BMC Ophthalmology

RESEARCH

Open Access

The relationship between pain intensity and anxiety, injection speed, and intraocular pressure changes during intravitreal anti-vascular endothelial growth factor injection: the observational pilot study

Ali Kurt[1*] and Emin Utku Altındal[2*]

Abstract

Purpose To evaluate the relationship between the pain severity and the injection speed, anxiety, and intraocular pressure changes during the intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF) agents.

Methods The 84 eyes were prospectively registered in the study. The severity of the pain was evaluated with the visual analogue scale (VAS). The severity of the anxiety was measured with the Beck Anxiety Inventory. All patients were naive to IVI. Bevacizumab or Ranibizumab 0.05 mL was administered intravitreally. The intraocular pressure (IOP) was measured before and after the procedure.

Results Correlation analyses were performed between VAS and the injection speed, the IOP difference, and anxiety. There was a negative significant correlation between injection speed and VAS ($p=0.024$ r=-246). There was a positive significant correlation between the IOP difference and VAS ($p=0.001$, $r=0.365$). In addition, there was strong positive correlation between the anxiety level and VAS ($p<0.001$ $r=0.77$). Linear stepwise regression analysis was used to determine which of these three independent variables (VAS, IOP difference, Anxiety) influenced pain the most, and Anxiety and IOP difference were found to affect the dependent variable of VAS more. There was no significant difference between the IOP difference ($p>0.05$) and anxiety scale values ($p>0.05$) between the two anti-VEGF agents while there was statistically significantly more pain felt during the Bevacizumab IVI ($p=0.005$).

Conclusions The parameter with the most influence on pain severity was anxiety in this study, followed by the postop-preop IOP difference. There was also a significant negative correlation between injection speed and VAS.

Keywords Anti-vascular endothelial growth factor, Intravitreal injection, Pain, Anxiety, Visual analogue scale, Injection speed

*Correspondence:
Ali Kurt
dralikurt@gmail.com
Emin Utku Altındal
drutkualtindal@gmail.com

[1]Ophthalmology Department, Alanya Alaaddin Keykubat University Education and Research Hospital, Antalya, Turkey
[2]Ophthalmology Department, Antalya City Hospital, Antalya, Turkey

Introduction

Treatment protocols for anti-vascular endothelial growth factor (Anti-VEGF) agents include intravitreal injections (IVIs) with a volume of 50 μL administered monthly, using a small caliber needle and usually without performing paracentesis [1]. However, different doses may be required according to the treated disease together with different injection intervals according to the treatment regimes [2]. It is very important to ensure a favorable first experience for patients undergoing intravitreal injections. The possibility of the patient refusing further treatment increases if the first injection is traumatic. A positive experience may increase the visual improvement potential by encouraging the patients to continue the injections. In addition, adequate information should be provided after the first injection about the procedure's risks and benefits and the steps after the injection, using words and concepts that the patient and/or relative can understand [3].The most common symptom during IVI is pain of variable intensity, as seen in a fourth of the patients [1]. Various strategies have been tried in many studies to alleviate the pain, considering that it would increase the patient's comfort and compliance with treatment. It has been postulated that the entry of the needle is the most uncomfortable step during IVI. This has resulted in the anesthesia method and the diameter of the used needle being the most commonly evaluated factors to decrease the pain. The IVI quadrant and technique and the environmental and psychological factors have also been evaluated [4–6]. However, there is no study that has evaluated the relationship between the pain occurring during IVI and several clinical parameters together. The primary objective of our study was to determine whether the intravitreal injection speed and the pain severity are associated. The secondary objection was to evaluate whether the pain development was influenced by the intraocular pressure difference, anxiety, and drug selection.

Methods

Study design and subjects

This prospective observational pilot study was conducted between 11 August 2021 and 29 November 2021 and included the 84 eyes of 84 patients. The study was approved by the institutional Ethics Committee and complied with the Helsinki Declaration principles. The study was conducted at the Alanya Alaaddin Keykubat University Education and Research Hospital. A complete ocular examination including the best-corrected visual acuity, slit lamp examination of the anterior segment, and IOP measurement with the Goldmann Applanation Tonometer was performed in all patients. Patient age, gender, indication for therapy, laterality, lens status, type of anti-VEGF used, and the injection eye were the demographic and clinical data analyzed. All patients provided written informed consent once the procedure, potential risks, and benefits were explained. The same surgeon (EUA) performed all the injections.

Inclusion criteria

The presence of an IVI injection indication, and the ability to score and report perceived pain and anxiety were conditions of taking part in the trial. The patients had not received any injections before registration.

Exclusion criteria

These were illiterate people, those with severe cognitive pathologies who cannot understand instructions; those whose native language is not Turkish, ocular pain prior to the procedure, a preoperative IOP ≥ 20 mmHg, punctate epitheliopathy that would affect post-IVI IOP measurement, previous ocular surgery other than cataract extraction with posterior chamber intraocular lens, a history of Nd: Yag laser posterior capsulotomy, use of IOP lowering drugs, the pseudoexfoliation syndrome, any corneal disease that might interfere with tonometry, IVI contraindications such as active ocular infection or inflammation, diabetic patients with known peripheral neuropathy, known trigeminal neuralgia, development of vitreous reflux after IVI, and having used any systemic or topical NSAID or sedative medication on the day of injection and within the previous 7 days.

The intravitreal injection procedure

Following the cleaning of the periocular skin, eyelid margins and eyelashes with 10% povidone iodine, 5% povidone iodine was administered into the conjunctival cul-de-sacs 3 min before the injection. Topical anesthesia consisting of 3 drops of Alcaine 0.5% (Proparacaine hydrochloride ophthalmic solution; Alcon, Fort Worth, TX, USA) was then administered one minute before the injection. After placing a sterile lid speculum, the superotemporal quadrant was used to perform the injection. The needle entry site was at a distance of 3.5 mm from the limbus in pseudophakic patients while 4.0 mm was used in phakic patients. The IVI technique was similar to that described in the Özkaya et al. [7] studies where a scleral tunnel technique that decreased vitreus reflux was used. Ranibizumab (Lucentis®; Genentech Inc, South San Francisco, California, USA) or Bevacizumab (Avastin®, Genentech, San Francisco, CA, USA) at a volume of 0.05 mL was injected using a 30-gauge ½ inch needle (Becton Dickinson & Co., Franklin Lakes, NJ, USA, Precision Glide No: 305106). A cotton tip was placed over the sclera for 5 s immediately after needle removal for all injections. The cotton tip was then removed, and the incision site observed regarding reflux under the operation microscope. The injection was determined to be

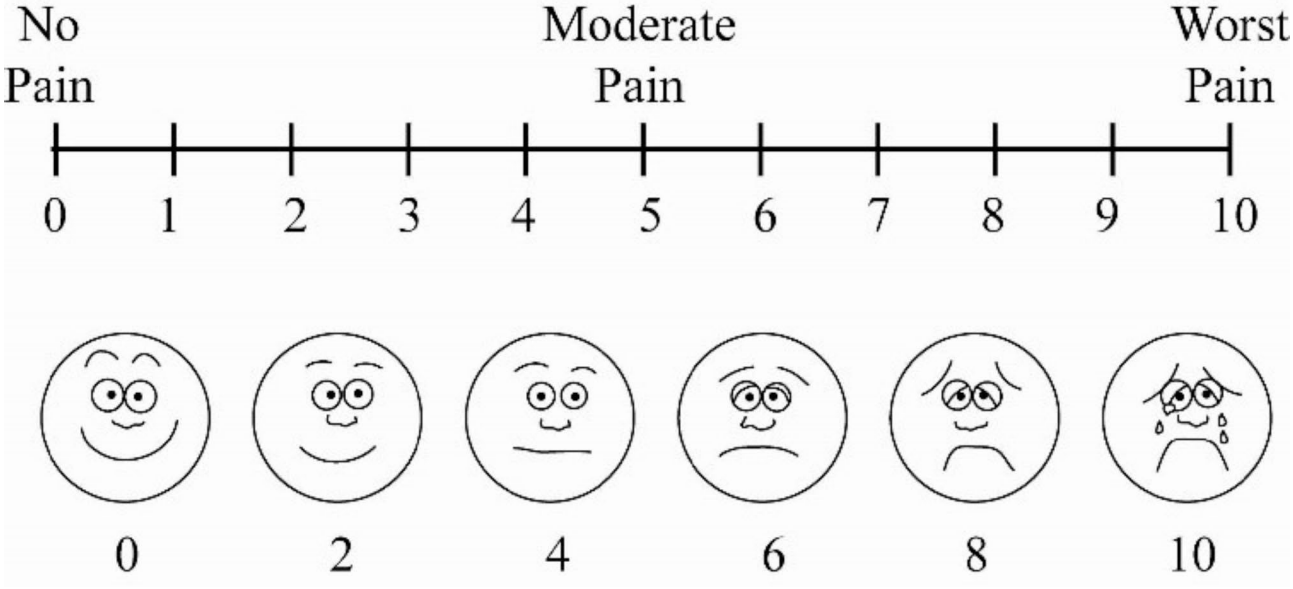

Fig. 1 Visual analogue scale

reflux positive if any subconjunctival bleb was observed. An ophthalmic solution of moxifloxacin was administered 5 times a day for 1 week following the procedure. The procedure was performed between 9 AM and 10 AM. The IOP was measured and recorded 30 min before and 30 min after the IVI.

A visual analogue scale (VAS) was used to score the severity of the patient's perceived pain between 1 and 10 [8–9] (Fig. 1). The patients were told how to evaluate the pain with VAS following the injection.

The Beck Anxiety Inventory (BAI) was the used to measure the severity of anxiety. The BAI has 21 items, each rated from 0 to 3) assessing the various physical and cognitive symptoms of anxiety that have been experienced in the past week. The total score is between 0 and 63, and higher scores indicate a higher level of anxiety [10]. The BAI was explained before the IVI procedure. Patient BAI results were recorded.

Statistical analysis

Sample size analyses were performed via the G Power 3.1 software. It was estimated that a sample size of 84 patients would have >90% confidence (two-tailed alpha level 0.05). Exact-Correlation: The bivariate normal model was used. Power (1- β) was 0.80, and effect size 0.30 (Lower critical r=-0.215, upper critical r = 0.215).

Statistical analyses were performed via the SPSS 23 software (SPSS, Inc., Chicago, IL, USA).

The Kolmogorov-Smirnov test was used to evaluate whether the data conformed to a normal distribution. Parametric tests were employed for data conforming to a normal distribution and nonparametric analysis methods for other data. Linear stepwise regression analysis was used for data that were shown to be linked during correlation analysis and a Multiple Regression model was created.

Table 1 Demographic and ocular profile, and the VAS and anxiety scores

		p
Gender (M/F)	44(52.4%) / 40 (47.6%)	
Right/Left	42(50%) / 42(50%)	
Age (years)	63.37 ± 10.22(44–80)	
Pre-IVI IOP (mmHg)	15.54 ± 2.75 (9–19)	>0.001
Post-IVI 30 min IOP (mmHg)	22.81 ± 5.33 (12–39)	
Postop-preop IOP difference (mmHg)	7.26 ± 4.38 (1–21)	
Anxiety Score	8.95 ± 5.28 (2–26)	
VAS	3.25 ± 1.60 (1–8)	
Phakic/Pseudophakic	59(70.2%) / 25(29.8%)	
AMD/RVO/DME	28(33.3%)/11(13.1%)/45(53.6%)	
Ranibizumab/Bevacizumab	35(41.7%) / 49(58.3%)	

IVI: Intravitreal injection, IOP: Intraocular pressure, VAS: Visual Analogue Scale, AMD: Age-related macular degeneration, RVO: Retinal vein occlusion, DME: Diabetic macular edema

Results

The 84 eyes of 84 patients were included in the study. The demographic and ocular data of these patients have been presented in Table 1 together with the VAS and anxiety scores.

Correlation analyses between the VAS results and the injection speed, IOP difference, and anxiety. A significant correlation was detected between VAS and all 3 variables (Table 2).

Linear stepwise regression analysis was performed to determine which of these 3 independent variables (VAS,

Table 2 Result of correlation analysis between VAS and the injection speed, IOP difference and anxiety

	VAS
Anxiety	$r=0.77$ p<0.001
Postop-preop IOP difference	$r=0.365$ $p=0.001$
Injection rate	$r=-0.246$ $p=0.024$

VAS: Visual Analogue Scale, IOP: Intraocular pressure

Table 3 The injection rate, VAS, IOP difference and anxiety score distribution of the two anti-VEGF agents, with P values

	Ranibizumab (*N* = 35 (41.7%)	Bevacizumab (*N* = 49(58.3%)	*p*
Injection rate (sec)	2.09 ± 0.32(1.45–2.41)	1.93 ± 0.40(1.07–2.49)	0.066
VAS	2.63 ± 1.11(1–5)	3.69 ± 1.75 (1–8)	0.005
Anxiety Score	7.54 ± 3.95(2–16)	9.96 ± 5.89(1–26)	0.063
Postop-preop IOP difference (mmHg)	7.23 ± 4.91(2–21)	7.29 ± 4.02(1–21)	0.526

VAS: Visual Analogue Scale, IOP: Intraocular pressure

IOP difference, Anxiety Scale) influenced the pain the most. The independent variables that most influenced the VAS dependent variable were found to be anxiety and IOP difference. However, these two variables explained the VAS change at a rate of 63.5% ($F(2.81)=73.257$ $p<0.001$) Multiple Regression model; VAS = 0.834 + Anxiety*0.227 + IOP difference*0.053. The p value was < 0.001 for anxiety and 0.036 for IOP difference.

The presence of absence of a difference regarding VAS for the IVI of the two anti-VEGF agents was also evaluated. There was no significant difference for pressure change ($p>0.05$) and anxiety scale ($p>0.05$) values between the two anti-VEGF agents but Bevacizumab IVI caused significantly more perceived pain ($p=0.005$) (Table 3).

Discussion

The number of IVI applications of anti-vascular endothelial growth factor agents have gradually increased to make it the most common method of treatment after cataract surgery in many ophthalmic centers. Despite the reputation of the IVI procedure for a low number of complications, the large recurrence rate of the relevant condition and the short half-life of the drug makes it necessary to use multiple treatments in general [1]. The patients also describe various degrees of ''pain" during the procedure. Pain is defined as ''an unpleasant sensory or emotional experience associated with real or potential tissue damage or similar" by the International Pain Studies Association. The "sensory and emotional experience" phrase in this description indicates that pain is complex and may be associated with many factors [11]. In this context, the pain measurements in the studies are expected to be associated with various factors that are not related (such as anxiety) to the injection procedure factors (such as anesthetic agent and techniques, needle diameter) [4]. Various studies have been conducted to ensure an IVI procedure that is as painless as possible, taking all these into account [4, 5, 12, 13]. However, we did not come across a study that evaluated the severity of the pain together with the injection speed, anxiety and IOP change during IVI in the literature.

The sudden increase in IOP following an intravitreal injection, although temporary, has been reported to be associated with pain in the literature. The mean IOP within the one minute after IVI has been found to be 41–50 mm Hg [14–16]. A meta-analysis of 46 articles (2872 eyes) has found the mean difference between the post-anti-VEGF injection and pre-injection state to be 23.41 mmHg right after the injection and 2.51 mmHg 30 min later [17]. Another study has found the IOP difference at 30 min to be 9.5 mmHg [14]. The VAS result had a negative correlation with the IVI speed in our observational study, indicating that the VAS result increased as the IVI duration of the anti-VEGF agent decreased in general. An ex vivo study in pig eyes has shown that the IOP increase will show a direct relationship with the injection speed increase. Although the injection volume was 0.05 mL in this study, the pressure increase during the injection was significantly larger in the faster injection group than the slower injection group (IOP increase with 0.05, 0.02 and 0.01 mL/sec was 16.65 ± 5.0, 13.79 ± 1.5 and 11.78 ± 1.7 mmHg, respectively) [18]. This result demonstrates that rapid injection could increase the pain severity due to the sudden IOP increase. We found a statistically significant increase in the IOP after the injection of either anti-VEGF agent when compared to the preoperative IOP.

In addition, we found that the VAS results showed a positive correlation with anxiety in this study. Following the correlation analyses, regression analysis was performed to show which clinical parameter was most associated with the pain. Although a significant correlation was found between the injection speed and pain, the factors found to be most associated with the pain on regression analysis (63.5%) were IOP difference and anxiety, with anxiety taking first place. Anxiety is a common response to many factors during IVI such as whether the patient is awake and conscious, the suspicion regarding whether there will be a response to treatment, the fear of going blind, the sounds and lights of the operating theater, the sensation of being touched by the surgeon, and the sound level in the operating theater, etc. Studies have shown that many factors can influence the anxiety level and that this in turn can modify the perception of pain [19, 20]. Many studies have shown a direct relationship between preoperative anxiety and pain perceived during IVI. For example, patients with higher anxiety levels have reported high pain scores during the IVI procedure

compared to patients with lower anxiety levels. This relationship shows that anxiety not only affects the emotional response to pain but can also increase the sensitivity to painful stimuli [1, 13, 20].

Evaluation of whether the pain severity was different following the IVI of the two anti-VEGF agents revealed a significant difference between the two agents regarding the pain while there was no difference related to the other clinical parameters. The pain scores were higher with Bevacizumab injection. The reason could be the higher pre-IVI anxiety scores of the patients receiving a Bevacizumab injection, which could increase the pain severity. Some studies have reported that the pain perceived during the IVI procedure is higher with Bevacizumab than with Ranibizumab. The reason has been though to be the different diameters of the needles used for injection, although the volumes of the effective substance used in the studies was the same, and the different composition and pH values of the drug solutions leaking into the subconjunctival area [21, 22]. Ranibizumab and Bevacizumab were administered with needles of the same caliber in the current study, and patients with reflux following the injection were excluded.

Our study has some limitations in addition to those specified above. The first one is that the axial length of the eyes was not considered. However, axial length has been reported not to be a significant factor regarding the IOP increase following IVI [23]. In addition, the preoperative waiting duration, the level of light and sound in the injection room, personal characteristics or psychosocial factors could also influence the results [14] and have not been considered in this study.

In conclusion, we found a significant negative correlation between the injection speed and pain score. In addition, anxiety was found to be the most influential parameter on the pain score, followed by the postop-preop IOP difference. It may therefore be beneficial to first evaluate and take precautions to decrease the anxiety associated with intravitreal injections.

Abbreviations

IVI	Intravitreal injection
Anti-VEGF	Anti-vascular endothelial growth factor
VAS	Visual analogue scale
IOP	Intraocular pressure
BAI	Beck Anxiety Inventory
AMD	Age-related macular degeneration
RVO	Retinal vein occlusion
DME	Diabetic macular edema

Acknowledgements
Not applicable.

Author contributions
AK participated in the design of the study, carried out the study and drafted the manuscript and performed the statistical analyses. EUA has participated in the study's coordination and has helped to draft the manuscript and has been involved in revising the manuscript carefully. All authors read and approved the final manuscript.

Funding
Not applicable.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients provided written informed consent once the procedure, potential risks, and benefits were explained. This study was approved by the ethics committee of Alanya Alaaddin Keykubat University Faculty of Medicine with the date of November 10, 2021 and number 17 – 05.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 11 January 2025 / Accepted: 7 April 2025
Published online: 16 April 2025

References

1. Segal O, Segal-Trivitz Y, Nemet AY, Cohen P, Geffen N, Mimouni M. Anxiety levels and perceived pain intensity during intravitreal injections. Acta Ophthalmol. 2016;94:203–4. https://doi.org/10.1111/aos.12802.
2. Lam LA, Mehta S, Lad EM, Emerson GG, Jumper JM, Awh CC. Task force on intravitreal injection supplemental services. intravitreal injection therapy: current techniques and supplemental services. J Vitreoretin Dis. 2021;5:438–47. https://doi.org/10.1177/24741264211028441.
3. van Asten F, van Middendorp H, Verkerk S, et al. Are intravitreal injections with ultrathin 33-G needles less painful than the commonly used 30-G needles? Retina. 2015;35:1778–85. https://doi.org/10.1097/IAE.0000000000000550.
4. Butler ETS, Bjerager J, Eriksen NS, et al. Effect of needle gauge size on pain during intravitreal Anti-VEGF injection: A systematic review and network Meta-Analysis. Ophthalmol Ther. 2024;13:801–17. https://doi.org/10.1007/s40123-023-00879-7.
5. Han J, Rinella NT, Chao DL. Anesthesia for intravitreal injection: A systematic review. Clin Ophthalmol. 2020;14:543–50. https://doi.org/10.2147/OPTH.S223530.
6. Shin SH, Park SP, Kim YK. Factors associated with pain following intravitreal injections. Korean J Ophthalmol. 2018;32:196–203. https://doi.org/10.3341/kjo.2017.0081.
7. Özkaya A, Alkin Z, Celik U, et al. Comparing the effects of three different intravitreal injection techniques on vitreous reflux and intraocular pressure. J Ocul Pharmacol Ther. 2013;29:325–9. https://doi.org/10.1089/jop.2012.0144.
8. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14:798–804. https://doi.org/10.1111/j.1365-2702.2005.01121.x.
9. Laborda A, Medrano J, de Blas I, Urtiaga I, Carnevale FC, de Gregorio MA. Endovascular treatment of pelvic congestion syndrome: visual analog scale (VAS) long-term follow-up clinical evaluation in 202 patients. Cardiovasc Intervent Radiol. 2013;36:1006–14. https://doi.org/10.1007/s00270-013-0586-2.
10. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56:893–7. https://doi.org/10.1037/0022-006X.56.6.893.
11. Raja SN, Carr DB, Cohen M, et al. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161:1976–82. https://doi.org/10.1097/j.pain.0000000000001939.
12. Nguyen NCI, Fabro F, Ambresni A, et al. Factors associated with pain during intravitreal injection of anti-vascular endothelial growth factor. Eye (Lond). 2018;32:1544–6. https://doi.org/10.1038/s41433-018-0126-z.

13. İnaltekin A, Bozkurt E, Kıvrak Y. Factors associated with pain level in patients receiving intravitreal injection. J Curr Ophthalmol. 2021;33:323–9. https://doi.org/10.4103/joco.joco_6_21.
14. Karakahya RH. Anterior chamber paracentesis offers a less painful experience during intravitreal anti-vascular endothelial growth factor administration: an intraindividual study. Cureus. 2021;13:e20051. https://doi.org/10.7759/cureus.20051.
15. Levin AM, Chaya CJ, Kahook MY, Wirostko BM. Intraocular pressure elevation following intravitreal Anti-VEGF injections: Short- and Long-term considerations. J Glaucoma. 2021;30:1019–26. https://doi.org/10.1097/IJG.
16. Meyer CH, Melo GB, Khanani AM. Can intravitreal injections with higher volume cause higher intraocular eye pressure? Considerations for anti-complement injections in normal and glaucomatous eyes. Int J Retina Vitreous. 2023;9:80. https://doi.org/10.1186/s40942-023-00517-1.
17. de Vries VA, Bassil FL, Ramdas WD. The effects of intravitreal injections on intraocular pressure and retinal nerve fiber layer: a systematic review and meta-analysis. Sci Rep. 2020;10:13248. https://doi.org/10.1038/s41598-020-70269-7.
18. Park I, Park HS, Kim HK, Chung WK, Kim K. Real-time measurement of intraocular pressure variation during automatic intravitreal injections: an ex-vivo experimental study using Porcine eyes. PLoS ONE. 2021;16:e0256344. https://doi.org/10.1371/journal.pone.0256344.
19. Muralidharan S, Ichhpujani P, Bhartiya S, Singh RB. Eye-tunes: role of music in ophthalmology and vision sciences. Ther Adv Ophthalmol. 2021;13:25158414211040890. https://doi.org/10.1177/25158414211040890.
20. Yiallouridou C, Acton JH, Banerjee S, Waterman H, Wood A. Pain related to intravitreal injections for age-related macular degeneration: a qualitative study of the perspectives of patients and practitioners. BMJ Open. 2023;13:e069625. https://doi.org/10.1136/bmjopen-2022-069625.
21. Güler M, Bilgin B, Çapkın M, Şimşek A, Bilak Ş. Assessment of patient pain experience during intravitreal 27-gauge bevacizumab and 30-gauge Ranibizumab injection. Korean J Ophthalmol. 2015;29:190–4. https://doi.org/10.3341/kjo.
22. Belmonte C, Tervo TT, Gallar J. Lasensory innervations of the eye. In: Leonard LA, editor. Adler's physiology of the eye. 11th ed. Edinburgh: Elsevier; 2011. pp. 363–84.
23. Hoang QV, Jung JJ, Mrejen S, Freund KB. Influence of axial length and postinjection reflux on sustained intraocular pressure elevation as a result of intravitreal anti-vascular endothelial growth factor therapy. Retina. 2014;34:519–24. https://doi.org/10.1097/IAE.0000000000000039.

Publisher's note