustained IOP elevation	9 (1.29)

IOP intraocular pressure, *RRD* rhegmatogenous retinal detachment

Cases of sustained IOP elevations

Sustained IOP elevations occurred in 1.29%/injection (9/698) in 7 patients. Table 4 shows the percentages of the sustained IOP elevations in eyes with AMD, DME, and RVO. Preexisting glaucoma was present in 4 eyes; the other 5 eyes did not have a history of glaucoma. IOP elevations occurred significantly more often in eyes with preexisting glaucoma ($P < .0001$) and tended to occur significantly more often in eyes treated with intravitreal ranibizumab injections ($P = .058$). In the current study, 4 of the 9 eyes with sustained IOP elevations had been treated with antiglaucoma

Table 4 Percentages and characteristics of sustained IOP elevations

Indications	IOP elevation			*P* value*
	Detectable No. (%)	Undetectable No.	Total No.	
AMD	4 (0.97)	409	413	.12
DME	3 (4.11)	70	73	
RVO	2 (0.94)	210	212	
Drugs				
Aflibercept	5 (0.87)	569	574	.058
Ranibizumab	4 (3.2)	120	124	
Preexisting glaucoma				
Yes	4 (28.6)	10	14	< .0001
No	5 (0.73)	679	684	

AMD age-related macular degeneration, *DME* diabetic macular edema, *IOP* intraocular pressure, *RVO* retinal vein occlusion

*Fisher exact test

medication before the injections. Because their sustained IOP elevations were mild (5.0–6.5 mmHg) and the IOPs were in the range of 21.5 to 22.0 mmHg, they did not need urgent antiglaucoma medication, and therefore they were followed up. If the elevation, though mild, lasted for a long period of time, additional medication may have been considered. Fortunately, the IOPs decreased to the target range in a relatively short period of time (1.5–3 months), and no additional antiglaucoma medication was needed during the follow-up period.

Discussion

This retrospective study evaluated the efficacy and preliminary safety of intravitreal drug injections using a short 34-gauge needle. First, we assessed the effect on the therapeutic efficacy of the anti-VEGF drugs delivered by intravitreal injection using the short 34-gauge needle and found that administration with this needle was efficacious. The drugs injected with a shorter needle might be farther from the retina than those injected with a longer needle, although the full length of a long needle is not inserted, but we inserted the short needle almost to its base. The guidelines of an expert panel suggested that the needle length should be 18 mm or shorter [26], but the updated guidelines did not mention a minimal needle length. In the current study, the BCVA and CRT improved significantly overall for injections performed using the short 34-gauge needle ($P < .0001$ for both comparisons), results that were not inferior to those of previous reports [3–10]. However, further evaluation is needed to clarify the dynamics of the drugs injected with the short needle into the vitreous.

Second, we assessed the safety of the short 34-gauge needle. In the current study, a few complications occurred. A retinal tear occurred in 0.14%/injection (1/698) and no RRDs developed (0%), which agreed with the findings of previous reports [19, 28]. Boyer and colleagues [28] reported that the incidence rate of retinal tears was 0.095%/injection, and Meyer and colleagues [19] reported that the incidence rate of RRDs was 0.013%/injection. A longer needle requires that the needle tip be injected only halfway into the vitreous cavity to avoid a retinal injury due to unexpected ocular movements during intravitreal injections, while the shorter needle allows insertion of the needle fully to its base. The short needle might reduce surgeon concerns about retinal injury during the injection, particularly in patients who move unexpectedly [29]. Use of the short needle made targeting of the needle tip to the injection point on the sclera easier. Although the incidence of retinal tears or RRDs is rare after intravitreal injections [19, 28, 30], the complications are serious and the peripheral retina should be examined carefully.

No other serious complications such as endophthalmitis, choroidal detachment, or vitreous hemorrhage occurred during the follow-up period. This tolerable safety level may have resulted because the scleral wounds were small and the intravitreal injections were performed at a straight angle instead of obliquely. We avoided creating an oblique scleral tunnel because the 34-gauge needle causes less reflux than does a conventional 30-gauge needle [27]. A previous laboratory examination using porcine eyes also found smaller scleral wounds and less structural damage with a thinner needle [25]. Smaller needles might reduce reflux after injections, minimize vitreous incarceration, and contribute to decreased risk of serious complications such as retinal detachment and endophthalmitis, although the current study was not a randomized, controlled study.

In the current study, the IOP decreased significantly overall ($P < .0001$). We previously reported that while the IOP immediately after the injection was significantly higher with the 34-gauge needle than with the 30-gauge needle, it decreased to the normal range 20 minutes after the injection in both groups and did not differ significantly between the groups [27]. In this study, the reduction in IOP might have been due to the effect of the anti-VEGF drugs, considering that the change in the IOP was observed at about 1 month after the first injection. The authors of a previous large study of the effect of anti-VEGF drugs on IOP also reported that the IOP in eyes injected with drugs decreased significantly from baseline when compared with the IOP in the fellow eyes [31]. We do not know the exact reason for the IOP decrease but theorize that the statistical significance was detected because of the very small difference in the SD of the IOP between baseline (13.6 ± 3.0 mmHg) and the IOP (12.9 ± 3.1 mmHg) at 4.4 ± 2.9

weeks after the first injection. We think this statistical significance is not clinically relevant, because the magnitude of the change was as low as 0.7 mmHg.

Sustained IOP elevations were seen in 1.29% of injections (9/698), whereas another study reported that the incidence of IOP elevations was 2.6% [31]. This result might imply that the incidence of sustained IOP elevations is equivalent to that of a previous report [31] even if the 34-gauge needle is used for intravitreal injections. Regarding the drug as the cause of the sustained IOP elevation, those IOP elevations associated with ranibizumab tended to be higher than those with aflibercept ($P = .058$). Atchison and colleagues [31] reported the same result, ie, that the IOP elevation was significantly higher in eyes treated with bevacizumab (Avastin; Genentech) or ranibizumab than in eyes treated with aflibercept. That study considered that aflibercept is the only agent with an affinity for placental growth factor, which might have an unknown effect on the trabecular meshwork. Further studies should clarify whether the differences in the incidence of sustained IOP elevations are associated with different anti-VEGF drugs. Although a sustained IOP elevation was observed in several eyes, it was moderate and controllable. The rates of sustained IOP elevations were significantly higher in eyes with preexisting glaucoma than in nonglaucomatous eyes ($P < .0001$). Good and colleagues [16] reported the same result, ie, that patients with preexisting glaucoma had higher rates of IOP elevations than those of patients without preexisting glaucoma. Preexisting glaucoma may be a risk factor for sustained IOP elevations after anti-VEGF therapy regardless of the needle size used to inject the drugs.

The current study had some limitations associated with its nonrandomized, uncontrolled, and retrospective design. Although a total of 698 injections using the 34-gauge needle were administered during the 1-year study period, that number was too small to conclude that the anti-VEGF treatment using the short 34-gauge needle is more efficacious and safer than a longer, conventional 30-gauge needle because the incidence of ocular adverse effects was very low, ie, 0.01% for RRDs [19]. Further studies with more patients should investigate the efficacy and safety of intravitreal drug injections using the 34-gauge needle as compared with conventional needles.

In conclusion, the short 34-gauge needle is a commercially available tool that is just as effective, if not more so, than conventional needles and might reduce concerns about injection-related complications in routine clinical practice, especially in patients requiring repeated injections, such as in those with AMD.

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