Assessment of Pain Scores During Intravitreal Injections of Aflibercept Versus Ranibizumab

Hastaların İntravitreal Aflibercept ve Ranibizumab Enjeksiyonu Sırasındaki Ağrı Skorlarının Değerlendirilmesi

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ABSTRACT

Purpose: To evaluate pain scores of patients during intravitreal (IV) aflibercept versus ranibizumab injections.

Materials and Methods: In this interventional study, 88 eyes of 88 patients who received IV anti-vascular endothelial growth factor (anti-VEGF) therapy were included. Fourty three patients received IV 2.0 mg/0.05 ml aflibercept injection with 30-gauge needle and 45 patients received IV 0.05 mg/0.05 ml ranibizumab injection with 30-gauge needle. The diagnoses of the patients were: 40 age related macular degeneration, 39 diabetic macular edema, 4 central and 5 branch retinal vein oclusion. Immediately after the injection, patients were asked to grade their pain using the visual analog scale (VAS) of 0 (no pain) to 10 (unbearable/ worst pain). The main outcome measure was the pain score assessment. Additional parameters recorded included demographics (age, gender, education level) and clinical characteristics (indication for the injection, number of previous IV injections).

Results: The VAS pain scores in the aflibercept and ranibizumab groups were 1.67± 0.81 (range, 0-7) and 1.24 ± 1.15 (range, 0-6), respectively (p = 0.10). Multivariable regression analysis revealed that pain perception was significantly lower in patients of older age, male patients, with higher number of previous injections and higher educational status.

Conclusions: Pain associated with both aflibercept and ranibizumab IV injection is generally mild, and may be associated with epidemiologic factors and the number of previous IV injection.

Key words: Aflibercept, Intravitreal injection, Pain, Ranibizumab, Visual analogue scale.

ÖZ

Amaç: Hastaların intravitreal (IV) aflibercept ve ranibizumab enjeksiyonu sırasındaki ağrı skorlarını değerlendirmek.

Materyal ve Metod: Kesitsel çalışmamıza IV anti vasküler endotelyal büyüme faktörü (VEGF) yapılan 88 hastanın 88 gözü dahil edildi. Kırk üç hastaya 30-gauge iğne ile IV 2,0 mg/0,05 ml aflibercept enjeksiyonu ve 45 hastaya 30-gauge iğne ile IV 0,05 mg/0,05 ml ranibizumab enjeksiyonu yapıldı. Hastaların tanıları incelendiğinde; 40 yaşa bağlı makula dejenerasyonu, 39 diyabetik makula ödemi, 4 santral ven ve 5 ven dal tıkanıklığı mevcuttu. Enjeksiyondan hemen sonra, hastalara görsel analog skalasına (GAS) (0 ağrı yok-10 dayanılmaz şiddetli ağrı) göre algıladıkları ağrıları derecelendirmeleri istendi. Çalışmada ana değerlendirme ölçütü olarak ağrı skoru değerlendirilmesi yapıldı. Ayrıca hastaların demografik (yaş, cinsiyet, eğitim seviyesi) ve klinik karakteristikleri (enjeksiyon endikasyonu, önceki IV enjeksiyon sayısı) kaydedildi.

Bulgular: Hastaların GAS ağrı skorları aflibercept ve ranibizumab grublarında sırasıyla 1,67± 0,81 (0-7) ve 1,24 ± 1,15 (0-6) idi (p = 0.10). Çok değişkenli regresyon analizinde ağrı algısının daha yaşlı, erkek, daha önce çok sayıda enjeksiyon yapılan yüksek eğitim seviyesi olan hastalarda anlamlı olarak daha düşük olduğu gösterildi

Sonuç: Aflibercept ve ranibizumab IV enjeksiyonu ilişkili ağrı genellikle hafif düzeyde olmakta ve önceki IV enjeksiyon sayısı ve epidemiyolojik faktörlerle ilişkili olabilmektedir.

Anahtar kelimeler: Aflibercept, İntravitreal enjeksiyon, Ağrı, Ranibizumab, Görsel analog skalası.

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INTRODUCTION

Intravitreal (IV) injection has become widely used delivery route of various therapeutic agents to the posterior segment of the eye.[1] In the last decade, anti–vascular endothelial growth factor (anti-VEGF) agents began to be used for the treatment of neovascularization in age-related macular degeneration (AMD),[2] diabetic macular edema (DME),[3] macular edema secondary to central and branch vein occlusion.[4] Frequent and repeated IV injections are often required for the treatment of several retinal diseases.

The most common side effect caused by intravitreal injection is discomfort and pain during and after the injection.[5] Pain results in anxiety of patient and might even reduce compliance to the treatment.[5, 6] Additionally, Segal et al.[5] reported a relationship between preprocedural anxiety and pain in IV injections. In order to minimize pain and reduce anxiety, addressing the patient's injection-related concerns is important.[5]

Current anti-VEGF therapies delivered via IV injections include ranibizumab (Lucentis; Genetech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY), as well as off-label bevacizumab. Both ranibizumab and aflibercept delivered similar, good anatomical and visual outcomes for treatment of DME[7] and AMD.[8]

In the current literature, there is no study comparing the patient comfort after IV ranibizumab and aflibercept injection. In this study, we aimed to evaluate pain scores of patients during IV aflibercept versus ranibizumab injections.

METHODS

This interventional, non-randomized, comparative study was carried out at the Department of Ophthalmology, University Hospital of Erciyes University, from January to March 2016 after review and receiving approval from the Institutional Review Board of the University Hospital. Signed informed consent was obtained from all the participants.

All patients of the medical retina department of our clinic, who were scheduled to receive IV injections of ranibizumab or aflibercept in one eye and had already undergone at least one IV injection of anti-VEGF agent, were evaluated for inclusion into the study.

Exclusion criteria were a history of previous eye surgery other than cataract extraction surgery, herpetic eye disease, uncontrolled glaucoma, ocular pain prior to the procedure and any contraindication for IV injection such as active ocular infection or inflammation, patients using systemic analgesics or sedative medications. Patients with poor cooperation in understanding and answering the questions of the visual analog scale (VAS) and diabetic patients with known peripheral neuropathy were also excluded.

Intravitreal injection procedure

The IV injection was performed under sterile conditions as recommended in the previously reported guidelines.[1] The injections were administered by the same surgeon (S.S.) in each patient. One drop of Proparacaine HCl 0.5% eye drop (Alcaine; Alcon Laboratories, Inc.) was installed every 5 minutes for three times before injection. The periocular skin, eyelid margins and eye lashes were cleaned with 10% povidone iodine, and 5% povidone iodine was instilled in the conjunctival cul-de-sacs 3 min before the injection. A sterile lid speculum was inserted, and 2.0 mg/0.05 ml aflibercept IV injection with 30-gauge needle and 0.05 mg/0.05 ml ranibizumab IV injection with 30-gauge needle performed at the superotemporal quadrant. The entry site of the needle was 3.5 mm from the limbus in aphakic/pseudophakic patients and 4.0 mm in phakic patients. The conjunctiva was displaced anteriorly using a cotton-tipped applicator, and the needle was inserted perpendicularly through the sclera. After removing the needle, a sterile cotton-tipped applicator was used to prevent reflux. The patients were instructed to self-administer antimicrobial/anti-inflammatory drops during the following 7 days.

Immediately after the IV injection, patients were asked to grade their pain using the visual analog scale (VAS) 0 (no pain) to 10 (unbearable/worst pain),the health professionals should explain prior to the test.

STATISTICAL ANALYSES

All statistical analyses were carried out using the SPSS 21.0 software (SPSS, Inc, Chicago, IL). The data were tested for normal distribution using the Kolmogorov–Smirnov test. The Wilcoxon nonparametric test was used for pair-wise comparisons of nonparametric values. Multivariable regression analysis was applied to evaluate any association of pain perception with independent variables such as age, sex, indication for treatment, number of previous injection and educational level. For all statistical analyses performed, P values of <0.05 were considered significant.

RESULTS

A total of 88 eyes of 88 patients were included in the study. Table 1 summarized the baseline characteristics of two study groups. The mean age was 64.32 ± 11.67 (range, 42 to 89) in the aflibercept group and 62.86 ± 13.39 (range, 41 to 83) in the ranibizumab group. There was no statistically significant difference between the groups with respect to age, gender, treated eye, the number of previous IV injections and educational level. Indications for the treatment with IV anti-VEGF agent included exudative age-related macular degeneration, diabetic macular edema, macular edema secondary to central and branch retinal vein occlusion.

Table 1. *Demographic and Clinical Characteristics of the Patients in the Study*

	Aflibercept group (n:43)	Ranibizumab group (n:45)	P value*
Age, mean±SD, years	64.32 ± 11.67	62.86 ± 13.39	0.10
Gender Male/Female	20/23	21/24	0.42
Eye Right/Left	21/22	23/22	0.72
VAS pain score (mean±SD, range)	1.67± 0.81 (0-7)	1.24 ± 1.15 (0-6)	0.10
Number of previous injection (n, mean±SD, range)	9.83±10.15 (1-36)	8.81± 6.39(1-32)	0.12
Indication For treatment (%) AMD DME CRVO BRVO	 19 (44.1) 20 (46.5) 2 (4.6) 2 (4.6)	 21 (46.6) 19 (42.2) 2 (4.4) 3 (6.6)	0.54
Education Level (%) Low High	 28(65.1) 15(34.9)	 31 (68.9) 14 (31.1)	0.21

AMD, age-related macular degeneration; DME, diabetic macular edema; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.
*Wilcoxon test, P value <0.05 was considered statistically significant

The VAS pain scores in the aflibercept and ranibizumab groups were 1.67± 0.81 (range, 0-7) and 1.24 ± 1.15 (range, 0-6), respectively (figure 1) (p = 0.10).

Multivariable regression analysis revealed a statistically significant correlation between VAS pain score and age, sex, number of previous IV injections and education level (P = 0.03, 0.02, 0.04 and 0.03, respectively). Accurately, VAS pain scores were lower in patients of older age, male sex, with higher number of previous injections and higher education level (Table 2). Regression analysis did not reveal any statistically significant correlation of VAS pain score and the following parameters: study eye and underlying disease. (P= 0.18 and 0.58, respectively).

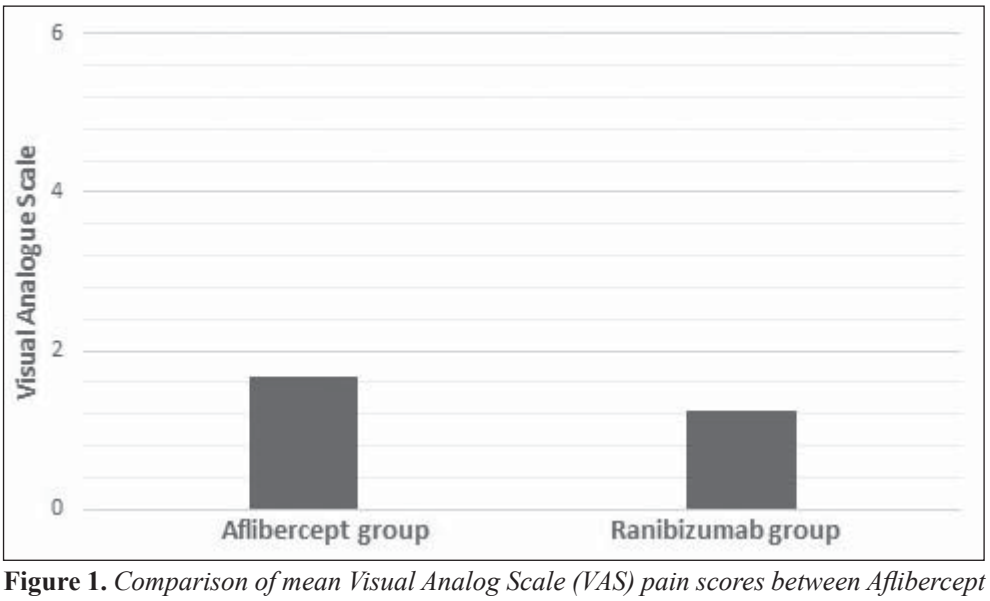

Figure 1. *Comparison of mean Visual Analog Scale (VAS) pain scores between Aflibercept and Ranibizumab group during intravitreal injection. The difference was not statistically significant (P=0.10).*

Table 2. *Visual Analog Scale Pain Score (Mean ± SD) in Groups Defined by Patients' Demographics*

Parameters	Aflibercept group (n:43)	Ranibizumab group (n:45)	P value*
Age			
>65years (n=38)	1.28±0.96	0.88±1.16	0.03
≤65 years(n=50)	2.18±1.02	1.71±1.34	0.03
Eye			
Right (n=44)	1.70±1.45	1.29±1.24	0.18
Left (n=44)	1.64±1.38	1.19±1.12	0.21
Gender			
Male (n=41)	1.01±0.98	0.82±1.06	0.02
Female (n=47)	1.24±1.32	1.60±1.24	0.02
Number of previous injection			
>8 (n=40)			
≤8 (n=48)	1.12±0.96	0.76±0.84	0.04
	2.12±1.62	1.64±1.32	0.04
Education level			
Low (n=59)	2.06±0.82	1.53±1.54	0.03
High (n=29)	0.87±1.01	0.65±0.84	0.03

*Wilcoxon test, P value<0.05 was considered statistically significant

DISCUSSION

Pain associated with intravitreal injections reported in previous studies is generally mild.[9-12] Pain sensitivity is thought to be mediated by sociocultural, psychological and biological factors.[13]

Ranibizumab and aflibercept are current anti-VEGF therapies and they delivered similar, good anatomical and visual outcomes for treatment of DME and AMD. In this study we found that the pain associated with 2.0 mg/0.05ml aflibercept IV injection with 30-gauge needle and 0.05 mg/0.05 ml ranibizumab IV injection with 30-gauge needle is generally mild and comparable.

A 27-gauge needle has a diameter of 413 mm, a 30- gauge needle has a 311-mm diameter. A recent study showed that use of a 30-gauge versus a 27-gauge needle may decrease drug reflux, thus making treatment more likely to be effective.[14] However, the needle gauge did not yield a statistically significant difference in pain score.[14] Similarly, Haas et al.[13] reported the use of a 30-gauge needle for IV injections showed no significant effect in pain relief compared to the use of a 27-gauge needle. However, a 30-gauge needle was preferred by all surgeons.[13] Moisseiev et al.[11] evaluated the pain associated with IV dexamethasone implant versus bevacizumab injections. Despite a larger needle gauge and tunneled injection technique, IV injection of dexamethasone implant is not associated with increased pain compared with bevacizumab. Guler et al. compared pain scores of patients with IVT 27-gauge bevacizumab and 30-gauge ranibizumab injection.[15] They found lower VAS pain scores with 30-gauge ranibizumab IV injection.

Rifkin et al.[12] injected ranibizumab, and bevacizumab using a 50-µL volume and the combination of bevacizumab and triamcinolone acetonide using a 100-µL volume in their study. They concluded that patient pain scores did not reflect the difference in volume and substance injected.

Several studies[16, 17] have reported that women have lower pain thresholds, show increased sensitivity to induced pain, and experience greater clinical pain than men. Hormonal and genetic variation and psychosocial factors and cognitive differences between the sexes have been attributed to this difference.[17] Imaging studies of the brain have shown differences between men and women in the spatial pattern and intensity of response to acute pain. Females are more sensitive than males to noxious stimuli and have lower levels of stress-induced analgesia.[18] Our study also indicated that women reported higher average pain scores with IV injection that their male fellows.

Age has previously been shown to be correlated with pain relief, older patients have reported lower pain scores with analgesia.[19] Age-related decrease in tactile sensitivity con-

tributed to this finding.[20] We found that VAS pain scores were lower in patients older than 65 years.

Rifkin et al.[12] reported that the average pain score decreased substantially with each consecutive IV treatment. They speculated that desensitization may play a role in this finding and patients simply knew what to expect and were able to prepare themselves mentally for the procedure.[12] Similarly, VAS pain scores were lower in our patients with higher number of previous injections both aflibercept and ranibizumab groups.

The indication for treatment did not change the perception of pain in the present study. It was hypothesized that patients undergoing IV injection for DME would experience less pain, as neuropathy is a common finding in diabetic patients.[21] However, diabetic patients with known peripheral neuropathy were excluded in our study.

Most of our patients had low education level and VAS pain scores were higher in this patient subgroup. We thought that personality, emotional state, sociocultural state and consciousness to the disease and the therapy contributed to this difference.

CONCLUSION

Our study had several limitations, particularly due to the quantification of pain and lack of double blinded assessmnet of VAS. Additional studies with a large sample size, consideration of co-medications and intra-ocular pressure variations would be helpful.

We conclude that the pain associated with both aflibercept and ranibizumab IV injection is generally mild, and may be associated with demographic factors (gender, age, education level) and the number of previous IV injection.

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