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ORIGINAL RESEARCH

Potential Risk Factors for Ocular Pain in Patients Undergoing Multiple Intravitreal Injections of Anti-Vascular Endothelial Growth Factor

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Purpose: To assess ocular pain in patients undergoing multiple intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) who have previous factors that may influence pain sensitivity.

Methodology: This is a prospective, observational, case series study involving patients who underwent multiple (≥3) pro re nata intravitreal injections of ranibizumab or aflibercept to treat any cause of chorioretinal vascular disease. Ocular pain was assessed by the numerical analog scale during intravitreal injection. For this study, the main variable was ocular pain and the secondary variables included age, sex, previous history of glaucoma, primary retinal vascular disease, severe dry eye history, trigeminal pain, scleral buckle surgery, collagen diseases, fibromyalgia, severe migraine history, pars plana vitrectomy, scleral thickness measurements, and type of anti-VEGF.

Results: In a total of 894 patients, 948 eyes (4822 intravitreal injections), 793 patients (88.6%) had ocular pain sensitivity between no pain to mild pain, 80 patients (8.9%) had moderate ocular pain, 15 patients (1.6%) had severe ocular pain, and 6 patients (0.7%) had extremely severe ocular pain. Patients with severe dry eye ($p = 0.01$) and previous history of scleral buckle surgery ($p = 0.01$) showed a significant correlation with ocular pain during intravitreal injection. Pars plana scleral thickness (>550 um) and diabetic neuropathy were associated with ocular pain but did not meet the criteria for statistical significance ($p = 0.09$ and $p = 0.06$, respectively).

Conclusion: Dry eye and prior scleral buckle surgery may contribute to pain associated with intravitreal injection. These issues should be taken into consideration in patients undergoing multiple intravitreal injections.

Keywords: Ocular pain, multiple intravitreal injections, anti-VEGF, special risk factors

Introduction

Anti-vascular endothelial growth factor (anti-VEGF) delivered by intravitreal injection (IVI) is standard for treating chorioretinal vascular diseases such as diabetic macular edema, neovascular age-related macular degeneration, and macular edema associated with retinal vein occlusion, among others.[1–8] Currently, this therapy has a favorable safety profile, with patient pain tending to be mild regardless of topical anesthesia.[9–11] However, multiple treatments are often required because of the short half-life of these drugs and the high rate of disease recurrence.[9,12]

The objective of the current study was to assess ocular pain in patients receiving multiple IVIs of anti-VEGF who have previous factors that may influence the degree of pain.

Methodology

This was a prospective, observational, case series study of patients receiving multiple IVIs between October 1st, 2023, and January 31st, 2024, at the Navy Hospital in Rio de Janeiro, Brazil.

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The current study was approved by the Research and Ethics Committee under No. 71622623.4.0000.5256 and adhered to the guidelines and norms of the Declaration of Helsinki for Research with Human Beings (National Health Council Resolution 196/1996). All participants provided written informed consent before entering the study. Inclusion and exclusion criteria were applied.

The inclusion criteria included patients who received at least 3 IVIs of ranibizumab or aflibercept, before entering in this study, in a pro re nata regimen to treat various causes of chorioretinal vascular diseases. Exclusion criteria included patients who received less than 3 IVIs of anti-VEGF, patients who did not agree to participate, age less than 18 years, inability to comprehend the pain scale, eyes operated on less than 6 months, and the presence of active ocular infection, among others.

Twenty-five patients were excluded from this study, 20 for having received <3 anti-VEGF injections, 2 did not agree to participate, and 3 were unable to understand the pain scale.

The collected data included age and sex, ocular history (glaucoma, dry eye, scleritis, episcleritis, anterior uveitis, scleral hyaline plaque, collagen disease, fibromyalgia, trigeminal pain, migraine, diabetic neuropathy, systemic pain, and herpes zoster), ocular surgical history, and diagnostic indication for treatment were collected.

Severe dry eye was defined as prior history of canalicular lacrimal plug therapy.

All patients were submitted to a complete ophthalmologic examination that included best-corrected visual acuity (BCVA) with the Snellen chart, slit-lamp biomicroscopy (Takagi Inc., Nakano Gen, Japan), intraocular pressure (IOP) with Goldmann tonometer, indirect ophthalmoscopy (Welch Allyn Inc., Skaneateles Falls, NY, USA), and scleral thickness at the injection site (3.5 mm from the limbus in pseudophakic eyes and 4 mm from the limbus in phakic eyes) measured with spectral domain optical coherence tomography – DRI-OCT Triton Swept Source (Topcon, Tokyo, Japan).

Ocular Pain

Ocular pain was defined as an adverse event that occurred during pars plana injection of anti-VEGF and lasted at least 30 seconds. Ocular pain was measured only during the last IVI. All patients were asked to grade the IVI 1 minute after the procedure, using an analogic ocular pain scale (AOPS) of 0 to 10 levels, which was classified for this study in four levels as follow:

Level 0, 1 and 2 - Absent to mild ocular pain

Level 3, 4, and 5 - Moderate ocular

Level 6, 7, and 8 - Severe ocular pain

Level 9 and 10 - Extremely severe ocular pain

For this study, the number of injections was defined as the number of previous injections in the eye plus the number of injections done during the study.

Ocular AnesthesiaTechnique and Injection Procedure

The eyelid was washed with 4% povidone-iodine, and a sterile plastic drape was placed over the eyelashes. All patients were anesthetized with tetracaine drops on the ocular surface 3 times, 1 minute before the procedure. Next, 4% povidone-iodine was applied to the ocular surface and a sterile speculum was placed. Lidocaine gel was applied with a cotton swab to the IVI site (3.5 mm from the limbus for pseudophakic patients and 4 mm from the limbus for phakic patients), 30 seconds before. This was the routine anesthetic technique used in all patients. The injections were performed on the superotemporal quadrant of each eye using a 30-gauge needle.

Investigated Variables

The main variable was the ocular pain level, which was classified into four levels.

The secondary variables were the demographic data, ocular data, and systemic comorbidities data as below:

The demographic data were sex, age (mean and standard deviation), and age groups (up to 40 years old, and over 40 years old);

The ocular data were lens status (phakic or pseudophakic); scleral thickness at the injection site (up to 550 µm or more than 550 µm); laterality (unilateral or bilateral); type of anti-VEGF used (ranibizumab or aflibercept); primary diagnosis (diabetic macular edema, retinal vein occlusion, exudative age-related macular degeneration, myopic neovascular membrane, among others), prior scleral buckling surgery, presence of scleral hyaline plaque; history of severe dry eye, glaucoma, scleritis, episcleritis, and anterior uveitis; and history of ocular herpes zoster.

The data on systemic comorbidities were collagen diseases, fibromyalgia, trigeminal pain, severe migraine, diabetic neuropathy, and history of systemic pain.

Statistical Analysis

The main variable was correlated with the secondary variables to assess the risk factors for pain. Fisher's test or chi-square test was used to analyze nominal variables such as sex, lens status, retinal vascular disease, prior scleral buckle surgery, presence of hyaline plaque, severe dry eye, history of glaucoma, scleritis, episcleritis, and anterior uveitis, and associated comorbidities as well. Kruskal–Wallis test was employed to evaluate categorical variables with ordinal subcategories such as age group and pars plana scleral thickness measurement. The numerical variables age was exhibited by mean and standard deviation (SD) and analyzed with the Student's *t*-test. McNemar's chi-square test evaluated paired nominal variables such as laterality.

The software SPSS version 23.0 (2015, IBM Corporation, Chicago, USA) was used for statistical analyses. The level of significance was set at 5% ($p < 0.05$).

Results

A total of 894 patients (948 eyes) were included in the current study, of whom 88.6% of patients reported absence to mild ocular pain, while a 2.3% of patients reported severe to extremely severe ocular pain during IVIs. The total number of injections was 4822 injections, 2168 injections performed before entering the study and 2654 injections performed during the study. The demographic and clinical data are shown in Table 1.

Table 1 Demographic and Clinical Data of Study Participants

Collected Data n = 948 Eyes / 894 Patients		Sub-Items	Sample Number (%)
Patients demographic characteristics	Sex	Male	415 (46.2)
		Female	479 (53.8)
	Age - years old	Mean ± SD	62.4 ± 22.8
	Age group	Up to 40	262 (29.2)
		Over 40	632 (70.8)
Anatomical features of the eye	Lens status	Phakic	299 (31.5)
		Pseudophakic	649 (68.5%)
	Pars plana scleral thickness measurements	Up to 550 µm	695 (73.3%)
		More than 550 µm	253 (26.7%)
	Laterality	Bilateral	222 (23.3)
		Unilateral	726 (76.7)
Eye intervention Characteristics	Anti-VEGF type	Ranibizumab	491 (51.8)
		Aflibercept	457 (48.2)

(*Continued*)

Table 1 (Continued).

Collected Data n = 948 Eyes / 894 Patients		Sub-Items	Sample Number (%)
Primary Eye Disease	Chorioretinal Diseases	AMD	318 (33.5)
		DME	461 (48.6)
		RVO	132 (13.9)
		High myopia	37 (3.9)
Operated Eyes	Scleral buckle surgery	Present	42 (4.4)
		No	906 (95.6)
Eye Disorders	History of glaucoma	Present	367 (38.7)
		No	581 (61.3)
	History of severe dry eye	Present	45 (4.7)
		No	903 (95.3)
	Scleral hyaline plaque	Present	255 (26.8)
		No	693 (73.2)
	History of scleritis, episcleritis, and anterior uveitis	Present	18 (1.8)
		No	930 (98.2)
Patients Systemic Disorders	Trigeminal pain	Present	72 (8.1)
		No	822 (91.9)
	History of severe migraine	Present	52 (5.9)
		No	842 (94.1)
	Collagen disease	Present	141 (15.6)
		No	753 (84.4)
	Diabetic neuropathy	Present	356 (39.8)
		No	538 (60.2)
	Fibromyalgia	Present	22 (2.5)
		No	872 (97.5)
	History of other systemic pain disorders	Present	27 (3.1)
		No	867 (96.9)

Abbreviations: n, number of patients and percentage of patients (%); AMD, age-related macular degeneration; DME, diabetic macular edema; RVO, retinal vein occlusion.

The main outcomes from the correlation between ocular pain and the demographic and eye data, and intervention characteristics are displayed. (Table 2 and Table 3). Age, age group, sex, lens status, hyaline plaque, eye laterality and type of anti-VEGF did not show significant correlation with eye pain in patients undergoing IVIs. There were no cases of ocular herpes zoster among patients.

The primary eye disease and past history of ocular illness such as glaucoma, scleritis, episcleritis, and anterior uveitis did not influence ocular pain during IVIs (Table 4). Regarding non-ocular pathologies associated with pain, such as

Table 2 The Correlation of the Demographic Data with the Level of Ocular Pain

Population Studied 894 Patients			Analog Ocular Pain Scale (AOPS)				
			Absent to Mild n= 793 (88.6)	Moderate n = 80 (8.9)	Severe n = 15 (1.6)	Extremely Severe n = 6 (0.7)	P
Demographic Data	Sex	Male	373 (47.1)	34 (42.4)	6 (39.1)	2 (28.5)	0.73#
		Female	420 (52.9)	46 (57.6)	9 (60.9)	4 (71.5)	
	Age	Mean ± SD	59.7 ± 18.9	63.7 ± 11.7	61 ± 15.6	67.1 ± 2.5	0.16*
	Age group	Up to 40 years	221 (27.9)	31 (38.8)	7 (46.7)	3 (50.0)	0.53‡
		Over 40 years	572 (72.1)	49 (61.2)	8 (53,3)	3 (50.0)	

Notes: #Chi-square test, ‡Kruskal–Wallis test, *Student *t*-test, p-value statistical significance, (%) – sample percentage. Items analyzed as significant data through statistical tests ($p < 0.05$).

Table 3 The Correlation of Eye Data and Intervention Characteristics with the Level of Ocular Pain

Population Studied 948 Eyes			Analog Ocular Pain Scale (AOPS)				
			Absent to Mild n= 840 (88.6)	Moderate n = 85 (8.9)	Severe n = 16 (1.6)	Extremely Severe n = 7 (0.7)	P
Anatomical features of the eye	Lens status	Phakic	251 (35.8)	34 (43.7)	7 (39.1)	3 (42.9)	0.15#
		Pseudophakic	589 (64.2)	51 (56.3)	9 (60.9)	4 (57.1)	
	Pars plana scleral thickness measurements	Up to 550 µm	622 (74.1)	61 (71.7)	9 (81.2)	3 (42.9)	0.09‡
		More than 550µm	218 (25.9)	24 (21.3)	7(18.8)	4 (57.1)	
	Laterality	Unilateral	636 (75.7)	71 (83.6)	13 (81.2)	6 (85.7)	0.16#§
		Bilateral	204 (24.2)	14 (16.4)	3 (18.8)	1 (14.3)	
Intervention characteristics	Anti-VEGF type	Ranibizumab	432 (51.4)	47 (55.2)	9 (56.2)	3 (42.9.)	0.84#
		Aflibercept	408 (49.6)	38 (44.8)	7 (43.8)	4 (57.1)	
Operated eyes	Scleral buckle surgery	Present	31 (3.6)	6 (7.1)	3 (18.8)	2 (28.5)	**0.01#**
		No	809 (96.4)	79 (92.9)	13 (86.2)	5 (71.5)	
Primary eye diseases	Chorioretinal diseases	AMD	282 (37.1)	30 (38.8)	4 (25.0)	2 (28.5)	0.98#"
		DME	409 (48.4)	39 (48,2)	9 (60.9)	4 (57.1)	
		RVO	118 (14.4)	11 (12.9)	2 (12.5)	1 (14.4)	
		High Myopia	31 (3.6)	5 (5.8)	1 (6.25)	0	

Notes: #"Exact Fisher Test, #Chi-square test, #§McNemar Chi-square paired test, ‡Kruskal–Wallis test, p-value statistical significance, (%) – sample percentage. Items in bold analyzed as significant data through statistical tests ($p < 0.05$).

a history of trigeminal pain, severe migraine, collagen diseases, fibromyalgia, and other pathologies followed by complaints of pain elsewhere, no correlation with ocular pain during IVIs was observed (Table 5).

Pain score with respect to previous scleral buckle surgery ($p = 0.01$) and history of severe dry eye ($p = 0.01$) yielded statistically significant results, while scleral thickness ($p = 0.09$) and diabetic neuropathy ($p = 0.06$) demonstrated a certain degree of correlation but without statistical significance ($p > 0.05$) (Tables 3–5).

Of the 45 patients with severe dry eye, 4 had severe ocular pain and 3 had extremely severe ocular pain measured by AOPS.

Concerning patients who underwent previous scleral buckle surgeries, 30 out of 42 had round silicone encircling band plus silicone tire, while 12 out of 42 patients had round silicone encircling band only.

Table 4 The Correlation of Ocular History Disorders and Findings with Level of Ocular Pain

Population Studied 948 Eyes			Analog Ocular Pain Scale (AOPS)				
			Absent to Mild n= 840 (88.6)	Moderate n = 85 (8.9)	Severe n = 16 (1.6)	Extremely Severe n=7 (0.7)	P
Eye history disorders and findings	History of glaucoma	Present	318 (37.8)	36 (41.1)	9 (60.9)	4 (57.1)	0.29#
		No	522 (62.2)	49 (58.9)	7 (39.1)	3 (42.9)	
	History of severe dry eye	Present	32 (3.9)	6 (7.1)	4 (25.0)	3 (42.9)	**0.01#**
		No	808 (96.1)	79 (92.9)	12 (75,0)	4 (57.1)	
	Scleral hyaline plaque	Present	235 (27.9)	16 (18.8)	4 (25.0)	0	0.35#"
		No	605 (72.1)	69 (81.2)	12 (75,0)	7 (100)	
	History of scleritis, episcleritis, anterior uveitis	Present	14 (1.7)	3 (3.6)	1 (6.3)	0	0.34#"
		No	826 (98.3)	82 (96.4)	15 (93.7)	7 (100)	

Notes: #"Exact Fisher Test, #Chi-square test, p-value statistical significance, (%) sample percentage. Items analyzed as significant data through statistical tests ($p < 0.05$).

Table 5 The Correlation of the Systemic Comorbidities with the Level of Ocular Pain

Population Studied 894 Patients			Analog Ocular Pain Scale (AOPS)				
			Absent to Mild n= 793 (88.6)	Moderate n = 80 (8.9)	Severe n = 15 (1.6)	Extremely Severe n=6 (0.7)	P
Systemic comorbidities	Trigeminal pain	Present	66 (8.3)	05 (5.9)	1 (12.5)	0	0.99#"
		No	727 (91.7)	75 (94.1)	14 (87.5)	6 (100)	
	History of severe migraine	Present	42 (5.3)	9 (11.3)	1 (12.5)	0	0.98#"
		No	751 (94.7)	71 (88.7)	14 (87.5)	6 (100)	
	Collagen disease	Present	123 (15.6)	13 (16.2)	4 (26.7)	1 (16.7)	0.70#
		No	670 (84.4)	67 (83.8)	11 (73,3)	5 (83.3)	
	Diabetic neuropathy	Present	305 (38.4)	38 (47.5)	10 (66.7)	3 (50.0)	0.06#
		No	488 (61.6)	42 (52.5)	5 (33.3)	3 (50.0)	
	Fibromyalgia	Present	18 (2.2)	2 (2.5)	1 (6.7)	1 (16.6)	0.10#
		No	775 (97.8)	78 (97.5)	14 (93.3)	5 (83.4)	
	History of other systemic pain complaint	Present	21 (2.6)	4 (5.0)	1 (6.6)	1 (16.7)	0.11#
		No	772 (97.4)	76 (95.0)	14 (93.4)	5 (83.3)	

Notes: #"Exact Fisher Test, #Chi-square test, p-value statistical significance, (%) – sample percentage. Items analyzed as significant data through statistical tests ($p < 0.05$).

Discussion

In 2004, in light of the increasing number of IVIs in retinal pharmacotherapies, a group of experienced investigators established a consensus of recommendations to optimize this procedure.[13,14] Currently, IVIs have become the standard treatment for a variety of chorioretinal vascular diseases.[15–17] To the best of our knowledge, this is the first study so far to evaluate ocular pain in patients subjected to IVIs who have previous factors that may influence the sensation of pain, as studies generally list these factors as exclusion criteria.

In 2012, Rifkin et al prospectively analyzed factors that could be related to ocular pain during in-office IVI in patients who received at least 5 consecutive monthly injections. In their study, improvement in vision from previous injections, female sex, and age >65 years resulted in a significant correlation with ocular pain score, while ocular pain decreased with each consecutive injection. Furthermore, they observed that ocular pain may last for at least 3 to 7 days after the procedure. In relation to their results, they assumed that female sex might have optimism with favorable outcomes, ageing process decreased the tactile sensitivity, and patients became emotionally prepared for the next injections. Of note, patients with diabetic peripheral neuropathy and any other prior ocular surgery other than uncomplicated cataract surgery were excluded from their study.[18] Yu et al reported that diabetic peripheral neuropathy might be associated with reduced and sparse distribution of corneal nerves, which implied reduced sensitivity.[19] Despite the lack of statistical significance in our study, patients with diabetic neuropathy achieved greater pain scores, which can be explained by the intense stress that these patients are constantly submitted to when dealing with a chronic disease. Rifkin et al found no changes in pain perception related to the diagnosis for which patients were being treated.[18] Recently, Chandrasekaran and coauthors conducted a study to assess ocular pain at the time of IVIs in patients undergoing cooling anesthesia. They excluded from their study patients with severe dry eye and past history of uveitis and vitrectomy.[20] Although, in the real world, chorioretinal vascular diseases can occur in patients with other ocular or systemic comorbidities.

In a study by Moisseiv et al, they compared the pain between IVI of Ozurdex versus IVI of bevacizumab. Sex, age, number of injections, injection indications, and type of intravitreal medication did not show significant correlation with the pain score.[21] Likewise, our results are similar to those of Moisseiv et al regarding these pain risk factors in patients receiving anti-VEGF injections. In their study, pseudophakia demonstrated greater eye pain during Ozurdex injections.[21] By contrast, lens status was not a significant risk factor for eye pain in patients undergoing bevacizumab injections.[22] We observed the same results in relation to this risk factor. It's important to observe that Ozurdex needle is 2.25 times wider than bevacizumab needle, which could influence the higher pain score.

Segal et al detected eye pain level ≥6 in 10% of their patients, while we detected the same level in 2.3% of our patients, despite their exclusion of patients with conditions that could affect pain sensation.[23] Moreover, Nguyen et al reported 5% of patients with eye pain level ≥6. They thought that the level of preoperative anxiety and pain during prior IVIs played a role in this finding.[24] In the current study, we only included patients who had already received ≥ 3 IVIs before entering the study to reduce the impact of anxiety during the first injections.

Pain at the IVI site is very common, mainly in patients undergoing multiple injections.[3] Shiroma et al conducted a systematic review to evaluate the effectiveness of various local anesthetic techniques for IVI.[10] Shiroma et al and Kozak et al observed a mild eye pain regardless of the topical anesthesia technique that was used, whereas Blaha et al detected mild to moderate eye pain.[10,25–27] Generally, pain during intravitreal injections is mild.[28–32] LaHood et al found a statistical difference between patients with eye pain who received the first injection and those who received it more than once.[33] Nevertheless, there are some controversies regarding the correlation between the number of injections and pain level. In our study, we identified eye pain during IVIs in patients that received prior multiple injections, although we only measured it once. In the same way, in many studies, eye pain has been collected in a single intravitreal injection.[9] Besides, Massamba et al did not identify association between previous injections and the degree of pain.[34]

We investigated eye pain in patients undergoing IVIs, especially those who had prior characteristics that could interfere with the sensation of pain. Severe and extremely severe eye pain were significantly associated with past history of scleral buckling surgery and severe dry eye. Thus, in a prospective study by Nadyr et al, eye pain was evaluated in patients submitted to scleral buckling surgeries. After surgery, eye pain resolved in 72% of patients within 30 days, whereas in 18% of patients, it coursed chronically for at least 6 months. Patients who exhibited the highest pain score at the beginning of the postoperative period were the same ones who developed chronic pain. Additionally, the authors thought that the chronic eye pain was caused by compression of the ciliary nerve endings against the sclera, particularly in cases where larger scleral implants were used.[35] Likewise, we suppose that nociceptive stimulation may predispose to severe eye pain in patients with previous scleral buckling surgery during IVI. In patients with severe dry eye, a subclinical inflammation may be activated when IVI is applied, although self-limited.

The lack of baseline measurement of ocular pain is a limitation for this study, as it could provide information on whether patients already had a certain degree of chronic pain. However, patients did not complain of eye pain during ophthalmological examinations at the beginning of this study.

In conclusion, prior history of scleral buckle surgery and severe dry eye may impact pain sensitivity during intravitreal injections of anti-VEGFs.

Disclosure

The authors report no conflicts of interest in this work.

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