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Effect of needle size on pain degree and intraocular pressure after intravitreal injection: a randomized observational study

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ABSTRACT

BACKGROUND: Intravitreal injection (IVI) is a common vitreoretinal procedure, and in most patients, multiple IVIs related to the course of their disease have to be performed. Pain sensations during IVI can reduce the desire to continue repeated IVI and can cause complications due to sudden eye movements. The purpose of this study was to compare the effect of needle size on immediate intraocular pressure (IOP), vitreous reflux, and pain experienced in patients after the IVI procedure.

MATERIAL AND METHODS: One hundred and ten eyes of 110 patients who were first administered intravitreal ranibizumab or aflibercept were randomized according to the needle size, 30-gauge (Group 1) or 26-gauge (Group 2). The reflux was graded per the IVI procedure. Immediately after IVI, patients were asked to assess the degree of pain with a visual analogue scale (VAS). The IOP measurements were performed 30 minutes after the operation. The average of VAS scores was used as the primary outcome.

RESULTS: Both groups consisted of 55 eyes. The mean VAS score was 2.18 ± 1.82 in Group 1 and 4.00 ± 2.36 in Group 2. The mean vitreous reflux was lower in Group 1 than in Group 2. The mean IOP was comparable between the groups (26.3 ± 5.66 / 25.4 ± 4.02 mm Hg). The groups were divided into subgroups according to intravitreal agent use; no statistical difference was observed in VAS scores.

CONCLUSIONS: The 30-gauge needle was more comfortable and safer than the 26-gauge needle for the IVI procedure.

KEY WORDS: intravitreal injection; visual analogue scale; vitreous reflux; anti-VEGF; needle size

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INTRODUCTION

Intravitreal injection (IVI) has recently become the most common vitreoretinal procedure [1]. The antivascular endothelial growth factor agent (anti-VEGF) is used effectively and safely in treating diabetic macular edema, retinal vascular occlusion, and age-related macular degeneration [2–4]. In most patients, throughout their disease, multiple anti-VEGF IVI procedures have to be performed. If the patient feels pain during the IVI procedure, the desire to continue the injections may decrease. Furthermore, the pain experienced by the patient during injection can cause complications due to sudden movements of the eye. The visual analogue

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scale (VAS) is a common and easy tool to measure pain sensation, and it is a reliable research method in previous ophthalmology studies [5–8]. Intraocular pressure (IOP) can increase after this procedure; however, increasing IOP is transient and generally normalizes spontaneously in 30 minutes [9, 10].

The main purpose of our study was to compare the effect of needle size on immediate IOP, vitreous reflux, and pain sensation in patients after an anti-VEGF IVI procedure.

MATERIAL AND METHODS

This retrospective, randomized, double-armed, single-blind study was approved by the Ethics Committee (2022/291), and the principles of the Declaration of Helsinki were followed. Informed consent was obtained from all individual participants.

Patients who were first administered intravitreal ranibizumab (Lucentis; Genentech, San Francisco, CA, USA) or intravitreal aflibercept (Eylea, Regeneron Pharmaceuticals Inc. Columbia, NY, USA) were randomized according to the use of needle size as 30 gauge (G) (0,30 x 13 mm, BD Microlance, Becton, Ireland) (Group 1) or 26 G (0.45 x 13 mm, BD Microlance, Becton, Ireland) (Group 2). Furthermore, gender, age, medication, indication, and laterality were investigated. The patients were blinded to the chosen needle size but not the medication. The exclusion criteria for the patients were: younger than 18 years, a history of ocular surgery other than cataract surgery, a mental disability or inability to respond to the questions about pain, any contraindication to intravitreal injection, any corneal disorder that can affect the measurement of intraocular pressure measurement such as bullous keratopathy, any anterior segment pathology that can alter pain sensation such as herpes keratitis and conjunctivitis, any ocular pain before injections, systemic analgesic and sedative use.

The same experienced ophthalmologist (AAEB) performed all the IVI in the operating room as follows. IVI was performed as recommended in the previously reported guideline [11]. First, the topical anesthetic agent (Proparacaine HCL, Alcaine 0,05%, Alcon, USA) was instilled three times at one-minute intervals for each patient. After the patient laid down on the operation table, the area around the eye was wiped with 10% povidone-iodine. Eye and eyelash were irrigated with povidone-iodine 5% after a speculum was inserted. Povidone-iodine was rinsed with a balanced salt solution after a three-minute wait. All the injections (ranibizumab 0.5 mg/0.05 mL, aflibercept 2 mg/0.05 mL) were applied to the superior temporal pars plana, 3.5 mm in patients with aphakic/pseudophakic and 4.0 mm in patients with phakic distance from the limbus with the same scleral tunnel technique. A cotton-tipped applicator was used to apply pressure on the injection site for 5 seconds immediately after injection. The reflux was graded by the same ophthalmologist who performed the injections as follows: 1: no or mild reflux, 2: moderate reflux, 3: significant reflux. Immediately after injection, patients were asked to assess the degree of pain with a visual analogue scale (VAS). VAS was explained in detail to all patients before the procedure; point 0 was no pain, and point 10 was unbearable pain. The IOP was measured 30 minutes before and after the IVI procedure with a Goldmann applanation tonometer.

Jamovi version 2.2.5 was used for statistical analysis. The sample size was calculated according to Eta Squared and was found to be 0.16. Continuous variables were identified with mean and ± standard deviations. Categorical variables were determined with proportion, median, and mode. After checking the normality and homogeneity of the variables, they were compared between the groups using the independent samples t-test, Mann-Whitney U test, and Chi-square test. Kruskal-Wallis analysis was performed to assess the difference in VAS pain scores between subgroups that were composed by dividing groups 1 and 2 according to the intravitreal agent. Ordinal logistic regression analysis was used to assess the significance of covariates in predicting their effect on the VAS pain score. A p-value < 0.05 was accepted as significant.

RESULTS

Both groups comprised 55 patients and were comparable according to age and gender ($p = 0.59$, $p = 0.34$, respectively). Furthermore, both groups were similar in terms of laterality, indication for intravitreal injection, intravitreal agent, lens status, and pre-IVI procedure IOP ($p = 0.70$, $p = 0.12$, $p = 1$, $p = 0.34$, $p = 0.57$, respectively). Characteristics of the groups were presented in Table 1.

The mean VAS pain score was observed to be lower in Group 1 (2.18 ± 1.82, median: 2, mode: 1) than in Group 2 (4.00 ± 2.36, median: 4, mode: 6) ($p < 0.001$). Similarly, the mean reflux grade was ob-

Table 1. Characteristics of the studied groups

	Group 1 (30-gauge)	Group 2 (26-gauge)	p-value
Sex	27 Female/28 Male	32 Female 23 Male	0.34*
Age	64.8 ± 10.3	63.7 ± 10.3	0.59**
Laterality	24 Right 31 Left	22 Right 33 Left	0.70*
Indication	42 DME 2 RVO 11 AMD	47 DME 4 RVO 4 AMD	0.12*
Medication	30 — aflibercept 25 — ranibizumab	30 — aflibercept 25 — ranibizumab	1*
Lens Status	26 — phakic 29 — pseudophakic	21 — phakic 34 — pseudophakic	0.34*
Preoperative IOP	18 ± 2.43 mm Hg	18.3 ± 2.26 mm Hg	0.57**

DRP — diabetic macular edema; RVO — retinal vascular occlusion; AMD — age-related macular degeneration; IOP — intraocular pressure; *Chi-square test.
**Independent samples t-test

served to be lower in group 1 (1.09 ± 0.29, median: 1, mode: 1) than in group 2 (2.05 ± 0.49, median: 2, mode: 2) ($p < 0.001$). The mean post-IVI procedure IOP was comparable between the groups (Group 1: 26.3 ± 5.66 mm Hg, Group 2: 25.4 ± 4.02 mm Hg $p = 0.90$). When Groups 1 and 2 were divided into subgroups according to intravitreal agent use, no statistically significant differences were found in VAS pain scores between subgroups ($p = 0,27$) (Fig. 1). Furthermore, when the study cohort was divided into older and younger than 65 years, no statistically significant differences were observed in VAS pain scores between subgroups ($p = 0.60$). In the ordinal logistic regression model, while gender, age, laterality, intravitreal agent, indication, lens status, and pre/post-IVI procedure IOP were not statistically significant, only needle size was statistically significant in predicting the VAS pain score [$p < 0.001$, odds ratio: 5.306, 95% confidence interval (CI): 2.457–11.85]. The details of the logistic regression model are demonstrated in Table 2.

DISCUSSION

Anti-VEGF IVI is a commonly accepted procedure; however, there is no clear consensus on the use of needle size [12]. Studies on the choice of needle size have been related to the pain experience of patients during injection and the immediate post-IVI procedure IOP.

IOP can increase after this procedure; however, increasing IOP is transient and generally normalizes spontaneously in 30 minutes. However, repeated spikes of IOP can damage the trabecular meshwork for sustained elevation of IOP in susceptible eyes [13]. Therefore, the IOP was measured 30 minutes after the IVI procedure in this study. Although post-IVI procedure IOP was higher in the 30-G

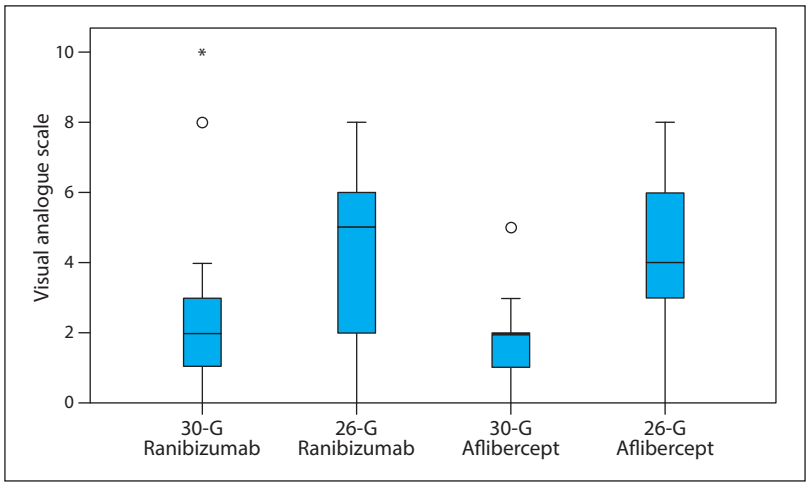

FIGURE 1. Visual analogue pain score in different anti-vascular endothelial growth factor (anti-VEGF) agents

Table 2. Details of the ordinal logistic regression model for Visual Analogue Scale (VAS)

	p	Odds Ratio	95% confidence interval	
			Lower	Upper
Gender	0.07	0.534	0.266	1.06
Age	0.30	1.032	0.973	1.09
Laterality	0.47	1.29	0.653	2.56
Indication	0.62	1.432	0.333	6.02
İntravitreal Agent	0.42	1.338	0.659	2.73
Lens status	0.19	0.483	0.163	1.42
Pre-IVI IOP	0.81	1.02	0.866	1.20
Post-IVI IOP	0.96	1.002	0.926	1.08
Needle Size	< 0.001	5.306	2.457	11.85

IVI — intravitreal injection; IOP — intraocular pressure

group than in the 26-G group, no statistically significant differences were observed between 2 groups and between the subgroups (group 1 ranibizumab or aflibercept and group 2 ranibizumab or aflibercept). Kim et al. observed a higher IOP with 30- and 32-G needles than 27-G needles [14].

On the other hand, post-IVI IOP was observed similarly between 27-G and 30-G needles by Loureiro et al. [9]. In this study, when both groups and subgroups were compared regarding post-IVI IOP, it was higher in the 30-G group. However, no statistical differences were observed between the groups and subgroups.

A lower post-IVI IOP could be associated with vitreous reflux [15]. Pang et al. investigated the effect of needle size on post-IVI IOP and vitreous reflux. They found that eyes injected with 32 G needles had a higher IOP and a lower incidence of vitreous reflux than those injected with larger 30-G needles [16]. These findings suggest that a larger diameter needle facilitates vitreous reflux, and thus, lower IOP spikes after the IVI procedure are expected. In our study, although 26-G group had lower IOP than 30-G group after the IVI procedure, no statistical differences were found between the two groups in terms of post-IVI IOP in relation to the subjective evaluation of the amount of vitreous reflux.

No statistically significant differences were observed in pain scores associated with the IVI procedure in terms of the location of injection by Moisseiev et al. [17]. So, all IVIs were performed in the superior-temporal quadrant in our study. Tunneled and the straight scleral IVI procedures were previously compared in terms of post-IVI IOP and patient discomfort and no significant differences were reported [18, 19]. Therefore, we used a tunneled scleral IVI technique in all patients, and only the impact of needle size was studied in our study.

The evaluation of pain associated with the IVI procedure is essential due to repetitive injections during the course of the disease. VAS is an appropriate tool that can be easily performed by anyone cognitively capable of understanding the parameters and responding to the physician's instructions. After a brief explanation, no patients had difficulty classifying the degree of their pain. VAS has been used frequently in ophthalmic research [13, 14, 20, 21]. In our study, we determined that the size of the needle was important to reduce pain sensation, and the small size needle was found to cause less pain. Although in terms of pain sensation for comparison of our study, similar findings were reported in previous studies [21–23], in contrast, some studies found that pain sensation was independent of needle size [9, 23–25]. These findings might seem like bias. Pulido et al. reported that 27-G needles require almost twice the force to penetrate the sclera, which theoretically can affect patient comfort [26].

Previous studies have shown that the pain score was not significantly related to diagnosis [17, 24]. Therefore, in this study, we did not evaluate the relationship between diagnosis and pain scores. Rifkin and Schaal [24] and Haas et al. [23] found that female sex was associated with a lower pain score after the IVI procedure. Moisseiev et al. [17] and Doguizi et al. [27] demonstrated no statistically significant differences in pain scores according to sex. Guler et al. [21] found that the female patients who received ranibizumab had lower average pain scores. In our study, no statistical differences were observed

regarding pain scores between the gender and anti-VEGF agents. Haas et al. [23] reported that older patients had more pain. However, no statistically significant differences were found in pain scores between the older and younger patients.

A limitation of our study was the smaller sample size. In addition, although the assessment of vitreous reflux could be of interest, it was subjective. Therefore, quantitative studies should be performed on vitreous reflux and vitreous reflux associated with post-IVI procedure IOP. However, the procedure being performed by the same surgeon and including patients who were applied IVI for the first time were advantages of our study in determining the pain score and vitreous reflux.

CONCLUSIONS

IOP increased significantly immediately after the IVI procedure, regardless of the size of the needle used. The post-IVI procedure IOP was lower in the 26-G group than in the 30-G group. However, no statistical differences were observed. Vitreous reflux could be associated with post-IVI IOP. When comparing the two groups in terms of pain sensation during IVI, the 30-G group had a lower pain score than the 26-G group, in our opinion, because the 30-G needle penetrates the sclera more easily and safely than the 26-G needle.

Data availability statement

The data that support the findings of this study are available from the corresponding author, A.A.E.B., upon reasonable request.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by A.A.E.B., S.I.K., K.D.B., M.D.K. and H.I.S. The first draft of the manuscript was written by E.Ç. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the ethics committee of the Sakarya University Medical Faculty, and tenets of the Declaration of Helsinki were followed (2022/291).

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