Original Article

Factors Associated with Pain Level in Patients Receiving Intravitreal Injection

Ali İnaltekin[1], Erdinç Bozkurt[2], Yüksel Kıvrak[3]

[1]Department of Psychiatry, Oltu State Hospital, Erzurum,Turkey, [2]Department of Ophthalmology, Umraniye Training and Research Hospital, İstanbul, Turkey, [3]Department of Psychiatry, Afyonkarahisar Health Sciences University School of Medicine, Afyonkarahisar, Turkey

Abstract

Purpose: To identify the factors associated with the pain level in patients receiving intravitreal injection.

Methods: A total of 120 patients were prospectively evaluated, and 104 were included in the study. Patients were asked to rate their pain intensity from 0 to 10 on the visual analog scale. Factors that were possibly associated with pain level were evaluated using a sociodemographic data form, state anxiety inventory, and the hospital anxiety and depression scale.

Results: Of the participants, 54 (51.9%) were female, and 50 (48.1%) were male, with a mean age of 65 ± 9.01 years. There was a positive correlation between pain level and state anxiety scores (r = 0.30; P < 0.001) and a negative correlation between hospital anxiety score (r = −0.23; P = 0.02) and hospital depression score (r = −0.27; P = 0.01). The correlation between pain score and education level was significantly higher in primary and secondary school graduates (P < 0.01). Smokers were observed to have higher pain scores (6.50 ± 2.21 in smokers and 4.87 ± 2.50 in nonsmokers; P = 0.01). Among diagnostic groups, pain scores were found to be significantly lower in the diabetic retinopathy (DR) group (6.82 ± 1.99 in age-related macular degeneration, 5.94 ± 2.27 in retinal vein occlusion, and 3.58 ± 1.97 in DR; P < 0.001). When pain scores were evaluated according to the drug injected, the group receiving bevacizumab injection was observed to have higher pain scores (7.32 ± 1.81 in bevacizumab, 4.00 ± 2.08 in aflibercept, and 3.92 ± 1.96 in ranibizumab; P < 0.001). Based on the multiple regression analysis, the state anxiety score, hospital anxiety score, hospital depression score, and smoking status were observed not to be significant predictors. The level of education, diagnosis, and active substance were found to have a statistically significant effect on pain perception.

Conclusion: In this study, pain levels have been found to be high in smokers, those with a low educational level, individuals receiving bevacizumab for intravitreal injection, and those having a higher level of state anxiety, whereas patients with DR have lower pain scores.

Keywords: Anti-vascular endothelial growth factor, Anxiety, Intravitreal injection, Pain, Visual analog scale

Address for correspondence: Ali İnaltekin, Department of Psychiatry, Oltu State Hospital, Erzurum, Turkey.
E-mail: aliinaltekin75@gmail.com
Submitted: 05-Jan-2021; **Revised:**10-May-2021; **Accepted:** 13-May-2021; **Published:** 22-Oct-2021

Introduction

Diabetic retinopathy (DR), retinal vein occlusion (RVO), and age-related macular degeneration (AMD) are common eye diseases affecting both the individual and society. The prevalence of DR among patients with diabetes is reported to be 35.4%.[1] The prevalence of RVO is 0.6%,[2] and the prevalence of AMD is approximately 10%.[3] Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) is used for the treatment of such diseases. Ranibizumab, aflibercept, and bevacizumab are the most commonly used intravitreal anti-VEGF agents.[4] Intravitreal injection of anti-VEGF is associated with several complications. Pain at the injection site is one of the most common complications. The pain associated with the injection can lead to eye movement and blepharospasm, which may result in injection-related complications (subconjunctival hemorrhage,

Access this article online

Quick Response Code:

Website: www.jcurrophthalmol.org

DOI: 10.4103/joco.joco_6_21

How to cite this article: Inaltekin A, Bozkurt E, Kıvrak Y. Factors associated with pain level in patients receiving intravitreal injection. J Curr Ophthalmol 2021;33:323-9.

lens perforation, endophthalmitis) or in the patient's refusal of further injections.[5] Many studies have been conducted on the perception of pain and factors associated with pain during intravitreal anti-VEGF injection. On the other hand, there are contradictory results regarding factors with a potential effect on pain scores, which include age, gender, number of injections, level of education, active substance used during injection, type of disease, and anxiety level of the patient.[6,7] Therefore, this study aimed to investigate the effects of the active substance, anxiety level, depression level, smoking, level of education, age, gender, body mass index (BMI), marital status, type of the disease, and the number of injections on the perception of pain associated with the injection.

Methods

All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, and the study was approved by the Ethics Committee of Kafkas University Faculty of Medicine.

The study included patients who received an intravitreal injection from October 2018 to January 2020. Based on previous studies, the study was planned to be conducted with 120 patients. Those who received intravitreal injection due to RVO, DR, or AMD, provided consent to participate in the study, were over 18 years of age, and had a postinjection intraocular pressure of <21 mmHg were included in the study. The exclusion criteria were having any ophthalmic disease that could affect the severity of pain (e.g., severe dry eye, scleritis, uveitis, or corneal diseases), using systemic analgesics, having a postinjection intraocular pressure of above 21 mmHg, having a mental illness or using medications like nonsteroidal anti-inflammatory drugs, having mental retardation or dementia, and refusing to participate in the study.

Patients were randomly selected on random days and were informed about the study. Written informed consent was obtained from those who provided consent to participate in the study. The participants were taken to a room where they could be alone and were asked to fill in the test battery consisting of the sociodemographic data form prepared by the authors, the state-trait anxiety inventory (STAI), and the hospital anxiety and depression scale (HADS). The questionnaires were filled by patients after preinjection intraocular pressure measurement, but patients who were illiterate got help from their attendant.

The active substance was selected randomly. We assigned one of the numbers 1, 2, and 3 to each participant with the SPSS program. In alphabetical order, we used aflibercept for 1, bevacizumab for 2, and ranibizumab for 3. Participants were given one drop of 0.5% proparacaine hydrochloride (Alcain, Novartis, Switzerland) three times at 5 min intervals. Then, the periocular skin and eyelids were disinfected three times with 10% povidone–iodine. After their eyes were covered with a sterile perforated dressing, a blepharostat was placed. Two drops of 5% povidone–iodine were administered to the conjunctival area. After waiting for 2 min, the conjunctiva was irrigated with sterile isotonic fluid. Bevacizumab (1.25 mg/0.05 mL, Genentech, San Francisco, CA, USA), ranibizumab (0.25 mg/0.05 mL, Novartis, East Hanover, NJ, USA), and aflibercept (2 mg/0.05 mL, Regeneron, Tarrytown, NY, USA) were injected from the pars plana into the vitreous cavity with the help of a 30-gauge needle through the superior temporal region. The injection was administered 4 mm behind the limbus for phakic eyes and 3.5 mm behind the limbus for pseudophakic eyes. The injection site was compressed for about 20–25 s with a sterile cotton swab to prevent the drug from flowing backward. Optic nerve perfusion was evaluated by checking the light sensation, and the eye was closed with antibiotic pomade. Intraocular pressures of all patients were measured about 5 min after the intravitreal injection. Patients were kept under observation for 3 h after intravitreal injection. The visual analog scale (VAS) was used to evaluate pain following the intraocular pressure measurement. All medical procedures were performed by the same clinician.

The questionnaires were filled by patients after intraocular pressure measurement, but illiterate patients received help from their attendants.

Sociodemographic data form

The form prepared by the authors consists of questions about the age, gender, marital status, occupation, educational background, and smoking status of the participants.

Visual analog scale

It is a type of psychometric scale using a continuous measurement indicator rather than multiple discrete indicators. Respondents to VAS make a subjective judgment on where their answer lies on a continuum and then, mark their response on a VAS line. Participants are shown a horizontal line rated from 0 representing "no pain" to 10 representing "maximum pain" and are asked to mark their pain level based on this rating. It was also previously used in ophthalmological studies[8] and shown to be valid and reliable. It can be easily applied by both patients and health-care professionals.[9]

State-trait anxiety inventory

The scale, which was developed by Spielberger *et al*.,[10] has two subscales: the state anxiety subscale and the trait anxiety subscale. It evaluates how the person feels under certain conditions. The Turkish validity and reliability study of the scale was performed by Öner and Le Compte.[11] The state anxiety subscale was used in the present study.

Hospital anxiety and depression scale

It was developed by Zigmond and Snaith.[12] The Turkish validity and reliability study of the scale was performed by Aydemir and Guvenir.[13] It has two subscales: anxiety and depression. The scale consists of 14 items, each scored from 0 to 3. It is used to investigate anxiety and depression in individuals with a physical illness.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0 software (IBM Corporation, Armonk, NY, USA). The student's *t*-test or one-way analysis of variance (ANOVA) was used in univariate analysis to analyze factors associated with the pain level after intravitreal injection. Correlation analysis was used to evaluate factors associated with the pain score. The patients were divided into three groups based on the diagnosis (RVO, DR, and AMD) and medication received (bevacizumab, ranibizumab, and aflibercept). Clinical factors were compared between the groups using the ANOVA test. $P < 0.05$ was considered statistically significant.

Results

Sixteen patients were excluded from the study due to missing data. A total of 104 patients were analyzed. There were 54 (51.9%) female and 50 (48.1%) male participants, and the mean age was 65 ± 9.01 years. Of the participants, 88 (84.6%) were married, 14 (13.5%) were widowed, and two (1.9%) were single. Considering the educational background, 31 (29.8%) were illiterate, 41 (39.4%) were primary school graduates, 14 (13.5%) were secondary school graduates, 11 (10.6%) were high school graduates, and seven (6.7%) were associate degree graduates. There were 39 (37.5%) patients in the AMD group, 48 (46.2%) in the DR group, and 17 (16.3%) in the RVO group. The bevacizumab group included 38 (36.5%) patients, the ranibizumab group included 29 (27.9%) patients, and the aflibercept group included 37 (35.6%) patients. Post injection, mean intraocular pressure was 17.38 ± 2.04 [Table 1].

Table 1: Baseline demographics of patients (n=104)

Variable	Value, *n* (%)
Sex (female:male)	54:50 (51.9:48.1)
Age, mean±SD (minimum-maximum)	65±9.01 (49-90)
Smokers: Nonsmokers	11:93 (10.6:89.4)
Marital status	
Married	88 (84.6)
Widowed	14 (13.5)
Single	2 (1.9)
Diagnosis	
AMD	39 (37.5)
DR	48 (46.2)
RVO	17 (16.3)
Injection drug	
Aflibercept	37 (35.6)
Bevacizumab	38 (36.5)
Ranibizumab	29 (27.9)
Education level	
Illiterate	31 (29.8)
Primary school	41 (39.4)
Secondary school	14 (13.5)
High school	11 (10.6)
Degree	7 (6.7)
BMI, mean±SD (minimum-maximum)	29.30±4.64 (21.88-53.33)
HAS, mean±SD (minimum-maximum)	6.33±4.37 (0-14)
HDS, mean±SD (minimum-maximum)	6.73±4.29 (0-15)
SAS, mean±SD (minimum-maximum)	46.74±11.53 (23-68)
Number of injections, mean±SD (minimum-maximum)	3.66±3.32 (1-20)
Vision, mean±SD (minimum-maximum)	0.15±0.12 (0.01-0.50)
IOP, mean±SD (minimum-maximum)	17.38±2.04 (12-20)

AMD: Age-related macular degeneration, DR: Diabetic retinopathy, RVO: Retinal vein occlusion, BMI: Body mass index, HAS: Hospital anxiety score, HDS: Hospital depression score, IOP: Intraocular pressure, SAS: State anxiety score, SD: Standard deviation

The level of pain was observed to have no correlation with age (r = 0.11; P = 0.24), BMI (r = 0.28; P = 0.77), vision (r = 0.34; P = 0.73), or number of injections (r = −0.90; P = 0.36). On the other hand, a positive correlation was observed between the pain level and state anxiety score (r = 0.30; P < 0.001), whereas there was a negative correlation with hospital anxiety score (r = −0.23; P = 0.02) and hospital depression score (r = −0.27; P = 0.01) [Table 2].

There was a significant difference between smokers and nonsmokers in terms of the mean pain scores (6.50 ± 2.21 and 4.87 ± 2.50, respectively; P = 0.01). No significant difference was found between the pain scores of the female and male participants (5.04 ± 2.52 and 5.31 ± 2.53, respectively; P = 0.58) [Table 2].

The ANOVA showed that marital status did not have a significant effect on the pain score (5.14 ± 2.56 in married, 5.50 ± 0.70 in single, and 5.43 ± 2.50 in widowed; P = 0.91). Considering the correlation between pain score and educational level, there was a significant difference between the primary school graduates and the other groups and between the secondary school graduates and the other groups in terms of pain scores (7.42 ± 1.33 in illiterate, 5.56 ± 2.05 in primary school graduates, 2.50 ± 1.16 in secondary school graduates, 3.00 ± 1.54 in high school graduates, and 1.86 ± 0.37 in associate degree graduates; for all comparisons P < 0.001). A statistically significant difference was observed between the DR group and the other two diagnosis groups (6.82 ± 1.99 in AMD, 5.94 ± 2.27 in RVO, and 3.58 ± 1.97 in DR; P < 0.001). When the pain scores of the groups divided according to the active substance were analyzed, a statistically significant difference was observed between the bevacizumab and the other two groups (7.32 ± 1.81 in bevacizumab, 4.00 ± 2.08 in aflibercept, and 3.92 ± 1.96 in ranibizumab; P < 0.001) [Table 2].

Multiple regression analysis was used to assess the pain predictive ability of diagnosis, state anxiety score, hospital anxiety score, hospital depression score, smoking status, drug type, and level of education. Preliminary analyses were conducted to investigate whether the normality, linearity, multiple common linearities, and homoscedasticity assumptions were neglected. The Durbin–Watson statistic in the present study was 2.43, which is within the acceptable range. The variance inflation factor values in the model were below 10, and the lowest tolerance value was higher than 0.10. The model explained 68.4% of the variance

Table 2: Factors associated with the level of pain

Variable	Mean pain score	*P*
Female	5.04±2.52	0.58**
Male	5.31±2.53	
Marital status		
Married	5.14±2.56	0.91*
Single	5.50±0.70	
Widowed	5.43±2.50	
Education level		<0.001*
Illutered	7.42±1.33	
Primary school	5.56±2.05	
Secondary school	2.50±1.16	
High school	3.00±1.54	
Degree	1.86±0.37	
Diagnosis		<0.001*
AMD	6.82±1.99	
DR	3.58±1.97	
RVO	5.94±2.27	
Injection drug		<0.001*
Aflibercept	4.00±2.08	
Bevacizumab	7.32±1.81	
Smoking		
Smokers	6.50±2.21	0.01**
Nonsmokers	4.87±2.50	
Variable	**Correlation (Pearson's coefficient)**	***P***
Age	0.11	0.24***
BMI	0.28	0.77***
SAS	0.30	<0.001***
HDS	−0.27	0.01***
HAS	−0.23	0.02***
Vision	0.34	0.73***
Number of injections	−0.90	0.36***

*Oneway analysis, ***T*-test, ***Correlation analysis. AMD: Age-related macular degeneration, DR: Diabetic retinopathy, RVO: Retinal vein occlusion, BMI: Body mass index, SAS: State anxiety score, HDS: Hospital depression score, HAS: Hospital anxiety score

($F[7, 93] = 28.7$, $P < 0.001$). The level of education, diagnosis, and active substance were found to have a statistically significant effect on pain perception. The level of education was observed to have the highest beta value, while the diagnosis group had the smallest beta value. The state anxiety score, hospital anxiety score, hospital depression score, and smoking status were observed not to be significant predictors [Table 3].

Discussion

The present study investigated the factors with potentials effects on pain perception during intravitreal injection, which is one of the most common intraocular procedures. Pain level perceived by the participants was found to be higher in smokers, those with lower educational level, individuals receiving bevacizumab, and those with high state anxiety scores, whereas it was lower in patients with DR. Furthermore, the level of education, diagnosis, and the active substance were found to be able to predict the pain score.

In line with the literature, a significant inverse correlation was observed between the level of education and pain scores.[14] The perceived pain level decreased with increasing level of education, which may be contributed by sociocultural status, awareness of disease, and emotional state. The notion that worrying about expected pain and feeling a lack of control over the pain make individuals sensitive to pain stimuli and thus increase the pain perceived has been widely supported.[15] A better understanding of the disease and procedure may contribute to better adaptation and tolerance of the expected situation, making the situation less threatening. In the present study, the perceived pain level in patients receiving bevacizumab was found to be higher than the other two groups. The literature review has shown that there is no study comparing bevacizumab, ranibizumab, and aflibercept in this context. The effect of the active substance used in the injection on the pain level has not been fully revealed yet.

Three studies comparing ranibizumab and aflibercept could be reached, two of which reported no significant difference between the two medications,[14,16] whereas one of them found the level of pain to be higher in the aflibercept group.[17] There was only one study comparing ranibizumab and bevacizumab, and in this study, the perceived pain was reported to be higher in the bevacizumab group than in the ranibizumab group.[18] Although the volumes of the active substance used in this study were the same, the size of the needle tip used for the injection was different. Ranibizumab was administered with a 30-gauge needle, whereas a 27-gauge needle was used for bevacizumab.[18] Different needle tip sizes may have affected the pain perceived by the patients. Unlike this study, not only ranibizumab and aflibercept were included in the present study but also bevacizumab, and the perceived pain was found to be higher in the bevacizumab group. Furthermore, the volumes and needle sizes used were the same. There are studies reporting that needles of a smaller size are less painful for the patients after intravitreal injections[19] and that a sudden increase in intraocular pressure after intravitreal injection is a factor affecting the pain perceived by the patient.[20] Such an effect was not expected in the present study since both the agents were injected into the eye at the same volume and using needles of the same size. The difference between pain scores may be attributed to different pH values and components of drug solutions. However, the retina has no pain receptors and sensory innervation to feel the pain associated with pH changes.[21] The pain felt during the injection is thought to be felt through the scleral sensory nerves. Medication injected into the vitreous chamber may leak into the subconjunctival area, and different components and pH values of drug solutions may cause pain of different intensities.

Similar to the study by Segal *et al*.,[6] the pain score was found to be statistically significantly lower in patients with DR. While there are studies supporting this result, there are also publications reporting otherwise. In two studies evaluating the correlation of pain score with diabetic macular edema, AMD, and RVO, no significant correlation was found between the

Table 3: Evaluation of pain predictors by multiple linear regression analysis

	B	SE	β	*t*	*P*	95% CI (lower-upper)
Constant	8.037	1.148		7.001	<0.001	5.757 - 10.317
Diagnosis	0.595	0.242	0.176	2.455	0.016	0.114 - 1.076
Education level	−1.184	0.135	−0.564	−8.764	<0.001	−1.45 - −0.916
SAS	0.015	0.015	0.069	0.999	0.320	−0.015 - 0.45
HAS	−0.06	0.056	−0.105	−1.079	0.283	−0.17 - 0.051
Smoking	0.123	0.482	0.015	0.256	0.799	−0.83 - 1.079
Injection drug	−0.970	0.205	−0.310	−4.727	<0.001	−1.38 - −0.563
HDS	0.048	0.064	0.083	0.751	0.454	−0.079 - 0.176

R^2=0.684, P<0.001. SE: Standard error, CI: Confidence interval, SAS: State anxiety score, HAS: Hospital anxiety score, HDS: Hospital depression score

diagnosis and the pain score.[7,22] In another study, the main pain score of patients with diabetes was found to be significantly higher during the procedure compared to nondiabetic patients.[18]

In the present study, intravitreal injection pain scores were found to be higher in smokers compared to nonsmokers. To the best of our knowledge, there is no study showing the effect of smoking on the pain score in patients receiving intravitreal injection. We believe that our study will contribute to the literature in this regard. Nicotine is reported to have analgesic properties both in animals and humans.[23-25] Several studies reported that despite this pain-relieving effect, among those with chronic pain, smokers complain of greater pain intensity and an increased number of painful sites.[26,27] Compared to nonsmokers, smokers deprived of nicotine tend to have a shorter pain latency to heat pain and reduced tolerance to electrical pain stimulation.[28,29] Furthermore, a study investigating the effects of smoking on ocular health showed that smoking increased the risk and severity of inflammation.[30] This may be due to the fact that smoking has a promoting effect on inflammation or that patients stay away from nicotine during the procedure.

Conflicting results have been reported regarding the effect of age on pain level in patients receiving intravitreal injection. While no correlation was observed in four of the studies,[18,21,31,32] one showed that elderly patients experienced more pain.[33] Two studies showed that level of pain was lower in patients 65 years of age or older.[7,14] However, no correlation was observed between the pain severity during intravitreal injection and age in the present study. Nerve density has been shown to decrease with age, particularly after the age of 70, suggesting that older patients should experience less pain during intravitreal injection.[34] In the present study, the mean age of the patients was 65 years, and the majority of them were younger than 70 years, which may be the reason for not finding a significant correlation between age and pain score.

We further observed that gender of the participants did not have any significant effect on pain scores. The results from studies investigating the correlation between gender and pain level are contradictory. Rifkin and Schaal[7] reported that women had lower pain scores after intravitreal injection compared to men, whereas Haas *et al*.[33] reported higher pain scores in women. On the other hand, Doguizi *et al*.[22] and Pieramici *et al*.[35] found no statistically significant difference between the genders in terms of pain scores after intravitreal injection. We attribute the difference in the pain scores between female and male patients to the educational and cultural differences, and we believe that this difference may not be clinically significant.

In the literature, a statistically significant positive correlation has been reported between the pain level and state anxiety levels or preprocedural anxiety levels in patients receiving intravitreal injection.[6,36] In these studies, VAS for anxiety was used to determine the level of anxiety. We used STAI and HADS scales in this study, and the results obtained from these scales showed a positive correlation between pain score and state anxiety score and a negative correlation between hospital anxiety and depression score. Although there is a positive correlation between anxiety and pain in general, this correlation is not demonstrated in some studies. In a study by Pani *et al*.[37] involving patients with dental implants and in a study by Kokanali *et al*.[38] involving patients undergoing hysterectomy, the authors reported no correlation between anxiety and pain scores. Baser *et al*.[39] showed that pain scores of patients undergoing colposcopy were positively correlated with state anxiety scores, whereas they showed no correlation with trait anxiety scores. In the present study, the pain score was found to be positively correlated with the state anxiety score and negatively correlated with the HADS score. This may be attributed to the fact that HADS measures general anxiety, while state anxiety scale measures current anxiety and that pain is affected by the state anxiety level rather than the general anxiety.

To the best of our knowledge, there is no pain study evaluating three different eye diseases and three different active substances. The present study can be useful in several fields. First of all, if the results of this study are supported by randomized prospective studies, it can be beneficial for clinicians. Knowing that the factors associated with pain level in patients receiving intravitreal injection may change the clinician's patient approach and may ensure them to prefer options causing less pain. It may further be beneficial for researchers. First of all, pain perception has not been fully understood yet. If clinicians know that the level of education and the type of medication given affect pain, this may pave the way for studies to be conducted to understand the pain

mechanism in this regard. Second, studies can be conducted to make the medications less painful.

This study had several limitations. First, it included both patients receiving treatment for the first time and those who had previously received intravitreal injection. Furthermore, the small number of participants may have reduced the ability to detect factors that may be associated with pain following intravitreal injections. There was no proper distribution in terms of number for education. However, we believe that this is an insignificant limitation because this distribution also reflects the profile of the patients presenting to our clinic. The mean age of the participants shows the insufficiency of the number of educational institutions in our region about 65 years ago. We were able to perform VAS only once since transportation in this geography is difficult, and the majority of the participants immediately wanted to go to their village. Moreover, patients' conditions could not be checked by phone due to poor communication infrastructure. There is a need for further studies to be conducted with a larger patient population in a controlled environment. Thus, beneficial results may be obtained for the variables, the effects of which on pain level particularly after intravitreal injection has been found to be contradictory.

In conclusion, neither age nor gender was found to be associated with the severity of pain following intravitreal injection. The pain level was observed to be high in smokers, those with lower educational level, individuals receiving bevacizumab, and those with high state anxiety scores, whereas it was lower in patients with DR.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, *et al.* Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.
2. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: The Beaver dam eye study. Trans Am Ophthalmol Soc 2000;98:133-41.
3. Colijn JM, Buitendijk GH, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, *et al.* Prevalence of age-related macular degeneration in Europe: The past and the future. Ophthalmology 2017;124:1753-63.
4. Fiebai B, Odogu V. Intravitreal anti vascular endothelial growth factor agents in the management of retinal diseases: An audit. Open Ophthalmol J 2017;11:315-21.
5. Kaderli B, Avci R. Comparison of topical and subconjunctival anesthesia in intravitreal injection administrations. Eur J Ophthalmol 2006;16:718-21.
6. 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.
7. Rifkin L, Schaal S. Factors affecting patients' pain intensity during in office intravitreal injection procedure. Retina 2012;32:696-700.
8. Tewari A, Shah GK, Dhalla MS, Blinder KJ. Surface anesthesia for office-based retinal procedures. Retina 2007;27:804-5.
9. McCarthy M Jr., Chang CH, Pickard AS, Giobbie-Hurder A, Price DD, Jonasson O, *et al.* Visual analog scales for assessing surgical pain. J Am Coll Surg 2005;201:245-52.
10. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. ???: Consulting Psychologists Press; 1983.
11. Oner N, LeCompte A. State-trait anxiety inventory handbook. 2nd ed. Istanbul: Bogazici University Issues; 1985.
12. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
13. Aydemir O, Guvenir T. Validity and reliability of Turkish version of hospital anxiety and depression scale. Turk J Psychiatry 1997;8:280-7.
14. Öner A, Ünlü M, Karaca a, Sevim DG, Sönmez S, Mirza GE. Assessment of pain scores during intravitreal injections of aflibercept versus ranibizumab. Retina-vitreus. J Retina-Vitr 2018;27:143-7.
15. Oshodi TO. The impact of preoperative education on postoperative pain. Part 1. Br J Nurs 2007;16:706-10.
16. Ertan E, Duman R, Duman R. Comparison of pain during intravitreal dexamethasone, ranibizumab and aflibercept injection. Clin Exp Optom 2020;103:630-3.
17. Bilgin B, Bilak Ş. Assessment of patient pain experience during intravitreal ranibizumab and aflibercept injection. Middle East Afr J Ophthalmol 2019;26:55-9.
18. Onakpoya OH, Akinwande JG. Evaluation of ocular pain during and after intravitreal injection of antivascular endothelial growth factors in South-West Nigeria. Niger J Ophthalmol 2019;27:1-7.
19. Rodrigues EB, Grumann A Jr., Penha FM, Shiroma H, Rossi E, Meyer CH, *et al.* Effect of needle type and injection technique on pain level and vitreal reflux in intravitreal injection. J Ocul Pharmacol Ther 2011;27:197-203.
20. Aref AA. Management of immediate and sustained intraocular pressure rise associated with intravitreal antivascular endothelial growth factor injection therapy. Curr Opin Ophthalmol 2012;23:105-10.
21. Belmonte C, Tervo TT, Gallar J. Lasensory innervations of the eye. In: Adler's Physiology of the Eye. 11th ed. Leonard LA, editor. Edinburgh: Elsevier; 2011. p. 363-84.
22. Doguizi S, Sekeroglu MA, Inanc M, Anayol MA, Yilmazbas P. Evaluation of pain during intravitreal aflibercept injections. Eur J Ophthalmol 2018;28:63-7.
23. Damaj MI, Glassco W, Aceto MD, Martin BR. Antinociceptive and pharmacological effects of metanicotine, a selective nicotinic agonist. J Pharmacol Exp Ther 1999;291:390-8.
24. Tripathi HL, Martin BR, Aceto MD. Nicotine-induced antinociception in rats and mice: Correlation with nicotine brain levels. J Pharmacol Exp Ther 1982;221:91-6.
25. Jamner LD, Girdler SS, Shapiro D, Jarvik ME. Pain inhibition, nicotine, and gender. Exp Clin Psychopharmacol 1998;6:96-106.
26. John U, Hanke M, Meyer C, Völzke H, Baumeister SE, Alte D. Tobacco smoking in relation to pain in a national general population survey. Prev Med 2006;43:477-81.
27. Vogt MT, Hanscom B, Lauerman WC, Kang JD. Influence of smoking on the health status of spinal patients: The National Spine Network database. Spine (Phila Pa 1976) 2002;27:313-9.
28. Nesbitt PD. Smoking, physiological arousal, and emotional response. J Pers Soc Psychol 1973;25:137-44.
29. Silverstein B. Cigarette smoking, nicotine addiction, and relaxation. J Pers Soc Psychol 1982;42:946-50.
30. Galor A, Lee DJ. Effects of smoking on ocular health. Curr Opin Ophthalmol 2011;22:477-82.
31. Massamba N, Elluard M, Agoune W, Guyader V, Ingram A, Pasquier B, *et al.* Assessment of ocular pain following ranibizumab intravitreal injection. Acta Ophthalmol 2015;93:e231-2.
32. Shin SH, Park SP, Kim YK. Factors associated with pain following intravitreal injections. Korean J Ophthalmol 2018;32:196-203.
33. Haas P, Falkner-Radler C, Wimpissinger B, Malina M, Binder S. Needle size in intravitreal injections – Pain evaluation of a randomized clinical trial. Acta Ophthalmol 2016;94:198-202.
34. He J, Bazan NG, Bazan HE. Mapping the entire human corneal nerve architecture. Exp Eye Res 2010;91:513-23.
35. Pieramici DJ, Rabena M, Castellarin AA, Nasir M, See R, Norton T, *et al.* Ranibizumab for the treatment of macular edema associated

with perfused central retinal vein occlusions. Ophthalmology 2008;115:e47-54.
36. Sii S, Aspinall P, Borooah S, Dhillon B. Exploring factors predicting changes in patients' expectations and psychosocial issues during the course of treatment with intravitreal injections for wet age-related macular degeneration. Eye (Lond) 2018;32:673-8.
37. Pani SC, AlGarni B, AlZain LM, AlQahtani NS. Assessment of the impact of stress and anxiety on pain perception in patients undergoing surgery for placement of their first dental implant. Oral Health Dent Manag 2014;13:464-8.
38. Kokanali MK, Cavkaytar S, Guzel Aİ, Topçu HO, Eroğlu E, Aksakal O, *et al.* Impact of preprocedural anxiety levels on pain perception in patients undergoing office hysteroscopy. J Chin Med Assoc 2014;77:477-81.
39. Baser E, Togrul C, Ozgu E, Esercan A, Caglar M, Gungor T. Effect of pre-procedural state-trait anxiety on pain perception and discomfort in women undergoing colposcopy for cervical cytological abnormalities. Asian Pac J Cancer Prev 2013;14:4053-6.