The effect of different forms of intravitreal ranibizumab administration on pain

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Abstract

Aim: To examine the effect of using the prefilled syringe formulation of intravitreal ranibizumab (ivr) on pain.

Materials and Methods: 30 patients received bilateral IVR injection due to diabetic retinopathy and macular edema and 30 eyes of these patients that received ready-to-use (PFS) IVR were considered as group 1, and the 30 eyes that received conventional IVR by withdrawing from the vial were considered as group 2. Patients who had previously received intravitreal injection, had intraocular surgery, used any eye drops, and were unable to cooperate with the assessment were excluded from the study. Pain experienced during the injection was assessed by using the numerical rating scale (NRS) and the verbal rating scale (VRS).

Results: The mean age of 30 female patients evaluated was 60.3 ± 7.94 years. While the NRS was 3.70 ± 0.79 in Group 1, it was 4.23 ± 0.77 in Group 2, the difference was statistically significant (p = 0.02). While the VRS was 2.13 ± 0.34 in Group 1, it was found to be 3.0 ± 0.58 in Group 2, the difference was statistically significant (p = 0.02).

Conclusion: IVR application in ready-to-use formulation causes less pain during intravitreal injection.

Introduction

The most valid definition of the concept of pain today is made by the International Organization for the Study of Pain (IASP). According to this organization, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]. Although the most reliable indicator in pain assessment is the patient’s own expression about experienced pain, it should be remembered that there will be patients who have difficulty in describing their pain or are unable to describe it. The easiest way to assess pain is to ask the patient whether he/she has pain. However, merely having or not having pain is not sufficient for assessment. One-dimensional scales used in pain assessment are intended to directly measure pain intensity, and the patient makes the assessment himself/herself. Currently, they are used principally in the assessment of acute pain and also in monitoring the effectiveness of the pain treatment. One-dimensional scales include the verbal category, numerical and visual comparison scale, and the Burford Pain Thermometer. The numerical scale is a method for determining pain intensity and aims to explain the patient’s pain with numbers. On numerical scales, it starts with absence of pain (0) and reaches the level of unbearable pain (10). The verbal category scale is also called the simple descriptive scale, and this scale is based on the patient choosing the most appropriate word to describe the pain situation. Pain intensity ranges from mild to unbearable [2-6].

Materials and Methods

30 patients who received bilateral intravitreal ranibizumab (IVR) in the same session due to diabetic retinopathy and macular edema in the eye department of Karabük University Faculty of Medicine Training and Research Hospital were evaluated following ethics committee approval (Decision No:2019/155). 30 eyes that received pre-filled syringe (PFS) form of IVR for intravitreal injection were accepted as Group 1, and 30 eyes that received IVR conventionally by withdrawing the drug from the vial were considered as Group 2. Patients who had previously received intravitreal injection, had intraocular surgery, used any eye drops, and were unable to cooperate with the assessment were excluded from the study.

Due to the exclusion criteria and the difficulties in prescribing the PFS and conventional form of intravitreal
ranibizumab at the same time, and the difficulties of injecting into two eyes in the same session, 30 patients could be included in the evaluation. All injections were administered under operating room conditions following the same protocol.

All injections were performed by the same surgeon and the same type of blepharostat was used in the patients. Following topical anesthesia, all patients underwent ocular surface cleaning with 10% povidone iodine. After sterile drape and blepharostat placement, 3.5 mm from the limbus was marked and an IVR 0.5 mg/0.05 ml was injected by using a 30 G syringe tip. Following the injection, the entrance site was massaged with a cotton swab. Patients were asked to assess their pain using the numerical rating scale (NRS) (Figure 1) and verbal rating scale (VRS) (Figure 2).

![Figure 1](image1.png)

**Figure 1.** Numerical Rating Scale (Black and Matassarin 1993).

![Figure 2](image2.png)

**Figure 2.** Verbal Rating Scale (Melzackand Katz 1992).

### Statistical analysis

Statistical analyzes were performed using SPSS version 16.0 (SPSS Inc, Chicago, Illinois, USA) and a p value < 0.05 was considered statistically significant. In the normal distribution test performed before the analysis with Kolmogorov-Smirnov test, it was seen that the variables fit the normal distribution. The mean and standard deviation values of the groups were calculated. Paired t test was used to compare numerical variables of two groups.

### Results

The mean age of the 30 female patients assessed was 60.3 ±7.94 years. While the NRS was found to be 3.70±0.79 in Group 1, it was found to be 4.23±0.77 in Group 2, the difference was statistically significant. (p=0.02) While the VRS was found to be 2.13±0.34 in Group 1, the VRS was found to be 3.0±0.58 in Group 2, the difference was statistically significant. (p=0.02) (Table 1).

### Discussion

Anesthesia technique used during intravitreal drug administration is of great importance. Repeat doses may be required in most patients; thus, effective anesthesia that lead to a painless and easy procedure will increase patient compliance. Because patients experience severe pain during the procedure, this may cause patients to refuse subsequent injections. Moreover, intravitreal drug injections also have important adverse effects such as infection, retinal detachment, lens damage, and bleeding (intraocular or subconjunctival) [7,8]. In preventing these conditions, the patient’s compliance as well as the experience and skill of the physician are extremely important. Although intravitreal drug injection is one of the most frequently performed intraocular procedures, there is no consensus on which anesthesia technique should be used during the procedure [9]. There are previous anesthesia studies in the literature for intravitreal injections performed with 27-30 gauge needles [10-14].

For an ideal intravitreal injection factors such as effectiveness, ease of use, rapidity, reliability and low cost are important for the physician; however, perhaps the most important criterion for the patient is that the procedure should be as painless as possible. Today, there are various local anesthesia methods used to this end. Although it has been reported in the literature that peribulbar and retrobulbar anesthesia provide effective anesthesia, they are not preferred for intravitreal injections, except for patients with painful endophthalmitis and non-compliant patients, due to the risks such as the pain caused by the procedure itself, globe perforation, retrobulbar bleeding, and permanent diplopia [7]. Subtenon anesthesia also may lead to complications such as chemosis, subconjunctival hemorrhage, ciliary nerve damage, scleral damage and very rarely orbital hemorrhage and globe perforation [15-17]. Thus, almost always topical drop anesthetics are used in this procedure. Completing the procedure quickly and as early as possible will reduce the patient’s anxiety, so repeated injections, if needed, may be done easily.

There are comparative studies in the literature regarding anesthesia methods used for intravitreal injection [7-11]. In some previous studies, no statistically significant difference was found between lidocaine gel and subconjunctival anesthesia in terms of pain experienced during injection [8,9]. Similarly, in another study, there was no statistically significant difference in the pain experienced during injection. Although pain was found to be relatively higher in topical anesthesia than in the subconjunctival group, this difference was not found to be statistically significant [7].

In his study, Cintra compared the pain scores during intravitreal injections with a 29 G needle while the patients were under topical, subconjunctival and peribulbar anesthesia. Pain scores wasn’t statistically significantly different between subconjunctival and topical anesthesia but pain scores during the injection accompanied by peribulbar anesthesia was found to be significantly lower [10].

<table>
<thead>
<tr>
<th>NRS</th>
<th>NRS</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Group 1</td>
<td>3.70±0.79</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>4.23±0.77</td>
<td>0.02</td>
</tr>
<tr>
<td>VRS</td>
<td>VRS</td>
<td>P value</td>
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<tr>
<td>Group 1</td>
<td>2.13±0.34</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>3.0±0.58</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Pain and anxiety that will occur during subtenon anesthesia may make the patient reluctant for repeat intravitreal injection.

While there is consensus upon what needs to be done to reduce the risk of infection in intravitreal drug injections, there is no such clear consensus on which anesthesia technique is most appropriate to reduce the pain and discomfort experienced during the injection [9]. In some studies in the literature, it has been argued that topical anesthesia can be preferred because it is fast, low cost and easy to use [10-13]. In our study, we used topical anesthesia in all our patients due to the above mentioned advantages. One-dimensional scales are intended to directly measure the severity of pain, and the assessment is made by the patient himself. In this way, the patient is able to evaluate the discomfort he experiences during the procedure. In our study, we used the numerical rating scale and verbal rating scale, which are unidimensional scales.

Recently, the PFS (pre-filled syringe) formulation has begun to be used more frequently in intravitreal ranibizumab injection procedures. With this ready-to-use formulation, time is not lost in drug preparation, and it is thought to protect against negative complications such as endophthalmitis. In our study, as a result of pain assessment by both NRS and VRS we found that the PFS is more comfortable for the patient than the conventional form.

In the literature, aflibercept and ranibizumab was compared by using VAS (Visual analoguescale) in a series of 72 patients and as a result aflibercept was found to be more painful [18]. 162 patients were compared by using VAS and no difference was found between aflibercept ranibizumab and dexamethasone implant in terms of pain. It has been stated that age, gender and lens condition may be related to pain [19].

The fact that all patients in our study were female eliminates gender factor, and comparing two eyes in the same patient eliminates age factor. This may allow a more objective pain assessment on the side of the patients. The relatively small number of patients and the lack of assessment of factors such as male, gender may be considered as the limitations of our study.

We assume that our study may contribute to the literature by assessing the relationship between the PFS formulation of intravitreal ranibizumab and pain by using both a numerical rating scale and a verbal rating scale.

Conclusion

In our study, we concluded that IVR in ready-to-use formulation caused less pain during injection in female patients who underwent bilateral IVR in the same session.

Ethical approval

Ethical approval was received for this study from Karabük University Non-Interventional Clinical Research Ethics Committee (Decision No: 2019/155).

References