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ORIGINAL RESEARCH

Evaluation of the Safety of Bilateral Same-Day Intravitreal Injections of Anti-Vascular Endothelial Growth Factor Agents: Experience of a Large Korean Retina Center

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Purpose: To evaluate the short-term ophthalmic side effects of bilateral same-day intravitreal anti-vascular endothelial growth factor (VEGF) injections.

Patients and Methods: We retrospectively analyzed patients who received intravitreal bevacizumab, ranibizumab, and aflibercept injections in both eyes on the same day between January 2014 and June 2019. The patients were followed up for 1 day, 1 week, and 1 month after the injections.

Results: A total of 323 patients (646 eyes) received 1418 bilateral same-day intravitreal anti-VEGF injections. The patients' mean age was 62.47 ± 13.97 years. The most common cause of bilateral injection was age-related macular degeneration (54.80%), followed by complications due to diabetic retinopathy (35.33%), retinal vein occlusion (2.40%), and central serious chorioretinopathy (1.27%). There were 22 cases of subconjunctival hemorrhage, 17 cases of temporary elevation of intraocular pressure, and no case of endophthalmitis. Twenty-one patients showed acute intraocular inflammation after the bilateral injection. All patients showed complete improvement within 2 weeks after the injection.

Conclusion: Bilateral same-day intravitreal anti-VEGF injection is a well-tolerated procedure on short-term follow-up. It is one of the more convenient approaches for both the patient and ophthalmologist.

Keywords: anti-vascular endothelial growth factor, bilateral intravitreal injection, bevacizumab, aflibercept, ranibizumab, safety

Introduction

Vascular endothelial growth factor (VEGF) plays a crucial role in the development and progression of age-related macular degeneration (ARMD), diabetic macular edema caused by diabetic retinopathy, retinal branch vein occlusion, and choroidal neovascularization. Therefore, the use of anti-VEGF agents in the treatment of these diseases is gradually increasing.[1–6] Bevacizumab (Avastin®, Genetech, Inc., San Francisco, CA, USA), the first anti-VEGF agent used in the ophthalmic field, is an FDA-approved drug used for the treatment of rectal cancer.[7,8] However, after Rosenfeld et al proved that intravitreal bevacizumab injection had a good effect in patients with ARMD,[9] multiple studies have demonstrated that bevacizumab had excellent functional and anatomical effects on other retinal diseases caused by neovascularization and diabetic retinopathy.[10,11] Subsequently, ranibizumab

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(Lucentis®; Novartis AG, Basel, Switzerland and Genetech Inc. San Francisco, CA, USA) and aflibercept (Eylea®, Regeneron, Tarrytown, NY, USA and Bayer HealthCare, Berlin, Germany), which have increased functional effects and longer half-lives than bevacizumab, have been developed, and the usage of both drugs is also rapidly increasing worldwide.[2,6,12]

As the above-mentioned diseases may occur in both eyes, a bilateral injection may be necessary. In this situation, the surgeon must decide between performing anti-VEGF injections for both eyes on the same day or performing such treatment with an interval of a few days. According to a previous report, only approximately 46% of retinal specialists performed same-day bilateral injections.[13] Although bilateral injections performed on different days may reduce the operator's anxiety regarding infection, the patient would have to visit the hospital twice, thereby increasing the time spent in seeking treatment and the economic burden on the patient.[14]

Therefore, the authors of this study attempted to observe and analyze the short-term clinical course of patients who underwent bilateral intravitreal anti-VEGF injections on the same day.

Methods

This study retrospectively analyzed the medical records of patients who received intravitreal anti-VEGF injection in both eyes on the same day between January 2014 and June 2019 at Hangil Eye Hospital, Incheon, Korea. This study was approved by the Institutional Review Board of Hangil Ophthalmology Hospital and was conducted based on the guidelines stipulated in the Helsinki Declaration.

Before injection, obtaining patient consent and history-taking for systemic disease was performed. Patients with cerebrovascular and cardiovascular diseases or malignant tumors who underwent surgeries or procedures within 1 year received anti-VEGF injections after consultation with the relevant department of the hospital. Patients were fully informed of the injection process and possible side effects of the injections, after which the injections were performed. Acute intraocular inflammation was defined as the occurrence of cellular activity predominantly localized to the anterior chamber immediately after injection without significant pain, in contrast to the presentation of endophthalmitis.[15]

Follow-up evaluations were performed at 1 day, 1 week, and 1 month after the injections. During visits before the injections and at 1 month after the injections, the measurements of best corrected visual acuity (BCVA) and intraocular pressure (IOP), slit-lamp microscopy, fundus examination, and optical coherence tomography were performed. One week after the injections, IOP measurement, slit-lamp microscopy, and fundus examination were performed. All patients were instructed to visit the hospital immediately, even if it was not the appointment date, in the event of any untoward complication.

Ranibizumab and aflibercept were provided as single-use vials; therefore, these drugs were taken immediately before injection. For bevacizumab, pre-packaged syringes that were produced through hospital dispensing were stored and used for injections. Bevacizumab dispensing was carried out by skilled doctors and pharmacists, and all dispensing procedures were carried out in a sterile laboratory. The pre-packaged bevacizumab syringes were refrigerated at 4 °C and stored in sterilized stainless-steel canisters to prevent exposure to light, in accordance with the manufacturer's instructions.

Intravitreal injection was performed in an independent treatment room. Both eyes were anesthetized with 0.5% proparacaine hydrochloride (Alcaine®, Alcon, Fort Worth, TX, USA), and then, both eyelids and the surrounding skin were disinfected with a cotton swab dipped in 5% povidone iodine solution. After covering the sterilized fabric, the surgeon put on sterile gloves aseptically, opened the patient's eye with a speculum, sterilized the eye with 5% povidone iodine solution, and then injected 0.05 mL of the anti-VEGF drug with a 30-gauge needle syringe approximately 3.5–4 mm away from the corneal limbus. After performing the injection in one eye, all used instruments and gloves were discarded, and a new set of instruments and gloves was used for intravitreal injection of the other eye. After the injections, patients were prescribed antibiotic eye drops (Cravit®, Santen, Japan) for instillation in both eyes, four times a day for 1 week.

Statistical comparisons between the two groups were conducted using the Mann–Whitney test and Pearson's chi-squared test, and statistical comparisons among the three groups were derived from one-way analysis of variance and Pearson's chi-squared test. Differences were considered statistically significant when the p-value was <0.05.

Results

During the study period, a total of 1418 bilateral same-day injections in 646 eyes of 323 patients were performed. The

patients' average age was 62.47 ± 13.97 years, and the study population consisted of 188 men and 135 women (Table 1).

The most common cause for anti-VEGF injection treatment was ARMD, accounting for 54.80% of the cases. The other common causes necessitating anti-VEGF treatment were diabetic retinopathy (35.33%), retinal vein occlusion (2.40%), and central serous chorioretinopathy (1.27%) (Table 1). When comparing the anti-VEGF drug groups, complications of diabetic retinopathy were the major cause of bevacizumab injection (47.51%), followed by ARMD (40.74%), although the incidences of the two causes were not significantly different. For patients receiving ranibizumab and aflibercept, the most common cause was ARMD (83.15% and 93.22%, respectively).

The average BCVA before injection was 0.50 ± 0.49 logarithm of the minimum angle of resolution (logMAR), and the average BCVA at 1 month after injection was 0.43 ± 0.39 logMAR. The average IOP before injection was 15.63 ± 4.73 mmHg, and the average IOP at 1 month after injection was 15.17 ± 3.53 mmHg.

None of the patients showed endophthalmitis after the injections, but 22 cases of subconjunctival hemorrhage were noted (Table 2). Table 3 shows the distribution of the side effects per year and the anti-VEGF agent used. Twenty-one patients showed acute intraocular inflammation after injection (Table 4). The degrees of anterior inflammation observed in patients with acute intraocular inflammation were trace amounts (n = 12), 1+ (n = 6), 2+ (n = 2), or 3+ (n = 1). There were no significant differences in the incidence of acute intraocular inflammation among the three anti-VEGF groups ($P = 0.082$). No patient complained of pain, discomfort, or deterioration of vision, other than inflammation. Acute intraocular inflammation occurred within an average of 2.13 ± 3.04 days after injection, and the BCVA of these patients was 0.49 ± 0.58 logMAR before injection, 0.68 ± 0.68 logMAR when inflammation occurred, and 0.46 ± 0.52 logMAR after treatment of the inflammation. There was no significant difference in the BCVA before injection and during inflammation (p = 0.247), or that before injection and after

Table 1 Demographics of Patients Who Underwent Bilateral Same-Day Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents

Parameter	Total (n = 1418)	Bevacizumab (n = 1004)	Ranibizumab (n = 178)	Aflibercept (n = 236)	P-value
Age (years)	62.47±13.97	61.44±14.04	75.06±9.09	68.86±9.53	<0.001*
Sex (n)					0.265†
Male	188	146	23	19	
Female	135	102	16	17	
Indications for injection (n, %)					<0.001†
DR	501 (35.33)	477 (47.51)	24 (13.48)	0 (0)	
ARMD	777 (54.80)	409 (40.74)	148 (83.15)	220 (93.22)	
RVO	34 (2.40)	32 (3.19)	2 (1.12)	0 (0)	
CSC	18 (1.27)	18 (1.79)	0 (0)	0 (0)	
Others*	88 (6.20)	68 (6.77)	4 (2.25)	16 (6.78)	

Notes: Data are presented as number of patients (%). *P-value was derived from one-way analysis of variance. †P-value was derived from Pearson's chi-squared test.
Abbreviations: DR, diabetic retinopathy; ARMD, age-related macular degeneration; RVO, retinal vein occlusion; CSC, central serous chorioretinopathy; *Others, polypoidal choroidal vasculopathy, myopic choroidal neovascularization, neovascular glaucoma, uveitic macular edema.

Table 2 Side Effects of Bilateral Same-Day Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents

Parameters	Total (n = 1418)	Bevacizumab (n = 1004)	Ranibizumab (n = 178)	Aflibercept (n = 236)	P-value*
Acute ocular inflammation	21 (1.48)	12 (1.20)	6 (3.37)	3 (1.27)	0.082
Subconjunctival hemorrhage	22 (1.55)	13 (1.29)	5 (2.81)	4 (1.69)	
Acute increase in IOP	17 (1.20)	17 (1.69)	0 (0)	0 (0)	
Vitreous floater	4 (0.28)	0	4 (2.25)	0 (0)	
Vitreous hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	
Endophthalmitis	0 (0)	0 (0)	0 (0)	0 (0)	

Notes: Data are presented as number of patients (%). *P-value was derived from one-way analysis of variance.
Abbreviation: IOP, intraocular pressure.

Table 3 Frequency of Side Effects Stratified by Year for Each Anti-Vascular Endothelial Growth Factor Agent

Side Effects	Anti-VEGF	2014	2015	2016	2017	2018	2019	Total
Bevacizumab	**Number**	40	120	158	264	294	128	1004
	Acute intraocular inflammation	0	1 (0.83)	6 (3.80)	2 (0.76)	1 (0.34)	2 (1.56)	12
	SCH	0	1 (0.83)	6 (3.80)	1 (0.38)	4 (1.36)	1 (0.78)	13
	IIOP	0	0	3 (1.90)	4 (1.52)	8 (2.72)	2 (1.56)	17
	Floater	0	0	0	0	0	0	0
Ranibizumab	**Number**	24	26	42	34	40	12	178
	Acute intraocular inflammation	0	0	2 (4.76)	2 (5.88)	1 (2.5)	1 (8.33)	6
	SCH	0	1 (3.85)	1 (2.38)	0	3 (7.5)	0	5
	IIOP	0	0	0	0	0	0	0
	Floater	0	0	2 (4.76)	0	2 (5.0)	0	4
Aflibercept	**Number**	10	34	42	42	74	34	236
	Acute intraocular inflammation	0	3 (8.82)	0	0	0	0	3
	SCH	0	0	4 (9.52)	0	0	0	4
	IIOP	0	0	0	0	0	0	0
	Floater	0	0	0	0	0	0	0

Note: Data presented as number of patients (%).
Abbreviations: SCH, subconjunctival hemorrhage; IIOP, increased intraocular pressure.

treatment (p = 0.231). The average number of injections in patients with acute intraocular inflammation was 2.81 ± 2.75, which was significantly different from the number of injections in patients without inflammation (5.92 ± 6.04; p = 0.007). There was no significant relationship between the severity of acute intraocular inflammation and the number of injections (p = 0.514). Patients with acute intraocular inflammation were followed up at short intervals until improvement, and steroid eye drops were instilled. All patients showed complete improvement with no visual deterioration within 2 weeks after the injections.

Discussion

In this study, we analyzed 1418 anti-VEGF intravitreal injections in a total of 646 eyes, and none of the cases showed vision-threatening sequelae after same-day injections in both eyes. Although some previous studies have reported findings for bilateral anti-VEGF injections, few studies have covered all three anti-VEGF drugs. Juncal et al, who analyzed the effects of all three drugs, administered a total of 7824 ranibizumab, 1860 aflibercept, and 114 bevacizumab injections to 252 patients for 1 year in 2016, and they observed one case of endophthalmitis (0.001%). They reported that this frequency was similar to the frequency of endophthalmitis after conventional monocular injection (0.022% to 0.078%), indicating the safety of bilateral same-day injections.[16] However, although they analyzed a large number of ranibizumab and aflibercept injections, the number of bevacizumab injections in their study was relatively small. In this study, the results included a large number of patients who received bevacizumab injections, making it the largest number of bilateral bevacizumab injections among studies reported to date.

In particular, with regard to infection-related concerns, bevacizumab may be relatively more prone to cause infections than aflibercept or ranibizumab. Ranibizumab and aflibercept are both sold in disposable containers. However, bevacizumab is sold in two formulations in South Korea: 100 mg/4 mL and 400 mg/16 mL. Therefore, it was dispensed as a single-injection dose of 1.25 mg/0.05 mL in a sterile laboratory in each hospital. The possibility of contamination during the dispensing process and the subsequent storage may pose an increased risk of infection. However, in this study, none of the cases showed side effects that permanently affected vision, such as endophthalmitis, even though a large number of bevacizumab injections were administered, and the incidence of acute intraocular inflammation associated with injections of bevacizumab was not significantly different from those of the other two anti-VEGF agents. Ornek et al also reported that bacterial contamination was not observed for 2 weeks after dispensing multiple syringes from a single bottle of bevacizumab.[17] Chen et al reported that the drug could be stored at 4 °C for 3 weeks without loss of efficacy, and that sterility was maintained for up to 6

Table 4 Comparison of Acute Intraocular Inflammation and Non-Acute Intraocular Inflammation

Parameters	Acute Intraocular Inflammation (n = 21)	Non-Acute Intraocular Inflammation (n = 1397)	P-value
Age (years)	61.86±16.35	62.56±14.00	0.869*
Sex (n)			0.043*
Male	7	181	
Female	14	121	
Initial VA	0.38±0.49	0.35±0.57	0.475*
Post VA	0.34±0.47	0.30±0.57	0.675*
Anti-VEGF agent (n, %)			0.087†
Avastin	12 (57.14)	992 (71.00)	
Lucentis	6 (28.57)	172 (12.32)	
Eylea	3 (14.29)	233 (16.68)	
Indications for injection (n, %)			0.006†
DR	10 (47.61)	501 (35.86)	
ARMD	8 (38.10)	798 (5.12)	
Others	3 (14.29)	98 (7.02)	
Number of injections	2.81±2.75	5.92±6.04	0.007*

Notes: *P-value was derived from Mann–Whitney test. †P-value was derived from Pearson's chi-squared test.

Abbreviations: VA, visual acuity; VEGF, vascular endothelial growth factor; DR, diabetic retinopathy; ARMD, age-related macular degeneration; Others, polypoidal choroidal vasculopathy, myopic choroidal neovascularization, neovascular glaucoma, uveitic macular edema.

months.[18] Woo et al used eubacterial polymerase chain reaction with a sensitivity of 10 CFU/mL or less to determine whether sterility was maintained when a drug from the same vial was injected into both eyes.[19] In their study, bevacizumab, ranibizumab, and triamcinolone were injected, and bevacizumab was dispensed several times from one vial, similar to that in our study. Over a total of 574 injections, no bacterial contamination was found in any case.

Ruão et al divided patients who received ranibizumab and aflibercept injections into monocular injection (n = 6560) and bilateral injection (n = 1612) groups, and compared the incidence of side effects, such as endophthalmitis and retinal detachment, between the two groups.[20] They observed one case of endophthalmitis in the monocular injection group and none in the bilateral injection group, although there was one case of temporary acute intraocular inflammation. Mahajan et al classified patients who received bevacizumab and ranibizumab injections into bilateral and monocular injection groups (n = 102 in each group) and compared the findings of the two groups.[14] Over an average follow-up period of 18.4 months, no cases of endophthalmitis and cerebrovascular disease occurred in either group. One case in each of the two groups developed cardiovascular diseases. The bilateral and monocular injection groups had two and three deaths, respectively, with no statistically significant intergroup difference. In addition, according to their survey, when patients who underwent bilateral same-day injections were asked whether they wished to continue receiving same-day injections or preferred injections on separate days, 91% of the patients wanted to continue receiving bilateral same-day injections. Similarly, Bakri et al performed bilateral injections of bevacizumab with dexamethasone, ranibizumab, and bevacizumab in only 35 patients, and with an average follow-up period of 39 days after 208 injections, one patient showed non-infectious endophthalmitis.[21] All of these previous studies emphasized the use of independent hygiene gloves, hygiene trays, syringes, needles, and speculums for each eye when performing bilateral same-day injections, which considerably helped to reduce the probability of endophthalmitis.[14,20,21]

Although our study had no case of endophthalmitis, anterior inflammatory cells, suggesting acute intraocular inflammation, were found in 21 eyes (1.48%). Trivizki et al analyzed non-infectious inflammatory reactions after intravitreal bevacizumab injections in 2018 and concluded that 1.78% of patients with uveitis presented with anterior inflammatory cells after injection.[22] However, when classifying the degree of inflammation as mild-to-moderate, they did not include traces and defined the minimum level of cell count as 1+. Therefore, according to their classification criteria, the frequency of acute intraocular inflammation in our study would be 0.85%, which was less than that reported by Trivizki et al Wickremasinghe et al analyzed acute intraocular inflammation after monocular bevacizumab injection. In 19 out of 1278 injections, inflammation occurred, and the frequency was 1.49%.[15] In addition, in their study, the average number of injections for patients with acute intraocular inflammation was 2.7 ± 1.3, and there was no significant correlation between the number of injections and the degree of inflammation. In our study, the average number of injections for patients

with acute intraocular inflammation was similar to that reported previously (2.81 ± 2.75), and our study also showed no significant relationship between the previous number of injections and the degree of inflammation. However, the number of injections received by patients with acute intraocular inflammation was significantly lower than that of the remaining patients. These results suggest that acute intraocular inflammation did not appear to occur more easily even though the number of injections increased.

Although it is difficult to identify the exact mechanisms underlying these inflammatory reactions, Fine et al reported that factors, such as a history of uveitis and the use of prostaglandin preparations, can exacerbate inflammation.[23] In addition, the possibility that contamination occurred during the process of transferring the drug to the syringe, and the changes in the drug components due to temperature changes during the transport and storage of the drug, may cause inflammation. Moreover, in the case of non-infectious intraocular inflammation, even though the visual acuity was reduced due to severe inflammation, the visual acuity could be restored to the pre-injection levels within 1 month if steroid eye drops were used. In our study, all patients who showed inflammation showed improvement with steroid eye drops within up to 2 weeks, and there were no cases showing sequelae. One more presumable pathophysiological mechanism for acute intraocular inflammation may be an immune response to the antibody molecule upon re-injection after the pre-exposure to the anti-VEGF drug. This finding can also be explained by a proinflammatory interaction between the Fc (crystallizable fragment) segment and the Fc receptor in the retina.[24–26] Therefore, because ranibizumab contains no Fc segment, it may show acute intraocular inflammation less frequently than bevacizumab or aflibercept, and previous studies reported fewer acute inflammations. However, in this study, ranibizumab did not show a significant difference when compared with the other two groups, which may be attributed to the influence of the other variables described above and the much smaller numbers of ranibizumab in comparison with bevacizumab and aflibercept. Finally, according to a previous study,[24] multiple injections promoted an immunization reaction to the drug, which resulted in a high probability of inflammation. Therefore, a greater number of injections may increase the possibility of inflammation. However, when referring to our study as well as the previous studies, this did not appear to be the case. For an accurate analysis, a larger number of patients with inflammation should be compared.

One limitation of this study was that, although we could confirm the short-term ophthalmic side effects after injections, it was not possible to sufficiently confirm the ophthalmic side effects and systemic complications that may occur later. However, in the previous studies, the incidence of systemic side effects did not appear to be higher after bilateral injections,[14,16] and some studies have reported that the frequency of side effects with bilateral injection, such as retinal detachment and retinal pigment epithelial rupture, is the same as that with monocular injection.[14,20,24] Second, the purpose of this study was to determine the complications of bilateral injection; thus, a comparison with a monocular injection group was not performed in this study. However, Mahajan et al previously conducted a retrospective case-control study to compare and analyze bilateral and monocular injections of bevacizumab and ranibizumab, and concluded that there was no ophthalmic or systemic difference between the two groups.[14] Third, in general, the incidence of endophthalmitis with monocular injections is approximately 0.022–0.078%;[27,28] thus, the number of injections in this study (1418) may be insufficient to determine the safety of procedure. More patients need to be included to reliably prove its stability.

Conclusion

Same-day bilateral intravitreal anti-VEGF injection is a well-tolerated procedure on the short-term follow-up and is considered to be one of the more convenient approaches for both the patients and doctors.

Abbreviations

ARMD, age-related macular degeneration; BCVA, best corrected visual acuity; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; Fc, crystallizable fragment; VEGF, vascular endothelial growth factor.

Data Sharing Statement

Available upon request from the correspondence author.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of Hangil Ophthalmology Hospital and was

conducted based on guidelines stipulated in the Helsinki Declaration. Since we reviewed the medical record retrospectively, no separate consent was obtained. All patient data complied with relevant data protection and privacy regulations.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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