

Concomitant Bilateral Intravitreal Injection of Anti-Vascular Endothelial Growth Factor: Experience in Covid-19 Pandemic

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Abstract

Purpose: To report the concomitant bilateral intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection preference rates of patients before and after the Covid-19 outbreak and to evaluate whether this practice is safe when compared to unilateral injection.

Materials and Methods: This is a single-center, retrospective study including consecutive series of 198 eyes of 112 patients received bilateral same-day (concomitant) or unilateral anti-VEGF injections of bevacizumab, ranibizumab, and aflibercept in the operating-room between January 2020 and January 2021. One-year medical record data including preference of bilateral over unilateral injection and adverse events were reviewed with 3-month intervals as before and after Covid-19 pandemic due to the labile Covid-19 outbreak course.

Results: A total of 504 injections with 234 concomitant bilateral (%46) were administered to 112 patients. The study group consisted of 58 neovascular age-related macular degeneration (nAMD- 63.7% had bilateral nAMD), 46 diabetic macular edema (DME- 67.3% had bilateral DME) and 8 macular edema complicating retinal vein occlusion (RVO- 25% had bilateral RVO) patients. Of the injections, 156 (31%) were bevacizumab, 144 (29%) were aflibercept, and 204 (40%) were ranibizumab. The mean follow-up time per patient was 7.4 ± 4.3 months (range 4-11 months) and the mean number of injections was 3.6 ± 2.1 (range 2-10). None of the patients experienced serious vision-threatening complications or non-ocular adverse events. 85% of patients whose both eyes involved strongly preferred concomitant bilateral injection during Covid-19 pandemic while it was %35 before Covid-19 ($P < 0.001$). The ratio of the number of concomitant bilateral injections to a total of injections increased from 30% to 57% after Covid-19 ($P = 0.03$). Only 3 patients (2.6%) requested alternating unilateral injections after receiving the second concomitant bilateral injections.

Conclusion: Concomitant bilateral injection approach was preferred by the majority of patients and did not increase the adverse event rate when applied under meticulous precautions; This intravitreal injection option may be preferred during still ongoing pandemic to reduce the clinical visits of patients at risk of Covid-19 related mortality due to their comorbidities and age.

Introduction

Vascular endothelial growth factor (VEGF) plays an important role in the development and progression of pathologic neovascularization in many diseases such as age-related macular degeneration (AMD), diabetic retinopathy, and retinal branch vein occlusion (RVO). Therefore, the use of intravitreal anti-VEGF agents became the most commonly performed intraocular procedure worldwide, and still gradually increasing with new indications.[1] According to the nature of these diseases and bioavailability of agents in vitreous, patients may require multiple injections over a period of months or years.[2] In addition to the multiple injections requirement, there is also an important factor that, these diseases tend to occur bilaterally with varying degrees of severity. The fellow eye involvement is frequently seen in patients with the diagnosis of diabetic macular edema (DME) and neovascular AMD (nAMD).[3] Especially involvement of the better-seeing eye significantly affects patient quality of life and patient compliance with the treatment protocol becomes crucial.[4, 5]

Among the anti-VEGFs, first bevacizumab (Altuzan®, Turkey, Roche) and then ranibizumab (Lucentis®; Novartis AG, Basel, Switzerland and Genetech Inc. San Francisco, CA, USA) and aflibercept (Eylea®, Regeneron,

Tarrytown, NY, USA and Bayer HealthCare, Berlin, Germany), have been used intravitreally in diseases involving pathological neovascularization. After three injections of bevacizumab, we can switch ranibizumab or aflibercept in our country, these three agents are authorized for the treatment of nAMD, DME, macular edema (ME) complicating RVO, choroidal neovascularization (CNV) complicating pathologic myopia and covered by the health insurance system.[6–8] The need for the treatment of patients is the main factor that determines the burden of intravitreal injections (IVI). However, as I mentioned above, the presence of disease in both eyes and the need for more than one IVI cause this burden to increase gradually on both the patient and the physician. Obviously, the most promising strategy to overcome this problem is to perform concomitant bilateral IVI on the same day instead of performing IVI on different days. Moreover, many patients demand injections in both eyes in the same session. According to a survey report, 46% of retina specialists in the United States routinely perform bilateral same-day injections.[9] Data from studies support the idea that bilateral same-day injections are a safe and convenient treatment to use in our clinical practice and revealed that this practice did not increase the rate of adverse events despite the presence of risk factors in a subset of patients.[10–21]

Especially after the Covid 19 pandemics, as patients did in the whole world, disruptions in the IVI treatments of our patients became apparent.[22]. Before March 2019, when the pandemic affected our country, we were doing relatively lesser amounts of bilateral IVI in the same session, but after March 2019, by taking the informed consent, we increased the concomitant bilateral IVI application with the preference of our patients. Worsening of the patient's clinic and involvement of fellow eye, as a result of missing routine control visits cause of Covid-19 outbreak, have necessitated concomitant bilateral IVI and forced us to overcome our fear of concomitant bilateral injection. In this way, we aimed to reduce the patient burden and risk of Covid-19 transmission. We conducted this study to investigate the frequency of concomitant bilateral injection preference of our patients before and after the Covid-19 pandemic and to evaluate whether this practice is safe when compared to unilateral injection.

Methods

Records of patients who received IVI of anti-VEGF agents from January 2020 to January 2021 at Giresun University Faculty of Medicine Education Research Hospital Eye Clinic were retrospectively collected and reviewed. This study followed the principles of the Declaration of Helsinki and received approval from the local ethics committee. Written informed consent was obtained from all the study subjects. We evaluated this 12-month period by dividing it into 3-month intervals due to the effect of the labile Covid-19 outbreak course on patients' IVI treatment compliance. Eyes those were previously treated with IVI of steroids and were excluded. Patients who had a diagnosis of DME, nAMD, RVO (complicated with ME) and underwent concomitant bilateral or unilateral IVI were included regardless of anti-VEGF agent used. All patients who underwent concomitant bilateral injections received the same drug in both eyes. After explaining the risks of concomitant bilateral IVI in detail, the choice of bilateral IVI or unilateral IVI was left to the patient. The patients' preferences (the same session bilateral IVI or unilateral IVI at different times) were evaluated and compared separately as the period before and after the Covid-19 pandemic. Patients with bilateral disease who had IVI in both eyes on the same day (concomitant bilateral injection) or unilateral IVI on different days were asked how they requested the next injection at each pre-injection control visit. Controls were made on the first day, week and month after IVI and recorded in their files. Data such as age, gender, ocular diagnosis, anti-VEGF agent used, number of bilateral IVI injections performed at the same session, best corrected visual acuity, intraocular pressure measurement (IOP),

slit-lamp microscopy findings, fundus examination findings, and optical coherence tomography results were obtained from these records. In addition to these data, as I mentioned before, our patients' records had information about their preference to have bilateral IVI in the same session or unilateral IVI in different sessions. Detailed analysis of adverse events experienced in post-injection period was made. Events such as ocular complications, endophthalmitis, intraocular inflammation, vitreous hemorrhage, retinal tear, retinal detachment, and increased IOP were evaluated within the scope of adverse events. The detailed anamnesis information obtained from the patients and the patient admission records made to other clinics of our hospital were examined and additional evaluation was made in terms of the presence of non-ocular medical problems and emerging systemic diseases. We avoided intravitreal anti-VEGF injection if the patient had a history of significant systemic events such as stroke, cardiac arrest, or uncontrolled hypertension within the last three months.

Ivi Protocol

Bevacizumab, 1.25 mg/0.05 mL; ranibizumab, 0.5 mg/0.05 mL; and aflibercept, 2.0 mg/0.05 mL were injected by two operators. Aflibercept syringes were withdrawn from single use vials at the moment of injection. Ranibizumab injections included both prefilled syringes or were loaded from single-use vials. Bevacizumab 4 mL vial was opened daily in number according to the need. 3–4 mL of bevacizumab was withdrawn from vial into a 5 mL syringe and distributed to the IVI syringes in an amount of 0.05 mL by the helping nurse just before injection. Bevacizumab was collected from the vial on a one-off basis and this vial was discarded, never used again. Intravitreal injections (IVIs) were performed in the ophthalmic operating rooms. These rooms have hepa-filter and periodic particle validating. IVI was applied by one operator (SO) with the same protocol for all patients. Operator and a helping nurse wore surgical scrubs with face mask and sterile gloves. The patients' own clothes were taken off, sterile patient gowns and face masks were put on. Patients were taken to the operating room one by one, before entering, anesthetization was done by assistant personnel with the instillation of 0.5% proparacaine hydrochloride (Alcaine®; Alcon, Turkey) to the inferior fornix and conjunctiva. Periorbital skin and eyelashes were disinfected by wiping from the center to the periphery with a sterile cotton swab previously soaked in 10% povidone iodine. The periocular area was cleaned and dried with a dry sterile cotton swab to allow the drape to adhere. Drape was put in place and then eyelids were separated by attaching blepharostat (eyelid speculum). The operator took off his glove, put on a new sterile glove, 5% povidone-iodine was instilled onto the conjunctiva and left for approximately 3 min. During the 3-minute waiting period, the patient was allowed to look right and left, up and down. To protect the cornea from povidone iodine, BSS (balanced saline solution) was instilled into the cornea. After washing the conjunctiva with 10 mL BSS, IVI was performed in the superotemporal or inferonasal (preferred by SO) sclera, 3–4 mm from the limbus, with a 30-gauge needle containing 0.05 mL anti-VEGF. After removal of the needle, a sterile cotton swab was used to tamponade the injection site. Blepharostat was then removed, and eyes were not patched. When performing bilateral same session IVIs; all used instruments and gloves were discarded after first injection, and a new set of instruments and gloves was used for IVI of the fellow eye, using the same procedure described above. The patient was given a prescription of moxifloxacin eye drops to be taken four times daily for seven days. The biomicroscopic examination was performed for each patient on the first day morning of IVI. Follow-up evaluations were performed at 1st week, and 1st month. Patients were advised to come to the hospital without delay and hesitation when they suspected painful or painless vision loss.

Statistical Analysis

All statistical analyses were conducted using SPSS, Version 24 (SPSS, Inc, Chicago, IL, USA). SPSS data entries consisted mainly of injection-based data, so repeated injections of the same patient were included in the count. Categorical variables were compared using a chi-square test and continuous variables were compared using a two-sample t-test. Statistical comparisons among the groups were derived from one-way analysis of variance and Pearson's chi-squared test. A p-value less than 0.05 was considered statistically significant.

Results

In the 12-month period included in the study, 504 injections were administered to 198 eyes of 112 patients. Of these injections, 234 (46%) were concomitant bilateral (Table-1). The mean age of the patients was 63 ± 16.1 years (range 44–82 years), and most were female (54.4%). The study group consisted of 58 nAMD (63.7% had bilateral nAMD), 46 DME (67.3% had bilateral DME) and 8 RVO (25% had bilateral RVO) patients. The majority of patients treated with IVI were AMD and DME patients, respectively. Due to disruptions in patient follow-up as a result of Covid-19, the mean follow-up time per patient was 7.4 ± 4.3 months (range 4–11 months) and the mean number of injections was 3.6 ± 2.1 (range 2–10). In the 3-month strict quarantine period after the first Coronavirus case was seen in Turkey, only 2 AMD patients received IVI treatment in our clinic. After the restrictions were loosened, the injections were resumed, but the patients' treatment compliance was low. Injection distribution according to diagnosis before and after Covid-19 is summarized in Table-1. It was clearly seen that there was no proportional correlation between the number of patients and the number of injections after the Covid-19 pandemic (Table-1). When the number and patient preference rates of concomitant bilateral injections were compared, before and after Covid-19, a statistically significant difference was found ($P < 0.05$). 85% of patients whose both eyes involved preferred concomitant bilateral injection during Covid-19 pandemic while it was %35 before Covid-19. The ratio of the number of concomitant bilateral injections to a total of injections increased from 30–57% after Covid-19. Only 3 patients (2.6%) requested alternating unilateral injections after receiving concomitant bilateral injections.

Of the injections, 156 (31%) were bevacizumab, 144 (29%) were aflibercept, and 204 (40%) were ranibizumab (Table-2). Distribution of adverse events were summarized in Table-2. The most common adverse event, which was mostly seen in bilateral injections, was punctate epitheliopathy and a painful sensitive eye on the first day after IVI. This situation completely resolved within 3 days in almost all patients. Pain complaints without visual loss persisted in only 2 patients, and improvement was achieved in the first month with artificial tear treatment. Floater, subconjunctival hemorrhage, and increased IOP were encountered in decreasing frequency, respectively, and it was observed that subconjunctival hemorrhage, increased IOP and floater regressed spontaneously within 2–7 days. Three patients who were injected unilaterally with aflibercept were followed up daily due to the continued increase in IOP in the range of 28–32 mmHg and IOP reduction was achieved by starting topical anti-glaucomatous (brinzolamide + brimonidine) treatment. These patients were followed up with visual field test and their anti-glaucomatous treatments were continued. Of the 156 injections with bevacizumab, 27 had 0.5+, 3 had 1+ aqueous inflammation. 0.5+ aqueous inflammation was observed in 9 of 144 injections using Aflibercept. 0.5+ aqueous inflammation was observed in only 2 of 200 patients in whom ranibizumab was used. Each patient with aqueous inflammation was prescribed steroid (prednisolone acetate) + moxifloxacin drops 4 times a day, and full recovery was achieved at the end of the first week. Adverse events did not show a

statistically significant relation with the anti-VEGF agent used, the diagnosis, the number of injections, and the procedure (concomitant bilateral or unilateral) ($P > 0.05$) (Table-2). There was no significant relationship between increase of concomitant bilateral injection preference after Covid-19 pandemic and the frequency of adverse events ($P = 0.065$). After the injections, none of the patients showed endophthalmitis or had non-ocular systemic emergencies like stroke and myocardial infarction.

Discussion

The requirement of ongoing treatment and involvement of both eyes has led to increased use of anti-VEGF agents for diseases that cause pathological neovascularization. After the coronavirus outbreak, an increase in the number of Covid-19 positive individuals resulted in serious restrictions by the Ministry of Health of the State of Turkey. Unfortunately, ophthalmologic patients requiring IVI chose not to attend pre-scheduled appointments, as they were at the highest risk for COVID-19-related mortality, depending on their age and comorbidities. Following a strict 3–4-month period of the outbreak, we encountered an accumulative and worsened patient group. This has put an increasing burden on both patients and practices. After restrictions eased, when able to come to the clinic, most of the patients with bilateral disease demanded injections in both eyes in one visit. We also preferred concomitant bilateral injection in these patients with the condition of providing detailed information to the patient.

Although the safety profile is major concern, according to previous study reports the applicability of bilateral injection in the same session is encouraging.[10–21] At this point there are adverse events and ocular complications that are feared or reasonably anticipated; like, endophthalmitis and the amount of anti-VEGF agent passed into the systemic circulation. Studies with large sample sizes evaluating the rates of endophthalmitis after conventional unilateral intravitreal anti-VEGF injections reported very low rates, ranging 0.027%- 0.0075%.[23–25] A meta-analysis by McCannel reported that 52 out of 105536 injections (0.049%) had endophthalmitis. They also suggested avoiding talking, coughing, and sneezing and wearing surgical mask during IVIs.[23] Casparis et al, reported that risk of endophthalmitis was very low (0.0075%) with the performing IVI under the sterile conditions of the operating room.[24]. A study by Rayess et al, with a large sample size (503890 anti-VEGF injections), analyzed all three anti-VEGF agents in terms of occurrence of endophthalmitis, and found that the rate of endophthalmitis was independent of the agent used.[25] Similar to these reports; we observed that adverse events were independent of the agent used, and we performed IVIs in the operating room by wearing a surgical mask with taking care not to speak.

Previous studies of bilateral same-day IVIs, reinforce that concomitant bilateral intravitreal anti-VEGF injections are safe and well tolerated by patients. Thus, the popularity of this application is increasing among clinicians, studies are conducted to evaluate this application through different factors. When we analyze the purposes of these studies, it was seen that the most frequently investigated outcomes were endophthalmitis and adverse events. Although our study is in this direction too, unlike other studies, the safety and preferability of concomitant bilateral IVI application during the covid 19 outbreak were investigated in this study. The number of bilateral injections in previous similar studies ranged from 208 to 101932. The largest retrospective cohort was reported by Borkar et al, they have encountered 28 (0.027%) endophthalmitis cases out of 101932 concomitant bilateral injections, none of the endophthalmitis were bilateral.[19] In another study with a large sample size of approximately 5000 bilateral injections, it was reported that unilateral endophthalmitis developed in only one

patient who had undergone 7 unproblematic bilateral ranibizumab injections before, and systemic side effects were not observed in any patient.[20] Jang et al who experienced higher numbers of bevacizumab than the others, stated that bevacizumab was relatively more prone to infections than aflibercept or ranibizumab due to the preparation phase, dispensing process and storage.[21] Considering the literature reporting the association of previous endophthalmitis outbreaks with multiple dose contamination and preparation by the compound pharmacy[26], we did not prefer prepackaged bevacizumab syringes in our study, instead we received bevacizumab from a 4 mL vial as much as needed just before injection, and we never used the remaining bevacizumab again. Injections of the recent studies mentioned above had been done in an office-based environment.[19–21] As an important difference, we performed the injections in the operating rooms where we performed our intraocular surgeries. In a study reporting a total of 1 (0.012%) culture-proven endophthalmitis and 19 (0.233%) acute intraocular inflammation in 6,560 unilateral and 1,612 bilateral injections, injections were performed in cabins with sterile laminar flow equipment. They claimed that these cabins had lower particle and microorganism levels, due to this sterile laminar flow equipment compared to normal office environments. In addition, in this study by Ruão et al, endophthalmitis was not observed in patients who underwent concomitant bilateral injection, whereas endophthalmitis developed in 1 patient who received unilateral injection.[18] Interestingly, Ruão et al, also reported that the patient who was diagnosed with acute intraocular inflammation in the bilateral injection group did not have any signs of inflammation in the other eye. As can be understood from here, vision-threatening complications are actually associated with a wide range of unpredictable variables. When the IVI application methods of different studies are analyzed, the common point that is emphasized in almost all of them is that none of the instruments used in the previous eye is reused in the fellow eye while making concomitant bilateral injection. Likewise, in our study, we treated the second eye of the same patient as if we were injecting it into a different patient using a new sterile set of equipment. There are many ocular complications and adverse events reported in previous studies such as floaters, painless subconjunctival hemorrhage, elevated IOP, ocular inflammation, uveitis, retinal epithelial tear, retinal detachment, subretinal hemorrhage and endophthalmitis. None of the patients included in this current study experienced serious vision-threatening complications or adverse events such as endophthalmitis, retinal detachment. The degrees of non-infectious anterior inflammation observed in our study were trace amounts ($\pm 0.5+$: 1–5 cells in anterior chamber, $\pm 1+$: 6–15 cells in anterior chamber) similar to recent reports [20, 21] and vitritis was not seen. Although this is not mentioned in the literature; we encountered considerable number of punctate epitheliopathy with or without sensitive painful eye complaint at first day after IVI. This may be happened due to the povidone iodine instillation and keeping it for 3 minutes on each eye or remnants of povidone iodine on conjunctival fornix or the underlying untreated dry eye disease. However, most of patient complaints resolved after 3 days. Albeit it has been reported that there may be permanent IOP elevation secondary to the cumulative effect of recurrent IVI[27], we did not encounter severe permanent IOP elevation in most of our patients. We observed subconjunctival hemorrhage in some patients due to conjunctival capillary injury at the injector insertion site, which regressed spontaneously in a short time. In studies evaluating subconjunctival hemorrhage, the relationship between this condition and any vision threatening outcome was not mentioned.[15, 20, 21] In this study population, there was no significant difference between bilateral and unilateral IVI application or anti-VEGF agent used in terms of adverse event ; however, among three anti-VEGF agents which we used, the least anterior chamber reaction was observed in patients who were administered ranibizumab. Similarly, previous studies reported fewer acute inflammations and also systemic exposure with ranibizumab.[28, 29] This has mostly been attributed to the absence of the Fc segment on ranibizumab, as known this segment was found

associated with intraocular inflammatory reactions. Souied et al, compared severe ocular inflammation rates in patients treated with ranibizumab versus aflibercept, and showed more frequent severe ocular inflammation following IVI with aflibercept than with ranibizumab during routine clinical use in patients with nAMD.[28] Although the analyzes of almost all studies conducted are not statistically strong enough because the incidence of a rare complication such as endophthalmitis is evaluated; few studies comparing unilateral application with bilateral application indicated that there was no difference between the two applications in the means of non-ocular adverse events and ocular complications.[14, 16, 18] Likewise to these published reports we did not observe any significant difference between unilateral and concomitant bilateral injections. Data regarding the amount of released anti-VEGF from eye to systemic circulation is still insufficient. In a prospective study by Wang et al., the amount of anti-VEGF (bevacizumab) entering the systemic circulation after concomitant bilateral administration was compared with unilateral administration by using the enzyme-linked immunosorbent test method, and as a result, no difference was found in serum levels.[16] In a similar study by Wang et al., serum and plasma VEGF concentrations were evaluated in nAMD patients treated bimonthly with an IVI of aflibercept or ranibizumab, and concluding that serum and plasma VEGF concentrations were not significantly affected by ranibizumab.[30] In our study, in which we administered more ranibizumab than aflibercept and bevacizumab, none of the patients experienced non-ocular systemic emergencies suggesting systemic exposure. Due to the uncertainty of systemic exposure, we also avoided intravitreal anti-VEGF injection if the patient had a history of significant systemic events such as stroke, cardiac arrest, or uncontrolled hypertension within the last three months. Another important logical expectation that should be considered is the increase in the risk of developing immune sensitization against the anti-VEGF agent used with the number of injections made. However, our study and recent reports in the literature, showed no significant correlation between the occurrence of inflammation and the number of injections the patient received.[10, 12, 21] Bakri et al., observed a sterile ocular inflammation in one eye of a patient in whom both eyes had previously received intravitreal bevacizumab, however, they also stated that if the expected immunization was to occur, there would have to be inflammation in both eyes.[10] When we evaluate the studies stating that concomitant bilateral injection, or in other words, same-session bilateral injection, can be tolerated by patients and preferred to conventional unilateral injection method, it is seen that the number of patients returning to unilateral injection after bilateral application is low or none.[10, 13–15, 17, 19] Despite the irritation of both eyes with povidone iodine residues, our patients tolerated concomitant bilateral injection well. Only a few of them (3 patients-2.6%) requested alternating unilateral injections after receiving the second concomitant bilateral injections. Studies that did not report any endophthalmitis after concomitant bilateral injection had relatively small sample sizes, such as ours, and acknowledged the need for larger studies.[10, 12–15, 17, 21] However, since there are multiple variables apart from sample size in each study that may alter the complication outcome, no firm conclusion could be drawn about the safety of concomitant bilateral injection. If we evaluate our results in our own conditions, without making a comparison with published studies with many different variables; we can attribute the absence of sight-threatening complications in our patients to the following measures: administration of IVI in operating rooms, keeping povidone iodine on the conjunctiva for three minutes, wearing a mask, using a new set of sterile equipment for both eyes, and avoiding the use of prepackaged bevacizumab syringes.

Study Limitations

This study is limited by its non-randomized retrospective design, relatively small sample size, and follow-up time. Moreover, the preference rates for simultaneous bilateral injections may be biased as some patients

demand this option themselves as well as their operators. Of course, it should be noted that the desire of our elderly patients to come to the hospital less under the influence of the pandemic also causes bilateral injection to be superior to unilateral. To the best of our knowledge, our study is the first to evaluate the increasing application requirement, preferability and outcomes of concomitant bilateral injections under the influence of covid-19 pandemic period. Despite aforementioned limitations, this study provides important data for patients and surgeons to make an informed decision about unilateral and bilateral injections in unusual circumstances such as covid-19, and to encourage them to apply this procedure under some precautions.

Conclusion

As the number of patients requiring intravitreal anti-VEGF treatment increases, the need for efficient and safe IVI approaches arises for both patients and surgeons in extraordinary conditions such as the covid-19 pandemic. Concomitant bilateral injection approach can significantly reduce the number of office visits required to treat patients with bilateral pathological neovascularization, hence the burden on the health care system and patients. Parallel to previous studies, this procedure was preferred by almost all our patients and even surgeons over unilateral injection. Our results demonstrate that this procedure can be safe if meticulous safety measures are taken to prevent infection at every step of the procedure for each eye. Considering the concomitant bilateral injection results of prior reports and our study; It is mandatory to validate this IVI approach that increases efficiency for both patients and ophthalmologists with masked clinical trials that have a larger sample size, longer follow-up, and more standardized conditions.

Declarations

Acknowledgements:

Ethics

Ethics Committee Approval: The study adhered to the principles of the Helsinki Declaration of Human Rights and received local ethics committee approval.

Informed Consent: Consent was obtained from all patients for the use of their medical records.

Authorship Contributions

Surgical and Medical Practices: S.O., Concept: S.O., H.K., Design: S.O., H.B K., Data Collection or Processing: S.O., M.A.O., Literature Search: S.O., H.K., Writing: S.O.

Conflict of Interest: The authors have no conflicts of interest.

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Tables

Table 1

Diagnostic characteristics of patients and the effect of covid-19 pandemic on concomitant bilateral injection preference

	Time period, total patient, injection (n)	Indication for injection per patient (n,%)	Patients with bilateral involvement (n,%)	Bilateral injections/ total injections (n,%)	Preference of concomitant bilateral injection per patient	P-value	
Before Covid-19 pandemic	(01.01.2020– 31.03.2020), 65, 200	AMD (30, 46%)	20, (66%)	60/200, 30%	16/46, 35%	< 0.001* (concomitant bilateral injection preference Before vs. After Covid- 19 Pandemic)	
		DME (30, 46%)	25, (83%)				
		RVO (5, 8%)	1, (20%)				
After Covid-19 pandemic	(01.04.2020– 30.06.2020), 2, 4	AMD (2, 100%)	2, (100%)	4/4, 100%	2/2, 100%	0.03*(bilateral injection amount Before vs. After Covid- 19 Pandemic)	
		AMD (35, 50%)	25, (71%)				
		DME (30, 43%)	20, (66%)				
	(01.07.2020– 30.09.2020), 70, 110	RVO (5, 7%)	3, (60%)				
		AMD (36, 42%)	26, (72%)	110/190, 58%	44/50, 88%		
		DME (43, 50%)	21, (49%)				
	RVO (7, 8%)	3, (43)					
	(01.10.2020– 11.01.2021), 86, 190						

Data presented as number (n) and percentage (%) of patients. * P value is derived from Pearson's chi-squared test. AMD: age related macular degeneration, DME: diabetic macular edema, RVO: retinal vein occlusion.

Table 2

Adverse Events of Concomitant Bilateral and Unilateral Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents

anti-VEGF Agent	Adverse Events	Adverse Events in Unilateral Injection (n),diagnosis (n)	Adverse Events in Concomitant Bilateral Injection (n), diagnosis (n)	P-value*
Bevacizumab (n = 156)	Punctate epitheliopathy ± sensitive painful eye complaint	46: 20 DME, 26 AMD	56: 25 DME, 21 AMD	0.06
	Subconjunctival hemorrhage	10: 5 DME, 5 AMD	14: 8 DME, 6 AMD	0.09
	Acute ocular inflammation	17 (0.5 + aqueous cells) †: 10 DME, 7 AMD 3 (1 + aqueous cells) †: 3 DME	10 (0.5 + aqueous cells) †: 6 DME, 4 AMD	0.06
	Increased IOP	10: 6 DME, 4 AMD	13: 7 DME, 6 AMD	0.09
	Floater	33: 18 DME, 15 AMD	36: 21 DME, 15 AMD	0.09
	Endophthalmitis	0	0	-
	Aflibercept (n = 144)	Punctate epitheliopathy ± sensitive painful eye complaint	45: 21 DME, 24 AMD	50: 29 DME, 21 AMD
Subconjunctival hemorrhage		13: 8 DME, 5 AMD	14: 7 DME, 7 AMD	0.07
Acute ocular inflammation		5 (0.5 + aqueous cells) †: 3 DME, 2 AMD	4 (0.5 + aqueous cells) †: 2 DME, 2 AMD	0.08
Increased IOP		13: 7 DME, 6 AMD	8: 4 DME, 4 AMD	0.06
Floater		22: 14 DME, 8 AMD	19: 11 DME, 8 AMD	0.09
Endophthalmitis		0	0	-
Ranibizumab (n = 204)	Punctate epitheliopathy ± sensitive painful eye complaint	46: 30 DME, 16 AMD	54: 21 DME, 23 AMD	0.07
	Subconjunctival hemorrhage	10: 6 DME, 4 AMD	11: 7 DME, 4 AMD	0.06
	Acute ocular inflammation	1 (0.5 + aqueous cells) †: 1 DME	1 (0.5 + aqueous cells) †: 1 DME	0.09

Data presented as number. * P value is derived from Pearson's chi-squared test and one-way analysis of variance. IOP: intraocular pressure, †0.5+: 1–5 cells in anterior chamber, †1+: 6–15 cells in anterior chamber. AMD: age related macular degeneration, DME: diabetic macular edema, RVO: retinal vein occlusion.

anti-VEGF Agent	Adverse Events	Adverse Events in Unilateral Injection (n),diagnosis (n)	Adverse Events in Concomitant Bilateral Injection (n), diagnosis (n)	P-value*
	Increased IOP	8: 3 DME, 3 AMD, 2 RVO	8: 3 DME, 4 AMD, 1 RVO	0.09
	Floater	5: 2 DME, 3 AMD	6: 2 DME, 3 AMD, 1 RVO	0.08
	Endophthalmitis	0	0	-

Data presented as number. * P value is derived from Pearson's chi-squared test and one-way analysis of variance. IOP: intraocular pressure, †0.5+: 1–5 cells in anterior chamber, †1+: 6–15 cells in anterior chamber. AMD: age related macular degeneration, DME: diabetic macular edema, RVO: retinal vein occlusion.