



Survey of Intravitreal Injection Techniques and Treatment Protocols Among Members of the Turkish Ophthalmological Association

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Abstract

Objectives: To describe the intravitreal injection (IVI) techniques, practices, and treatment protocols of ophthalmologists in Turkey from May 20, 2020 to June 4, 2020.

Materials and Methods: All members of the Turkish Ophthalmological Association were contacted by e-mail to complete an anonymous, 47-question internet-based survey.

Results: Thirteen percent of the participants prescribed prophylactic antibiotics pre-injection, 63.8% (406/636) used antibiotic drops immediately after injection, and 91.8% prescribed topical antibiotics. The majority of IVI procedures were performed in an operating room (65.3%) or clean room (33.6%). Most surgeons used sterile gloves, masks, sterile drape, sterile fenestrated cover, and sterile eyelid speculum. Multispecialists (M) preferred to wear sterile gloves more than retina specialists (RS) (99.0% vs. 95.3%; $p=0.004$). Also, M prescribed antibiotics more than RS (93.7% vs. 88.8%; $p=0.029$). RS dilated the pupil more frequently than M (48.3% vs. 39.0%) ($p=0.020$). RS were more familiar to use different quadrants (right $p=0.012$; left $p=0.001$). Most surgeons (82.8%) did not perform injections in both eyes on the same day.

Conclusion: Ophthalmologists in Turkey employ a wide range of techniques in care before, during, and after IVI. In addition, IVI techniques and treatment protocols differed between RS and M. Further research is needed to elucidate best practice patterns.

Keywords: Intravitreal injections, survey, retina specialists, anti-VEGF

Introduction

Intravitreal injections (IVI) are widely used by ophthalmologists for the treatment of various retinal diseases. The IVI technique was first described in 1911 and has been used to administer anti-vascular endothelial growth factors, corticosteroids, and other drugs for many years.^{1,2} There are several published guidelines describing the indications and procedures of IVI.^{3,4,5} However, there is no consensus among clinicians on the intravitreal injection technique or pre-injection and post-injection care.

The aim of this study was to determine the personal preferences of ophthalmologists in Turkey regarding IVI procedures.

Materials and Methods

All members of the Turkish Ophthalmological Association were contacted via e-mail in May 2020 to complete a 47-question internet-based survey. Three reminder e-mails were sent to the participants who had not completed the survey. SurveyMonkey (www.surveymonkey.com; SurveyMonkey, San

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Mateo, CA) was used for the data collection. The final results were collected on June 4, 2020. Thirty-five questions related to injection and follow-up procedures were evaluated. In the first 3 questions, participants were asked about demographic data (institution, society membership). The fourth question asked if the participant had experience with IVI. Participants who did not have any experience with IVI were directed to the end of the questionnaire. Reimbursement regulations in Turkey indicate 3 consecutive monthly injections of bevacizumab for the treatment of diabetic macular edema (DME), age-related macular degeneration (AMD), and retinal vein occlusion. Therefore, there was no question about the timing of IVI in the survey. Protocol differences regarding the injection techniques were also evaluated. Participants were divided into the retina specialist-only group (RS) and multispecialty group (M) and protocol differences were compared between groups.

Statistical Analysis

All P values were derived from chi-square tests using SPSS software version 20 (IBM Corp, Armonk, NY). The research protocol was initially submitted to the Institutional Ethics Committee and Review Board of the University of Kocaeli (registration number: KAEK 2020/219).

Results

A total of 892 ophthalmologists answered the questionnaire. Of these, 232 participants reported having no experience related to IVI. The other 660 participants who were actively performing IVI were included in our analysis of practice patterns.

Demographic Data

The participants' institutions are presented in Table 1. RS accounted for 30.6% (273/891) of all participants. The responses of RS and M are evaluated in Table 2. Of all respondents, 4.4% (39/882) were members of the Turkish Ophthalmological Association Medical Retina Society, 2.4% (21/882) were members of the Turkish Ophthalmological Association Vitreoretinal Surgery Society, and 4.4% (39/882) were members of both the Medical Retina and Vitreoretinal Surgery societies. The remaining 88.8% (783/882) of the participants were not members of any society.

Pre-injection Practices

Only 13.0% (84/646) of the participants prescribed prophylactic antibiotics before IVI. There was no statistically significant difference in prophylactic antibiotic use between RS and M (10.9% vs. 14.2%, respectively, p=0.216). In terms of setting, 65.3% (422/646) of the participants performed IVI in an operating room (OR), 33.6% (217/646) in a clean room (CR), and 1.1% (7/646) in an office or other setting. There was no significant difference between RS (OR: 61.5%, CR: 36.6%, office-others: 1.9%) and M (OR: 68.0%, CR: 31.5%, office/other: 0.5%) (p=0.083). Nearly all participants (97.8%; 633/647) administered topical anesthetics, 2 participants (0.3%) preferred peribulbar anesthesia, whereas 12 participants (1.9%) did not perform anesthesia before IVI. There was no difference

in topical anesthesia use between RS and M (96.9% vs. 98.5%, respectively, p=0.448).

Most surgeons draped before IVI, with 56.7% (367/647) saying they used a sterile drape and 34.9% (226/647) using a fenestrated towel. The rest of the surgeons did not use any covering. There was no significant difference in draping practices between RS (sterile drape: 55.3%; fenestrated towel: 34.2%; no covering: 10.5%) and M (sterile drape: 57.5%; fenestrated towel: 35.6%; no covering: 7.0%) (p=0.281).

Ninety-six percent (624/650) of the participants used a sterile eyelid speculum during the procedure. There was no difference in eyelid speculum use between RS and M (96.1% vs. 95.9%, respectively, p=0.886).

Povidone iodine (PI) antiseptics on the conjunctiva was used by almost all surgeons (98.9%, 643/650). However, different concentrations of PI were preferred by the participants (1% PI with frequent repetition: 11.4%; 5% PI: 71.9%; 10% PI: 15.7%). There was no difference in the PI concentrations used by RS (1% PI: 9.3%; 5% PI: 74.0%; 10% PI: 15.9%, no PI: 0.8%) and M (1% PI: 12.8%; 5% PI: 70.3%; 10% PI: 15.6%; no PI: 1.3%) (p=0.515). There was also variation in the contact time of PI on the conjunctiva (30 s: 25.9%, 60 s: 28.0%, 90 s: 14.6%, 180 s: 31.5%) but there was no difference in PI contact time between RS (30 s: 24.2%, 60 s: 27.7%, 90 s: 15.6%, 180 s: 32.4%) and M (30 s: 27.2%, 60 s: 28.2%, 90 s: 14.0%, 180 s: 30.6%) (p=0.804).

Nearly all participants (97.5%, 630/646) wore sterile gloves during IVI. The use of sterile gloves was higher in M (99.0%) than RS (95.3%) (p=0.004). Similarly, nearly all participants wore masks (98.3%). Eighty-one percent (523/646) of the participants said they cover their noses with the mask and all stated the importance of covering the nose. In addition, 72.4% (467/645) of the participants wore special surgical clothes. There was no difference between RS and M in terms of mask use (96.9% vs. 99.2%, respectively) (p=0.087) or the use of special surgical clothes (68.5% vs. 75.1%, respectively) (p=0.065).

Most surgeons (82.8%, 535/646) did not perform injections in both eyes on the same day. RS preferred same-day bilateral injection more frequently than M (21.8% vs. 14.2%, p=0.013). Most of the surgeons who performed bilateral same-day injections used a sequential procedure (79.6%, 86/108). There was no significant difference in sequential procedure use between RS and M (85.5% vs. 73.6%) (p=0.126).

| | n | % |
|--------------------------------|----------|----------|
| School of medicine | 239 | 26.9 |
| Private practice | 219 | 24.6 |
| Training and research hospital | 194 | 21.8 |
| Public hospital | 147 | 16.5 |
| City hospital | 48 | 5.4 |
| Foundation university | 46 | 5.2 |
| Clinic | 42 | 4.7 |

Pupil dilation before IVI was practiced by 42.7% of participants overall (276/646) and was significantly more common among RS than M (48.3% vs. 39.0%) (p=0.020).

Injection Practices

The most common quadrant for right eye injection was the superotemporal quadrant (78.5%, 499/636) followed by the inferotemporal (18.2%, 116/636), superonasal (2.2%, 14/636), and inferonasal (1.1%, 7/636) quadrants. Quadrant preferences were similar for the left eye. M preferred mostly the superotemporal quadrant (right: 82.5%, left: 74.1%), followed by the inferotemporal quadrant (right: 15.2%, left: 14.7%), superonasal quadrant (right: 1.8%, left: 9.7%), and inferonasal quadrant (right: 0.5%, left: 1.6%) quadrant. RS preferred mostly the superotemporal quadrant (right: 72.2%, left: 59.1%), followed by the inferotemporal quadrant (right: 23.0%, left: 21.4%), superonasal quadrant (right: 2.8%, left: 9.7%), and inferonasal quadrant (right: 2.0%, left: 0.5%). There was a significant difference in quadrant preference between RS and M (right: p=0.012, left: p=0.001)

When performing injections, 70.9% (449/633) of the participants said they hold the needle perpendicular to the globe. The tendency to use this needle position was higher in M than RS (74.0% vs. 66.4%, respectively, p=0.039).

Post-injection Practices

Most participants (93.1%, 591/632) did not use indirect ophthalmoscopy to evaluate retinal and optic nerve perfusion after injection. There was no significant difference in the use of indirect ophthalmoscopy between RS and M (5.6% vs. 7.9%, respectively, p=0.091).

Evaluation for central retinal artery occlusion (CRAO) after injection was performed using hand motion and finger counting by 42.5% (270/636) of participants and with light perception assessment by 17.1% (109/636) of participants. Another 2.2% (14/636) of participants used indirect ophthalmoscopy and 6.1% (39/636) of participants evaluated the retina 30 minutes after injection with a biomicroscope. The other 32.1% (204/636) of the participants did not check for CRAO. RS evaluated CRAO after injection more than M (76.6% vs. 62.0%, p=0.001)

Table 2. Comparison of intravitreal injection practice patterns between retina specialists (RS) and multispecialists (M)

| | RS | | M (n=) | | p value |
|---|---------|------|---------|------|--------------|
| | n | % | n | % | |
| Antibiotics before injection | 28/257 | 10.9 | 55/387 | 14.2 | 0.216 |
| Uses an operating room | 158/257 | 61.5 | 263/387 | 68.0 | 0.091 |
| Wears mask | 249/257 | 96.9 | 313/387 | 99.2 | 0.087 |
| Wears sterile gloves | 245/257 | 95.3 | 383/387 | 99.0 | 0.004 |
| Wears special surgical clothes | 176/257 | 68.5 | 290/386 | 75.1 | 0.065 |
| Uses sterile drape and fenestrated towel | 230/257 | 89.4 | 361/388 | 93.0 | 0.111 |
| Uses sterile eyelid speculum | 248/258 | 96.1 | 374/390 | 95.9 | 0.886 |
| Dilates pupil | 124/257 | 48.3 | 151/387 | 39.0 | 0.020 |
| Uses topical anesthetic drops before injection | 249/257 | 96.9 | 382/388 | 98.5 | 0.448 |
| Uses 5% povidone iodine before injection | 191/258 | 74.0 | 274/390 | 70.3 | 0.296 |
| Performs same-day bilateral injection | 56/257 | 21.8 | 55/387 | 14.2 | 0.013 |
| Uses superotemporal quadrant-right | 182/252 | 72.2 | 315/382 | 82.5 | 0.002 |
| Uses superotemporal quadrant-left | 149/252 | 59.1 | 283/382 | 74.1 | 0.000 |
| Holds the needle perpendicular to the globe | 166/250 | 66.4 | 282/381 | 74.0 | 0.039 |
| Uses indirect ophthalmoscopy | 14/251 | 5.6 | 30/382 | 7.9 | 0.091 |
| Checks for central retinal artery occlusion | 193/252 | 76.6 | 237/382 | 62.0 | 0.001 |
| Covers the eye until discharge | 170/252 | 67.5 | 216/382 | 56.5 | 0.006 |
| Uses antibiotic drops immediately after injection | 153/252 | 60.7 | 251/382 | 65.7 | 0.201 |
| Prescribes antibiotics for home use | 223/251 | 88.8 | 358/382 | 93.7 | 0.029 |
| Prescribes antibiotics for 1 week | 95/223 | 42.6 | 196/355 | 55.2 | 0.003 |
| Examines patients on postoperative day 1 | 102/251 | 40.6 | 198/380 | 52.1 | 0.006 |
| Performs same-day injections | 107/230 | 46.5 | 131/339 | 38.6 | 0.062 |

Statistically significant results shown in bold

A majority of the participants (63.8%, 406/636) administered antibiotic drops immediately after injection, 24.7% (157/636) used povidone iodine drops, and 0.2% (1/636) used topical anesthetic drops. 11.3% (72/636) of surgeon did not use drops after injection. There was no significant difference in use of drops after injections between RS (antibiotic drops: 60.7%, povidone iodine drops: 28.2%, no drops: 10.7%, topical anesthetic drops: all of but one) and M (antibiotic drops: 65.7%, povidone iodine drops: 22.5%, no drops: 11.8%, topical anesthetic drops: 0.0%) ($p=0.208$).

Nearly all participants (92.9%) covered the eye with a sponge, with 60.9% (287/636) reporting that they covered the eye until discharge and 32.1% (204/636) applying the sponge for 24 hours. More RS than M covered the eye until discharge (67.5% vs. 56.5%, respectively, $p=0.006$), whereas more M than RS preferred to cover the eye for 24 hours (56.5% vs. 36.1%, respectively, $p=0.006$).

Most of the participants (85.8%, 545/635) prescribed fluoroquinolone group antibiotics, 6.0% (38/635) prescribed aminoglycoside group antibiotics, and 8.2% (52/635) did not perform any antibiotherapy. M prescribed antibiotherapy more than RS (93.7% vs. 88.8%, respectively, $p=0.029$). Almost half of the participants prescribed antibiotics for 1 week and rest prescribed for 24 or 72 hours. M prescribed antibiotics for 1 week more than RS (55.2% vs. 42.6% respectively, $p=0.003$).

After the IVI procedure, 47.6% (301/633) of the participants examined the patients on postoperative day 1, 7.3% (46/633) on postoperative day 3, and 13.6% (86/633) both on postoperative day 1 and at postoperative 1 week. Approximately one-third of the surgeons (200/633) called the patients at postoperative 1 month and 81.1% (146/180) instructed patients to visit the clinic in case of any complaints. M examined patients on postoperative day 1 more than RS (52.1% vs. 40.6%, respectively, $p=0.006$), while RS examined patients at postoperative 1 month more than M. (38.7% vs. 26.8%, respectively, $p=0.002$). There was no significant difference between RS and M in terms of informing patients they should visit the clinic in case of any complaints (RS: 79.6%, M: 82.4%, $p=0.176$).

Injection Protocol

While 42.3% of participants reported performing IVI immediately after deciding to treat with IVI, the other participants scheduled an extra appointment for IVI. MS tended to perform IVI in another appointment more than RS, but the difference did not reach statistical significance (46.5% vs. 38.6%, $p=0.062$).

Almost half of all ophthalmologists examined patients monthly during the loading phase (first 3 injections), 24.7% (141/570) examined the patients on injection day, and 22.1% (126/570) examined patients only at 1 month after the loading phase. There was no significant difference in examination practices between RS (monthly: 53.3%, injection day: 24.9%, after loading phase: 21.8%) and MS (monthly: 52.8%, injection day: 24.8%, after loading phase: 22.4%) ($p=0.986$).

For patients with AMD, the most frequent treatment approach was 3 initial monthly injections, followed by pro re nata (PRN) treatment (64.5%). There was no significant difference in preference of AMD treatment protocol between R (PRN: 62.8%, treat and extend [TRES]: 35.5%, other: 1.7%) and M (PRN: 66.1%, TRES: 31.9%, other: 2.1%) ($p=0.651$).

Approximately half of the surgeons assumed that patients with AMD receive 6-7 injections per year, while this number was assumed to be 1-3, 4-5, and 8 or more by 6.2%, 33.9%, and 11.3% of participants, respectively. More RS than M assumed 6-7 injections yearly for AMD (60.2% vs. 40.5%, $p=0.000$).

For patients with DME, 42%, 38%, 11%, and 9% of participants assumed 6-7, 1-3, 4-5, and 8 or more injections per year, respectively. More RS than M assumed 6-7 injections for DME (49.4% vs. 36.5%, $p=0.002$).

Discussion

Several guidelines for intravitreal drug injections have been published in recent years.^{6,7} However, pre-injection preparation, injection technique, and post-injection care preferences vary in daily practice. In this study, we report the preferred IVI techniques of surgeons in Turkey.

Topical Antibiotics

Most participants did not use prophylactic antibiotics before IVI. Similarly, 76.8% of members of the American Society of Retina Specialists (ASRS) did not prescribe pre-injection antibiotics in a 2018 survey.⁸ A report of the American Academy of Ophthalmology in 2014 stated that there is insufficient evidence supporting the use of prophylactic antibiotics to reduce the risk of endophthalmitis.⁹ According to a EURETINA expert consensus report in 2018, perioperative antibiotic use was also not considered standard care.⁶ Furthermore, recent studies suggest that antibiotic prophylaxis may lead to antibiotic resistance.^{10,11}

Almost two-thirds (63.8%) of our respondents used topical antibiotic drops immediately after injection. In contrast, the rate of antibiotic use always or frequently immediately after injection was limited to 16.6% in the recent ASRS survey.⁸ In our survey, the rate of prescribing antibiotics for home use was very high at 91.8%. In the ASRS survey, this rate was 33%. Antibiotics were prescribed for home use more frequently and for longer duration by the multispecialty group than the retina specialist group. This may be related to retina specialists' ability to manage complications that may occur after IVI.

Guidelines do not recommend perioperative antibiotics.^{3,6} However, in the real world, 33% of ASRS members prescribed antibiotics after injections. This may be due to a lack of trust in guideline recommendations. Usage rates among Turkish surgeons were also higher than elsewhere in the world. This is associated with surgeons' reluctance to take risks and to avoid malpractice allegations.

Use of Masks, Gloves, and Drapes

Nearly all (91.65%) of the surgeons used a sterile drape. This rate is much higher than ASRS 2018 data (10.9%). Studies

suggest that sterile covers isolate the mouth and nose of patients and may reduce patient-induced transmission.^{12,13} However, the EURETINA 2018 consensus report noted that there is not enough evidence to reduce the risk of postoperative infection using sterile drapes, and they can be used according to surgeon preference.¹⁴

Most of the participants wore masks (98.30%) and sterile gloves (97.52%) before the procedure. In the ASRS survey 2018 data, only 32.9% of the participants wore masks and 54.8% wore gloves (50.4% sterile gloves). Forty-one percent of salivary isolates constitute *Streptococcus* species¹⁵ and post-IVI endophthalmitis are mostly caused by streptococci.^{16,17} Production of oropharyngeal droplets is thought to cause contamination of the sterile infection site.¹⁵ Studies show that wearing a mask during injection and adopting a “no talking” policy significantly reduces the formation of bacterial colonies on culture plates.¹⁸ The EURETINA 2018 consensus report recommended wearing a mask.⁶ Most of the participants in our study (81.0%) also preferred to cover the nose while wearing a mask. It was especially emphasized that the use of effective masks or respirators (covering both the mouth and nose) during the COVID-19 pandemic is effective in preventing aerosol formation and transmission.¹⁹

Interestingly, the rate of wearing sterile gloves was lower in the retina specialist group. This may also be related to retina specialists' higher level of confidence regarding the management of complications such as endophthalmitis. The World Health Organization's hand hygiene guideline recommends hand hygiene and wearing gloves before surgical interventions.²⁰ However, no study has directly evaluated the effect of sterile or non-sterile gloves and surgical hand washing before IVI in reducing the risk of endophthalmitis.

The vitreous is a rich medium for low-virulence bacteria and has immune privilege. Therefore, we believe that IVI should be considered an aseptic procedure.

Anesthesia

In the presented survey, the most commonly used anesthesia was topical drops (97.8%). Consistent with our results, Canadian retina specialists and ASRS members also preferred topical drops before injection.^{8,21} Although there is a lack of evidence regarding the anesthesia technique before IVI, topical anesthesia is recommended because it is the least invasive anesthesia method.

Eyelid Speculum

Nearly all of our participants (96%) used a sterile eyelid speculum. This was similar to the preferences of Canadian surgeons (91%).²¹ During IVI it is necessary to prevent involuntary closure of the lids and needle contamination by the eyelashes. An increase in the rate of endophthalmitis was reported when adequate lid retraction was not achieved.²² In the 2018 ASRS survey, 73% of all members used an eyelid speculum, which showed a decline from 92% in 2011. This was associated with the more frequent use of bimanual retraction technique.²³

Antisepsis

Nearly all (98.9%) surgeons used PI antisepsis in the conjunctiva. This rate was similar to those reported in Canada, ASRS members (92.2%), and the United Kingdom.^{8,21,24} Most of the surgeons (71.9%) preferred to use a 5% PI solution. PI has broad-spectrum microbicidal activity and is important for antisepsis. It reduces the pathogen load on the ocular surface prior to the surgical procedure and its use on the conjunctiva and periocular skin before IVI is strongly recommended.^{20,25} In order to achieve a bactericidal effect at PI concentrations in this range, it is necessary to wait 30-120 seconds after a single application, and a single application is sufficient.²⁵ The 2018 EURETINA consensus report suggested using 5% PI for 30 seconds before IVI.⁶

Injection Setting

The preferred setting for IVI was an operating room for 65.3% of the surgeons and a clean room for 33.6% of the surgeons. In contrast, IVIs are performed mainly as an office procedure in the United States and Canada, with a low incidence of post-injection endophthalmitis. A previous study indicated no significant difference between the office and operating room in terms of the incidence of endophthalmitis in IVIs.²⁶ In the 2018 EURETINA report, IVIs were reported to have similar risk in terms of infection frequency.⁶

Injection Practices

Most surgeons preferred the superotemporal quadrant (78.5% in the right eye, 68.2% in the right eye), followed by the inferotemporal quadrant (18.2% right, 17.3% left). In contrast, the inferotemporal quadrant was preferred by a majority of Canadian retina specialists (63%) and ASRS members (61.8% right, 61.0% left). Recent guidelines leave the choice of injection quadrant to the surgeon's preference.¹⁴ An advantage of performing IVI in the inferotemporal quadrant may be that it prevents the drug from interfering with the patient's vision. Conversely, if retinal detachment occurs after injection, the superotemporal quadrant may be more advantageous for pneumatic retinopexy. The retina specialists in our study are more familiar with using different quadrants because of their vitreoretinal surgery experience, and therefore may choose each quadrant separately.

Approximately 70% of the participants held the needle perpendicular to the globe. This method has been preferred by most surgeons for many years. However, recent studies indicate that the tunnel technique is superior in the prevention of vitreous reflux.²⁷ The tunnel technique involves inserting the needle at a 30 degree angle to the globe, then raising it perpendicular to the center. This approach may prevent trapping of the vitreous in the sclera, which is called vitreous wick syndrome, and/or bacterial entry into the vitreous.

Injection Protocol

More than half (58.0%) of the participants stated that they were not able to administer the injection on the same day they decided on the treatment. The rate of same day injection was

higher in the retina specialist group. This may be explained by the fact that retina specialists have more experience with IVI.

In our study, 64.5% of the participants stated that they examined the patients monthly and followed up with a PRN regimen after the first 3 injections for AMD. Another 33.6% of the participants said they followed a TREX regimen, treating monthly until patients' eye were dry and then extending the treatment interval at subsequent visits. Recent studies have confirmed that the TREX regimen maintains or improves visual acuity in patients with AMD.^{28,29} The number of examinations each year is lower in the TREX protocol than in the PRN protocol.²⁸ Studies indicate that the longer treatment intervals in the TREX protocol reduce patient anxiety.²⁸ Unlike American surgeons, our survey results demonstrate low usage of the TREX protocol for AMD in Turkey

Many surgeons in our study estimated that patients with AMD and DME require 6-7 injections per year. However, different results were obtained in real-life case studies in Turkey for AMD. The Bosphorus Retina Study Group stated in a real-life study conducted between 2013 and 2014 that the average annual number of injections was 4.1 for AMD.^{30,31} This suggests that the annual number of injections estimated by surgeons is not consistent with real-life practice.

Other Practices

Most of the participants preferred not to inject both eyes in the same appointment (82.8%). However, this rate differed in North America, as 71.5% of ASRS members and 57% of Canadian retina specialists were reported to prefer bilateral injection on the same day.^{8,21} Recent studies suggest that bilateral IVI does not increase the rate of adverse events compared to unilateral injections.^{32,33} The latest EURETINA guideline recommends same-day bilateral injection using separate equipment for each eye (sequential injections).⁶ The lower preference for same-day bilateral injections among ophthalmologists in Turkey may be related to the obligatory application of an initial 3 consecutive monthly injections of bevacizumab due to reimbursement regulations. In addition, dispensing multiple syringes from a single bevacizumab bottle may increase the risk of endophthalmitis.

Only 57.3% of the participants dilated the pupil before injection. This rate was much lower than Canadian retinal specialists (83%).²¹ There is currently no consensus to widen pupil before IVI. The 2018 EURETINA guideline states that the decision for pupil dilation before IVI depends on the practitioner. This guideline recommends pupil dilation for physicians who are newly performing IVI to enable immediate examination of retinal and optic nerve perfusion. In contrast, retina specialists preferred to dilate the pupil more frequently than multispecialists in our survey.

Over two-thirds (67.2%) of the surgeons evaluated retinal and optic nerve perfusion immediately after the injection. This rate was higher than in the ASRS survey (56.0%). It is known that a short-term increase in intraocular pressure occurs after IVI.³⁴ Visual acuity test (finger counting or hand movement

test), intraocular pressure measurement, or direct visualization of the optic nerve can be performed to assess ischemic optic nerve damage and check for perfusion. Although light perception indicates the presence of central retinal artery perfusion, the most reliable method of ensuring arterial perfusion is direct imaging.^{34,35}

Almost half of the surgeons (47.6%) reported performing clinical examination on postoperative day 1, whereas 31.6% did not perform an examination. Most surgeons (81.1%) who did not prefer clinical examination verbally informed the patients about potential complications, and a smaller group (11.7%) said they used an information form. In recent years, telephone contact has been more commonly used for the follow-up and reporting of complications after IVI.³⁵ According to a United States expert panel from 2014, patients should be informed before discharge about the symptoms of possible post-injection complications such as endophthalmitis, retinal detachment, and intraocular hemorrhage, and 24-hour contact information should be provided to the patient.¹⁴

Conclusion

In this study, the response rate was 90% and our results showed that ophthalmologists in Turkey have varying preferences regarding IVI techniques. Furthermore, their practices differ in some ways from those of Canadian surgeons and ASRS members. In many countries, IVI is considered a surgical procedure and is performed in an operating room. In the United States, IVI is performed as an office-based procedure to reduce costs and accommodate the large number of patients. Office-based procedures are generally performed in the examination room without using a sterile drape, sterile gloves, sterile surgical clothes, or mask. The results of our survey are more similar to European surgeon practices.³⁶

The results of this study are generally compatible with IVI guidelines, except for the high rate of postoperative antibiotic prescription and performing bilateral intravitreal injections on the same day.

IVI are generally administered only by retina specialists around the world, which differs from the practice of surgeons in Turkey. Current healthcare practices allow IVI to be performed not only by retina specialists, but also by other ophthalmologists. This may lead to differences in IVI practices of our country. These discrepancies should be considered when performing retrospective studies to examine the efficacy and safety of IVI. More evidence-based medicine is required to identify IVI techniques that combine safety and efficacy.

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Ethics

Ethics Committee Approval: The research protocol was initially submitted to the Institutional Ethics Committee and Review Board of the University of Kocaeli (registration number: KA EK 2020/219).

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Authorship Contributions

Surgical and Medical Practices: V.L.K., E.Ö.T., Concept: V.L.K., E.Ö.T., Design: V.L.K., E.Ö.T., Data Collection or Processing: V.L.K., E.Ö.T., Analysis or Interpretation: V.L.K., E.Ö.T., F.Ş., Literature Search: V.L.K., E.Ö.T., F.Ş., Writing: V.L.K., E.Ö.T., E.B.

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References

- Ohm J. Über die Behandlung der Netzhautablösung durch operative Entleerung der subretinalen Flüssigkeit und Einspritzen vom Luft in den Glaskörper. *Graef Arch Klin Ophthalmol.* 1911;79:442-450.
- Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol.* 2006;90:1344-1349.
- Aiello LP, Brucker AJ, Chang S, Cunningham ET Jr, D'Amico DJ, Flynn HW Jr, Grillo LR, Hutcherson S, Liebmann JM, O'Brien TP, Scott IU, Spaide RF, Ta C, Trese MT. Evolving guidelines for intravitreal injections. *Retina.* 2004;24(5 Suppl):S3-19.
- Korobelnik J-F, Weber M, Cohen SY, groupe d'Experts. Recommendations for carrying out intravitreal injections. *J Fr Ophtalmol.* 2009;32:288-289.
- Weber M, Cohen SY, Tadayoni R, Coscas G, Creuzot-Garcher C, Devin F, Gaudric A, Mauget-Fayssie M, Sahel JA, Soubrane G, Souied E, Korobelnik JF. Evolving intravitreal injection technique. *J Fr Ophtalmol.* 2008;31:625-629.
- Grzybowski A, Told R, Sacu S, Bandello F, Moisseiev E, Loewenstein A, Schmidt-Erfurth U; Euretina Board. 2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations. *Ophthalmologica.* 2018;239:181-193.
- Nikkhah H, Karimi S, Ahmadi H, Azarmina M, Abrishami M, Ahoor H, Alizadeh Y, Behboudi H, Daftarian N, Dehghan MH, Entezari M, Farrahi F, Ghanbari H, Falavarjani KG, Javadi MA, Karkhaneh R, Moradian S, Manaviat MR, Mehryar M, Nourinia R, Parvaresh MM, Ramezani A, Haghi AR, Riazi-Esfahani M, Soheilian M, Shahsavari M, Shahriari HA, Rajavi Z, Safi S, Shirvani A, Rahmani S, Sabbaghi H, Pakbin M, Kheiri B, Ziaei H. Intravitreal Injection of Anti-vascular Endothelial Growth Factor Agents for Ocular Vascular Diseases: Clinical Practice Guideline. *J Ophthalmic Vis Res.* 2018;13:158-169.
- Uhr JH, Xu D, Rahimy E, Hsu J. Current Practice Preferences and Safety Protocols for Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents. *Ophthalmol Retina.* 2019;3:649-655.
- Green-Simms AE, Ekdawi NS, Bakri SJ. Survey of intravitreal injection techniques among retinal specialists in the United States. *Am J Ophthalmol.* 2011;151:329-332.
- Storey P, Dollin M, Rayess N, Pitcher J, Reddy S, Vander J, Hsu J, Garg S; Post-Injection Endophthalmitis Study Team. The effect of prophylactic topical antibiotics on bacterial resistance patterns in endophthalmitis following intravitreal injection. *Graefes Arch Clin Exp Ophthalmol.* 2016;54:235e242.
- Hunyor AP, Merani R, Darbar A, Korobelnik JF, Lanzetta P, Okada AA. Topical antibiotics and intravitreal injections. *Acta Ophthalmol.* 2018;96:435-441.
- Casparis H, Wolfensberger TJ, Becker M, Eich G, Graf N, Ambresin A, Mantel I, Michels S. Incidence of presumed endophthalmitis after intravitreal injection performed in the operating room: a retrospective multicenter study. *Retina.* 2014;34:12-17.
- Wen JC, McCannel CA, Mochon AB, Garner OB. Bacterial dispersal associated with speech in the setting of intravitreal injections. *Arch Ophthalmol.* 2011;129:1551-1554.
- Avery RL, Bakri SJ, Blumenkranz MS, Brucker AJ, Cunningham ET Jr, D'Amico DJ, Dugel PU, Flynn HW Jr, Freund KB, Haller JA, Jumper JM, Liebmann JM, McCannel CA, Mieler WF, Ta CN, Williams GA. Intravitreal injection technique and monitoring: updated guidelines of an expert panel. *Retina.* 2014;34(Suppl 12):S1eS18.
- Gordon DF, Jong BB. Indigenous flora from human saliva. *Appl Microbiol.* 1968;16:428e429.
- McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. *Retina.* 2011;31:654e661.
- Casparis H, Wolfensberger TJ, Becker M, Eich G, Graf N, Ambresin A, Mantel I, Michels S. Incidence of presumed endophthalmitis after intravitreal injection performed in the operating room: a retrospective multicenter study. *Retina.* 2014;34:12e17.
- Doshi RR, Leng T, Fung AE. Reducing oral flora contamination of intravitreal injections with face mask or silence. *Retina.* 2012;32:473-476.
- Ogoina D. COVID-19: The Need for Rational Use of Face Masks in Nigeria. *Am J Trop Med Hyg.* 2020;103:33-34.
- Berkelman RL, Holland BW, Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. *J Clin Microbiol.* 1982;15:635-639.
- Xing L, Dorrepaal SJ, Gale J. Survey of intravitreal injection techniques and treatment protocols among retina specialists in Canada. *Can J Ophthalmol.* 2014;49:261-266.
- Mansour AM, Shahin M, Kofoed PK, Parodi MB, Shami M, Schwartz SG. Collaborative Anti-VEGF Ocular Vascular Complications Group: Insight into 144 patients with ocular vascular events during VEGF antagonist injections. *Clin Ophthalmol.* 2012;6:343-363.
- Rahimy E, Fineman MS, Regillo CD, Sporn MJ, Hsu J, Kaiser RS, Maguire JI, Brown GC, Chiang A. Speculum versus bimanual lid retraction during intravitreal injection. *Ophthalmology.* 2015;122:1729-1730.
- Anijeet DR, Hanson RJ, Bhagey J, Bates RA. National survey of the technique of intravitreal triamcinolone injection in the United Kingdom. *Eye.* 2007;21:480-486.
- Wykoff CC, Flynn HW Jr, Rosenfeld PJ. Prophylaxis for endophthalmitis following intravitreal injection: antisepsis and antibiotics. *Am J Ophthalmol.* 2011;152:717-719.e712.
- Tabandeh H, Boscia F, Sborgia A, Ciraci L, Dayani P, Mariotti C, Furino C, Flynn HW Jr. Endophthalmitis associated with intravitreal injections: office-based setting and operating room setting. *Retina.* 2014;34:18-23.
- Knecht PB, Michels S, Sturm V, Bosch MM, Menke MM. Tunnelled versus straight intravitreal injection: Intraocular pressure changes, vitreous reflux, and patient discomfort. *Retina.* 2009;29:1175-1181.
- Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, Abdelfattah NS, Sadda SR; TREX-AMD Study Group. Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: TREX-AMD 1-Year Results. *Ophthalmology.* 2015;122:2514-2522.
- Wykoff CC, Ou WC, Brown DM, Croft DE, Wang R, Payne JF, Clark WL, Abdelfattah NS, Sadda SR; TREX-AMD Study Group. Randomized Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: 2-Year Results of the TREX-AMD Study. *Ophthalmol Retina.* 2017;1:314-321.
- Erden B, Bölükbaşı S, Özkaya A, Karabaş L, Alagöz C, Alkin Z, Artunay Ö, Bayramoğlu SE, Demir G, Demir M, Demircan A, Erdoğan G, Erdoğan M, Eriş E, Kaldırım H, Onur İU, Osmanbaşoğlu ÖA, Özdoğan Erkul S, Öztürk M, Perente İ, Sarıcı K, Sayın N, Yaşa D, Yılmaz İ, Yılmazabdurrahmanoğlu Z; Bosphorus Retina Study Group. Comparison of two different treatment regimens' efficacy in neovascular age-related macular degeneration in Turkish population-based on real life data-Bosphorus RWE Study Group. *Int J Ophthalmol.* 2020;13:104-111.
- Özkaya A, Karabaş L, Alagöz C, Alkin Z, Artunay Ö, Bölükbaşı S, Demir G, Demir M, Demircan A, Erden B, Erdoğan G, Erdoğan M, Eriş E, Kaldırım H, Onur İU, Osmanbaşoğlu Ö, Özdoğan Erkul S, Öztürk M, Perente İ, Sarıcı K, Sayın N, Yaşa D, Yılmaz İ, Yılmazabdurrahmanoğlu Z. Real-World Outcomes of Anti-VEGF Treatment for Neovascular Age-Related Macular Degeneration in Turkey: A Multicenter Retrospective Study, Bosphorus Retina Study Group Report No: 1. *Turk J Ophthalmol.* 2018;48:232-237.

32. Borkar DS, Obeid A, Su DC, et al. Endophthalmitis Rates after Bilateral Same-Day Intravitreal Anti-Vascular Endothelial Growth Factor Injections. *Am J Ophthalmol*. 2018;194:1-6.
33. Juncal VR, Francisconi CLM, Altomare F, Chow DR, Giavedoni LR, Muni RH, Berger AR, Wong DT. Same-Day Bilateral Intravitreal Anti-Vascular Endothelial Growth Factor Injections: Experience of a Large Canadian Retina Center. *Ophthalmologica*. 2019;242:1-7.
34. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. *Am J Ophthalmol*. 2008;146:930-934. e931.
35. Doshi RR, Bakri SJ, Fung AE. Intravitreal injection technique. *Semin Ophthalmol*. 2011;26:104-113.
36. Huang K, Sultan MB, Zhou D, Tressler CS, Mo J. Practice patterns of ophthalmologists administering intravitreal injections in Europe: a longitudinal survey. *Clin Ophthalmol*. 2016;10:2485-2488.