

Subjective and objective measures of the patient experience before, during, and after intravitreal anti-vascular endothelial growth factor injections

Suresh Mekala, Pankaja Dhoble, Vishwaraj CR, Ashish M Khodifad, Olivia M Hess, Lavanya GS

Purpose: To assess patient experience of intravitreal injections using vital-signs, visual-experience, pain-rating and emotional response during intravitreal anti-VEGF injections. **Methods:** A prospective observational study of patient experience of intravitreal anti-VEGF injections done following metrics were collected pre-injection, during injection, and post-injection: pain assessment using visual analog score, fear-response rating, visual-experience questionnaire, and vital-signs. **Results:** A total of one-hundred-and-seventy-four patients undergoing intravitreal anti-VEGF injections for retinal pathologies were included in the study. Mean age was 58.8 ± 10.4 years in <5 injection group ($n = 133$) and 59.02 ± 9.0 years in ≥ 5 injection group ($n = 41$) ($P = 0.90$). During injection, 90.2% of patients in <5 injection group reported moderate or severe pain compared to 78% of patients in ≥ 5 injection group. In pre and post-injection phases, mild-to-moderate pain was reported in both groups ($P = <0.001$). Ninety-two (52.9%) patients reported having a mild frightening experience. There was no statistical significance in patients assessment of fear with respect to age, sex, or number of injections. The Systolic Blood Pressure (SBP) during and following injection ($SBP 171.7 \pm 21.1, 150.8 \pm 16.2$) procedures was significantly higher in cases with <5 injections when comparing to cases with >5 injections ($SBP 159.7 \pm 26.4, 143.2 \pm 17.0$) ($P = 0.003$), ($P = 0.011$). DBP, heart rate, pulse rate measurements were similar among patients in all phases of the study. **Conclusion:** We report a large sample size with comprehensive assessments of the patient experience. Higher pain ratings in the <5 injection group, the increase in the SBP in the pre-and during injection phases, and the overall rating of mild-to-moderate fear during the procedure.

Key words: Anti-VEGF, pain scale, visual experience, vital signs

Intravitreal injections are an indispensable tool for retina specialists in the treatment of chronic conditions such as age-related macular degeneration (ARMD), diabetic macular edema (DME), and retinal vein occlusions (RVO), often requiring frequent visits.^[1-3] Currently, intravitreal delivery is considered the most validated treatment option for various retinal and choroidal disorders by its ability to optimize the ocular therapeutic effects and reduce the incidence of severe systemic adverse events.^[4] Despite the demonstrated safety and efficacy of intravitreal injections, some patients may experience significant discomfort and anxiety while undergoing the procedure.^[5]

Despite the increasing popularity of intravitreal injections, there are no studies that simultaneously evaluate patients' discomfort, visual experiences, and vital signs throughout the procedure. Moreover, the patient experience has not been assessed in the context of prior injection history. The purpose of our study was to assess the patient experience of intravitreal injections throughout each stage of the procedure using both objective and subjective measures. The visual analog scale (VAS) is a common tool used in subjective assessment of pain.^[6-9] It has been successfully used in ophthalmic studies to evaluate pain associated with surgery, topical therapies, and intravitreal injections, thus is well-suited to assessment of pain

Aravind Eye Hospital and Research Institute, Pondicherry, India

Correspondence to: Dr Pankaja Dhoble, Senior Consultant, Department of Retina, Aravind Eye Hospital, Pondicherry, India. E-mail: pankajadhoble@yahoo.co.in

Received: 02-May-2020

Revision: 31-Aug-2020

Accepted: 30-Sep-2020

Published: 16-Mar-2021

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_1269_20

Quick Response Code:



in the setting of intravitreal injections. We hypothesized that mild discomfort would be experienced in the pre-injection phase and severe discomfort would be experienced in the injection phase. Our secondary analysis included the subjective and objective grading of visual experiences during the stages of intravitreal anti-VEGF injections.

Methods

The study protocol was approved by the institutional ethical committee of the Aravind Eye Hospital and written informed consent was obtained from all study participants. The study complied with the tenets of the Declaration of Helsinki. The trial was registered at the clinical trial registry of India (REF/2018/11/022322).

Participants

Patients aged 18 to 80 years with visual acuity better than 6/60 undergoing intravitreal anti-VEGF injections for retinal and choroidal pathologies were recruited from December 2018 to May 2019 at a tertiary eye care center in South-India. The

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Cite this article as: Mekala S, Dhoble P, Vishwaraj CR, Khodifad AM, Hess OM, Lavanya GS. Subjective and objective measures of the patient experience before, during, and after intravitreal anti-vascular endothelial growth factor injections. Indian J Ophthalmol 2021;69:890-4.

Patients with neovascular glaucoma, uveitis, uncontrolled systemic conditions like diabetes and hypertension were excluded from the study.

Clinical assessment

All patients received a description about the procedure before the injection occurred that explained the steps of the injection process by the study coordinator orally. Demographic data, past ocular history, and systemic history were collected from all patients. Best-corrected visual acuity (BCVA) and the intraocular pressure (IOP) was measured by trained technicians. Vitals Digital pulse rate, heart rate, and blood pressure were measured in the supine position in the brachial artery, SPO2 using pulse oximetry 15 mins prior to injection.

Intravitreal injection procedure

Topical drops (0.5% proparacaine eye drops) was instilled in the waiting area 5 minutes before shifting the patient to operation theatre. One drop of 0.5% proparacaine eye drops was applied in lower cul de sac. Using aseptic technique, a trained retina fellow injected the eye using a 30-gauge needle at a distance of 3.5/4 mm from the limbus in a pseudophakic/phakic eye in the inferotemporal quadrant with needle directed towards the optic disc. Gentle massage with a cotton-tipped applicator was applied at injection site. Vitals during the injection were recorded by study team staff. Fifteen minutes after the intravitreal injection, vitals were recorded again. Five retina fellows administered injections over the course of the study.

Assessment of patient experience

A questionnaire was administered by the study coordinator to assess the patients' comfort level in the pre-injection (waiting for injection, application of drape, cutting of drape, insertion of speculum, saline flush), injection (needle entry/injection) and post-injection (speculum and drape removal and instillation of antibiotics and pad bandage) periods at the end of the procedure asking about each phase. A visual analog score (VAS)^[10] graded from 0 to 10 (no pain to worst pain) was assessed for each step. Each patient's visual experience during the procedure was assessed using a standard questionnaire.^[11] The questionnaire addresses visual sensations experienced during the procedure (colors, light, and movement) as well as a rating of none, mild, moderate, or severe for the level of fear experienced by the patient. The results of the questionnaire were tabulated and analyzed with descriptive statistics.

Statistical analysis

Mean (SD) and frequency (percentage) were calculated for descriptive variables. *P* values < 0.05 were considered as statistically significant. Group differences in baseline variables were evaluated using Student's *t* test for continuous variables and Chi-square test for categorical variables. Patients were analyzed by the number of injections received in two groups: 1) <5 injections and b) ≥5 injections. All statistical analysis was done using statistical software STATA ver. 14.1 (Texas, USA).

Results

Our study included 174 patients who were eligible under the inclusion criteria for intravitreal injections. Baseline patient information and pre-operative characteristics are given in [Table 1]. Mean age in years was 58.8 ± 10.4 in <5 injections and 59.02 ± 9.0 in ≥5 injection group with maximum number of patients to be males 108 (62.1%).

Moderate pain and no pain were the most frequently reported discomfort levels during the pre-injection phase in both the groups. During the injection, 90.2% of patients in <5 injection group reported moderate or severe pain compared to 78% of patients in ≥5 injection group. Following the injection, 38.3% patients in <5 injection group and 58.5% patients reported moderate pain, with no pain being the second most reported discomfort level (29 in <5 injection, 19 in ≥5 injections patients). The Chi-square result shows that there is a significant difference in visual analog ratings (*P* = <0.001) [Fig. 1a and b].

Subjective assessment of visual experience and fear

There was no statistical difference in the patient visual experience immediately following the injection. All patients appreciated light, instruments, the surgeon's fingers, and the surgeon/healthcare team. Eight (4.6%) patients reported flashes and 15 (8.6%) patients reported floaters. Ninety-two (52.9%) patients in the total sample reported having a mild frightening experience [Fig. 2]. There was no statistically significant difference in patients' assessment of fear with respect to age, sex, or number of injections [<5 or ≥5] [Table 2]. Table 3 illustrates the fear rating of the small sub-group of patients with flashes and floaters and patients who did not experience visual disturbances.

Objective measures

The SBP during and following injection procedures was significantly higher in cases with fewer than 5 injections when comparing to cases with greater than 5 injections (*P* = 0.003), (*P* = 0.011). Diastolic blood pressure, heart rate, pulse rate measurements were similar among patients in all the phases of the study. Oxygen saturation at pre and post-injection timepoints was significantly higher in cases with fewer than 5 injections when comparing to cases with greater than 5 injections (*P* = 0.032, *P* = 0.029 respectively) [Table 4].

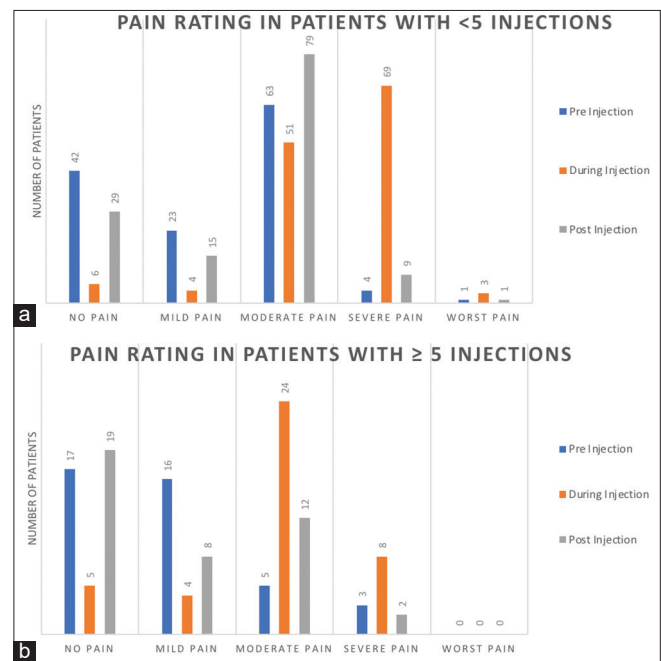


Figure 1: (a and b) Bar-diagram showing Patient VAS ratings of pain during pre, during, and post injection stages based upon number of injections received prior to visit (a) <5 injections, (b) ≥5 injections

Table 1: Patient Demographics

	<5 injections n (%) (n=133)	≥5 injections n (%) (n=41)
Age (years)		
Mean±SD	58.8±10.497	59.02±9.012
Minimum-Maximum	18-82	43-81
Gender		
Male	76 (57.1%)	32 (78%)
Female	57 (42.9%)	9 (22%)
Diagnosis		
Central retinal vein occlusion (CRVO)	12 (9%)	3 (7.3%)
Branch retinal vein occlusion (BRVO)	17 (12.8%)	1 (2.4%)
Moderate NPDR and DME	12 (9.1%)	0 (0%)
Severe NPDR with DME	29 (21.9%)	5 (12.2%)
DME	15 (11.3%)	6 (14.6%)
Proliferative diabetic retinopathy (PDR)	25 (18.8%)	15 (36.6%)
Choroidal neovascular membrane (CNVM)	16 (12.1%)	7 (17.1%)
	7 (5.3%)	4 (9.8%)

Table 2: Patient-reported level of fear following intravitreal injection according to number of injections received

No. of injections	Frightening Experience				Total
	None	Mild	Moderate	Severe	
<5	34 (25.6%)	68 (51.1%)	30 (22.6%)	1 (0.8%)	133
≥5	13 (31.7%)	24 (58.5%)	4 (9.8%)	0 (0%)	41

Chi-Square=3.699, P=0.296, Not Significant

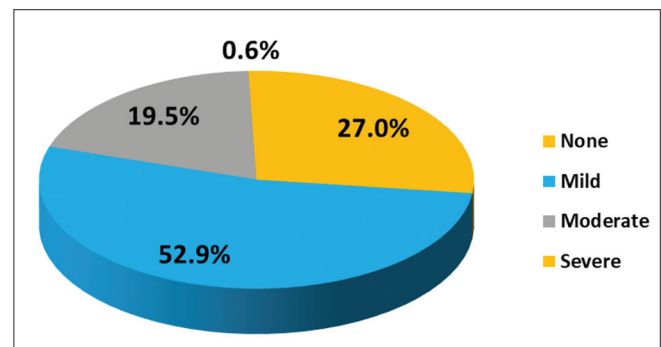
Table 3: Fear ratings for sub-group of patient with visual disturbances

Frightening experience	Patients with flashes n (%)	Patient with floaters n (%)	Patient without flashes/floaters n (%)
None	2 (25%)	3 (20%)	44 (27.8%)
Mild	4 (50%)	6 (40%)	85 (53.8%)
Moderate	2 (25%)	6 (40%)	28 (17.7%)
Severe	0 (0%)	0 (0%)	1 (0.6%)

Discussion

Our study offers the largest sample size to date of patient visual experiences during intravitreal injections. The patient experience was comprehensively assessed using multiple methods: pain and fear questionnaires, visual experience assessment, and vital signs. As hypothesized, patients reported maximum levels of discomfort and sympathetic arousal as indicated by systolic blood pressure during the injection. Stratifying the groups by the number of injections they have received in the past (<5 and ≥5 injections) allowed us to interpret patient ratings of fear and vital sign measurements with more context.

Pain was assessed in this study using a simple, validated scale of pain severity. The patient responses demonstrate a trend of maximum patient-reported pain levels during the injection which was significant in patients with <5 injection group, and mild-to-moderate pain levels in the pre-injection phase which was significant in ≥5 injection group. In the

**Figure 2: Pie-chart showing Patients reported level of fear following intravitreal injection for all patients**

pre-injection phase, pain is likely attributed to the tight speculum, forceful saline wash, and irritation due to betadine drops. During the injection phase, the pain is likely due to the needle prick, a finding that was also reported by Tailor *et al.*^[5] It has been found that pain is significantly higher with a 27-gauge needle as compared to 30-gauge needle,^[12] perhaps due to the fact that 27-gauge needles require almost twice the force to penetrate the sclera.^[13] Our study used a 30-gauge needle which may reduce the pain level experienced by patients in other clinical settings.

The other subjective component of the patient experience that we assessed was a retrospective rating of fear during the procedure. About 27% of patients reported their visual experience as non-frightening, and 72.4% patients described their visual experience as mild-moderately frightening. Perhaps most interestingly, there was no significant difference in fear ratings with respect to the number of injections the patient had received between groups with <5 or ≥5 injections in the past. Although the distribution of these groups is uneven ($n = 133$ <5, $n = 41$ ≥5), it is notable that around 50% of both groups reported mild fear regarding the injection process, with about two-times more patients in the <5 group reporting moderate pain compared to the ≥5 group. The experienced group may report lower fear levels due to increased familiarity with the

Table 4: Vital signs measured during each phase of the study

Phases	Vitals	<5 Injections (Mean±SD)	≥ 5 Injections (Mean±SD)	t	P
Pre-Injection	SBP	148.0±21.6	142.2±22.5	1.491	0.138
	DBP	86.0±12.1	84.5±10.8	0.727	0.468
	HR	82.7±11.4	81.9±13.2	0.370	0.712
	SPO ₂	99.0±0.6	98.7±0.7	2.159	0.032*
	PR	82.1±10.8	80.4±11.2	0.887	0.377
During Injection	SBP	171.7±21.1	159.7±26.4	3.000	0.003*
	DBP	96.9±13.1	93.7±15.8	1.273	0.205
	HR	84.6±12.4	80.8±13.0	1.692	0.092
	SPO ₂	98.9±2.4	98.8±0.8	0.387	0.699
	PR	84.1±11.7	80.2±11.4	1.868	0.063
Post-Injection	SBP	150.8±16.2	143.2±17.0	2.576	0.011*
	DBP	87.1±10.1	84.7±9.3	1.336	0.183
	HR	80.9±9.3	79.5±12.4	0.810	0.419
	SPO ₂	99.0±0.5	98.8±0.7	2.205	0.029*
	PR	81.1±9.2	78.9±10.9	1.267	0.207

Independent 't' test, *Significant. SBP=Systolic blood pressure (mmHg), DBP=Diastolic blood pressure (mmHg), HR=Heart rate, SPO₂: Oxygen Saturation, PR: Pulse rate (bpm)

procedure. The mild fear rating in both groups, however, indicates that a baseline level of patient anxiety may persist despite repeated exposure. It is also interesting to note that in the small subgroup of patients who experienced flashes and floaters, patients reported mild/moderate fear at almost the same rate as the group without visual disturbances. This may suggest that visual changes are not a significant factor in increasing patient fear during the procedure, however additional data would be necessary to support this idea.

In addition to assessing subjective measures of discomfort, our study surveyed patients regarding their visual experience during the procedure, as this may affect perceived pain or fear. All patients appreciated light, instruments, the surgeon's fingers, and surgeon/staff, which as anticipated as all patients had a visual acuity better than 6/60. In our study, 4.6% of patients reported flashes and 8.6% patients reported floaters during or immediately after the injection compared to Charalampidou *et al.* study in which 26.6% and 32% of patients reported flashes and floaters respectively following intravitreal injections which included triamcinolone acetate (TCA), pegaptinib and ranibizumab.^[14] Floaters can be attributed to the change in refractive index of the vitreous gel or accidental injection of small air bubble along with the injection of the drug. The exact mechanism of flashes and other visual phenomena remains elusive. One probable reason could be the difference in retinal pathology of the patient undergoing the intravitreal injection, however these are complex neuropsychological phenomena that may be influenced by environmental factors. The increase in floaters in Charalampidou *et al.* study could also be due to the use of TCA which is opaque compared to other agents. Our study included transparent anti-VEGF agents, which may explain the relatively low incidence of floaters.

A study by Berger *et al.* demonstrated significant increases in systolic blood pressure (SBP) during anti-VEGF injections.^[15] Our study supports these findings, indicating a marked increase in SBP from the pre-injection to during-injection time points. A similar trend of increase in heart rate was noted during the

injection phase. This finding may be attributed to pain, anxiety of injection, visual experience of seeing surgical instruments, or seeing the surrounding surgeon and staff. The increase in SBP from pre to during-injection timepoints is larger in the group with fewer than five injections compared to the group with ≥5 injections. Additionally, the SBP in the ≥5 injection group was 6 mmHg lower in the pre-injection stage and 12 mm Hg lower during the injection. A similar but more modest trend was observed in the heart rate. This data reflects the fear ratings reported by both groups, potentially suggesting an association between the patients' self-reported fear and their sympathetic arousal. As suggested by the work of Berger *et al.*, patients' vital signs may increase to dangerous levels during the procedure, potentially causing cardiovascular or cerebrovascular incidents. Identifying the most stressful periods of the injection process may better help the healthcare team comfort patients and prevent severe sympathetic arousal.

A strength of our study is the large sample size with comprehensive assessments of the patient experience. The other largest study to date included 201 participants, however, visual experience was not assessed, and patients were not analyzed based; upon previous exposure to injections, a modulator of pain ratings, and anxiety in this setting as demonstrated by our study. A weakness of our study is that intravitreal injections were given by different surgeons, which could have led to a variable experience during the procedure. Future studies may benefit from a reduced number of surgeons to control for this possible confounder.

Conclusion

In conclusion, most patients have a mild-to-moderate frightening experience during intravitreal anti-VEGF injections but experience a significant increase in systolic blood pressure in the pre-injection and during injection phases, which tends to decrease in intensity after multiple injections. The metrics of discomfort and stress in patients, particularly those who have historically received fewer injections, could be improved using a pre-operative video that counsels patients thoroughly

about the procedure and shows them what they might expect, ultimately reducing uncertainty around the procedure.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Semin Ophthalmol* 1999;14:223-32.
2. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group; Maguire MG, Martin DF, Ying GS, Jaffe GS, Daniel E, Grunwald JE, *et al.* Five- year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: The Comparison of age- related macular degeneration treatments trials. *Ophthalmology* 2016;123:1751-61.
3. Noma H, Funatsu H, Yamasaki M, Tsukamoto H, Mimura T, Sone T, *et al.* Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. *Am J Ophthalmol* 2005;140:256-61.
4. Blumenkranz M, Hernandez E, Ophir A, Norton EW. 5-fluorouracil: New applications in complicated retinal detachment for an established antimetabolite. *Ophthalmology* 1984;91:122-30.
5. Tailor R, Beasley R, Yang Y, Narendran N. Evaluation of patients' experiences at different stages of the intravitreal injection procedure—what can be improved?. *Clin Ophthalmol* 2011;5:1499-502.
6. Johnson C. Visual analog scale versus numeric pain scale: What is the difference?. *J Chiropr Med* 2005;4:43-4.
7. Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain* 2000;16:22-8.
8. Salo D, Eget D, Lavery RF, Garner L, Bernstein S, Tandon K. Can patients accurately read a visual analog pain scale?. *Ame J Emerg Med* 2003;21:515-9.
9. Davis MJ, Pollack JS, Shott S. Comparison of topical anesthetics for intravitreal injections: A randomized clinical trial. *Retina* 2012;32:701-5.
10. Flynn D, van Schaik P, van Wersch A. A comparison of multi-item likert and visual analogue scales for the assessment of transactionally defined coping function. *Eur J Psychol Assess* 2004;20:49-58.
11. Rengaraj V, Radhakrishnan M, Eong K-GA, Saw S-M, Srinivasan A, Mathew J, *et al.* Visual experience during phacoemulsification under topical versus retrobulbar anesthesia: Results of a prospective, randomized, controlled trial. *Am J Ophthalmol* 2004;138:782-7.
12. Güler M, Bilgin B, Çapkın M, Şimşek A, Bilak Ş. Assessment of patient pain experience during intravitreal 27-gauge bevacizumab and 30-gauge ranibizumab injection. *Korean J Ophthalmol* 2015;29:190-4.
13. Pulido JS, Zobitz ME, An KN. Scleral penetration force requirements for commonly used intravitreal needles. *Eye (Lond)* 2007;21:1210-1.
14. Charalampidou S, Nolan J, Ormonde GO, Beatty S. Visual perceptions induced by intravitreal injections of therapeutic agents. *Eye (Lond)* 2011;25:494-501.
15. Berger V, Munk MR, Lersch F, Wolf S, Ebnetter A, Zinkernagel MS. Association of intravitreal injections with blood pressure increase: The following excitement and anxiety response under intravitreal injection study. *JAMA Ophthalmol* 2019;137:87-90.