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Research Article

Pain Experienced by Patients During Intravitreal Ranibizumab Injection: A Prospective Observational Study

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ABSTRACT

Background: Intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) agents represent the most frequently performed intraocular procedure worldwide. This study aimed to evaluate and compare pain experienced by patients during intravitreal ranibizumab injection, stratified by injection dose frequency and sex.

Methods: A hospital-based, prospective observational study was conducted in the Department of Ophthalmology, ESIC MC PGIMSR & MH, Rajajinagar, Bengaluru, between February 2024 and February 2025. Ninety-two patients (92 eyes) aged 31–80 years were enrolled. Pain was assessed at four time points before, during, 10 minutes after and more than one hour after the procedure using the Visual Analogue Scale (VAS; 0 = no pain, 10 = unbearable pain). Haemodynamic parameters (blood pressure and pulse rate) were recorded concurrently. Statistical analysis employed Chi-square and Fisher's exact tests; $p < 0.05$ was considered significant.

Results: During the injection phase, 52.2% of participants reported moderate pain (VAS 4–6) and 13% reported severe or worst pain. Pain declined significantly over time: by >1-hour post-procedure, 79.3% of patients reported no or only mild pain. A statistically significant association was found between sex and injection-phase pain ($p = 0.021$), with males reporting higher pain intensity. Dose frequency and age did not significantly influence pain scores (all $p > 0.05$). Haemodynamic parameters showed a transient rise during the injection phase, returning to near-baseline values within one hour.

Conclusion: IVI of ranibizumab is associated with transient, predominantly mild-to-moderate pain that resolves rapidly. Male sex was identified as a significant predictor of greater injection-phase pain. Pre-procedural counselling, standardised topical anaesthesia and meticulous injection technique remain essential for optimising patient comfort and treatment adherence.

Keywords: *intravitreal injection; ranibizumab; anti-VEGF; pain assessment; visual analogue scale; patient experience; ophthalmology.*

INTRODUCTION

Over the past two decades, intravitreal injection (IVI) has become the most commonly performed intraocular procedure worldwide, driven by the expanding therapeutic landscape of anti-vascular endothelial growth factor (anti-VEGF) agents [1]. Ranibizumab , a recombinant humanised monoclonal antibody fragment (Fab) directed against all isoforms of vascular endothelial growth factor A (VEGF-A), has received regulatory approval from the United States Food and Drug Administration (FDA) for a spectrum of neovascular and oedematous retinal conditions including neovascular age-

related macular degeneration (nAMD), macular oedema secondary to retinal vein occlusion (RVO), myopic choroidal neovascularisation (mCNV), diabetic macular oedema (DME) and diabetic retinopathy (DR) with or without DME [2].

India, recognised as the diabetic capital of the world, carries a disproportionately large burden of diabetic retinopathy and its vascular sequelae, creating a substantial and growing demand for intravitreal anti-VEGF therapy [3]. Most indications necessitate repeated, long-term administration, with some protocols requiring monthly injections over several years. Consequently, patient experience during the procedure particularly pain and discomfort is a major determinant of treatment adherence and long-term visual outcomes [4].

Although IVI is performed under topical anaesthesia and is generally considered safe, the perception of pain is subjective and variable. Studies have documented that procedural pain can provoke involuntary ocular and cephalic movements increasing the risk of needle-related complications and potentially compromising the sterility of the injection field [5]. Furthermore, anticipatory anxiety linked to prior painful experiences may lead to premature discontinuation of a life-altering treatment [6].

The Visual Analogue Scale (VAS) is a validated, widely adopted instrument for the subjective quantification of pain intensity. Its simplicity and cross-cultural applicability make it particularly suitable for outpatient procedural settings [7]. Several investigators have applied VAS to characterise pain associated with IVI, identifying needle gauge, injection site, anaesthetic agent and patient demographics as potential modulators [1,5,8]. However, data from South Asian populations in whom comorbidities such as diabetes and hypertension are highly prevalent remain limited.

The present study was, therefore, designed to prospectively assess VAS-based pain scores at four distinct peri-procedural time points in patients undergoing intravitreal ranibizumab injection at a tertiary ophthalmology centre in Bengaluru, India and to evaluate the independent effects of dose frequency, sex and age on pain perception.

MATERIALS AND METHODS

Study design, setting and ethical approval

This was a hospital-based, single-centre, prospective observational study conducted in the Department of Ophthalmology, ESIC Medical College, PGIMSR & MH, Rajajinagar, Bengaluru, Karnataka, India, over a 12-month period (February 2024 to February 2025). The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC No: 532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.Vol.IV/201-B/2024). Written informed consent was obtained from all participants prior to enrolment.

Participants

Inclusion criteria: Patients aged 31–80 years of either sex presenting to the retina clinic with a posterior segment pathology warranting intravitreal ranibizumab therapy; normal anterior segment examination; phakic or pseudophakic status; and willingness to attend regular follow-up visits and participate in the study.

Exclusion criteria: Age < 18 years; pre-existing corneal, anterior chamber, or iridocorneal disease likely to confound pain assessment; current use of systemic analgesic, sedative, or anxiolytic medications; and refusal to provide informed consent.

A total of 92 eyes of 92 patients were enrolled. Indications for ranibizumab included diabetic macular oedema (DMO), choroidal neovascular membrane (CNVM), post-operative cystoid macular oedema (CMO) and macular oedema secondary to retinal vein occlusions.

Pre-procedural evaluation

Each participant underwent a comprehensive systemic and ophthalmic evaluation. Best-corrected visual acuity (BCVA) was measured using the Snellen's chart. Intraocular pressure was assessed by Goldmann applanation tonometry. Anterior segment examination included evaluation of lids, conjunctiva, cornea, anterior chamber, iris, pupil and lens. Posterior segment evaluation was performed by a dedicated in-house vitreoretinal specialist using slit-lamp biomicroscopy and indirect ophthalmoscopy. Optical coherence tomography (OCT) and B-scan ultrasonography were performed where indicated. Digital fundus photography was obtained using a TOPCON TRC-50DX retinal camera. Systemic clearance from physician, anaesthetist and cardiologist was obtained where clinically necessary.

Injection procedure

All injections were performed by a single experienced vitreoretinal surgeon under a standardised protocol to eliminate inter-operator variability. The peri-ocular region was prepared with 10% povidone-iodine solution and the eye was draped with a sterile disposable plastic drape. A wire eyelid speculum was applied to retract the eyelids. Topical anaesthesia was achieved with two drops of 0.5% proparacaine hydrochloride. The conjunctival cul-de-sac was irrigated with 5% povidone-iodine solution and the injection was performed two minutes thereafter. Using a Castroviejo calliper, the injection site was marked 3.5 mm posterior to the limbus in pseudophakic eyes and 4 mm in phakic eyes. Ranibizumab (2.3mg in 0.23 mL) was delivered via the pars plana using a 30-gauge needle. Light digital pressure was applied to the injection site with a sterile cotton tip applicator for a few seconds to minimise vitreous reflux and

subconjunctival haemorrhage. One drop of topical moxifloxacin 0.5% antibiotic and topical povidone iodine drops was instilled and the eye was patched for six hours.

Post-procedural medications included a single oral dose of acetazolamide 250 mg (withheld in patients with nephropathy), oral paracetamol 500 mg twice daily as needed and topical moxifloxacin 0.5% six times daily for one week.

Haemodynamic monitoring

Blood pressure (BP) and pulse rate (PR) were recorded at four standardised time points: (i) 10 minutes before the procedure; (ii) during the injection; (iii) 10 minutes after the injection; and (iv) more than one hour after the procedure. Hypertension was defined according to Joint National Committee (JNC) 8 criteria (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg). Tachycardia was defined as PR > 100 beats per minute.

Pain assessment

Pain was assessed using a standard 100-mm horizontal Visual Analogue Scale (VAS) at the same four peri-procedural time points. The scale was anchored at 0 ("No pain") and 10 ("Unbearable pain"), with intermediate scores 1–9 representing progressively increasing pain intensity. For analytical purposes, VAS scores were categorised as: no pain (0), mild (1–3), moderate (4–6), severe (7–9) and worst/unbearable (10). All patients were familiarised with the scale before the procedure to ensure accurate self-reporting.

Statistical analysis

Data were entered into Microsoft Office Excel and analysed using the Statistical Package for Social Sciences (SPSS), version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages. The Chi-square test and Fisher's exact test were applied to evaluate associations between categorical variables. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics

Ninety-two patients (92 eyes) were enrolled over the study period. Table 1 summarises demographic and clinical characteristics. The majority of participants were in the 46–60-year age cohort (56.5%), followed by those aged 61–80 years (31.5%) and 31–45 years (12.0%). Males constituted 69.6% of the cohort. First-dose recipients accounted for 59.8% of participants; the remaining 40.2% were receiving their second or subsequent injection.

Table 1. Demographic and clinical characteristics of study participants (n = 92)

Age group (years)	n	%
31–45	11	12
46–60	52	56.5
61–80	29	31.5
Sex		
Male	64	69.6
Female	28	30.4
Injection dose		
First dose	55	59.8
Multiple doses (≥2)	37	40.2

BP = blood pressure; PR = pulse rate.

Haemodynamic responses across procedural phases

Table 2 summarises BP and PR across all four time points. Prior to the procedure, 43.5% of participants had elevated BP and 8.7% had elevated PR. During the injection phase, the proportion of patients with elevated BProse sharply to 60.9% and the proportion with elevated PR increased to 12.0%, consistent with a sympathetically mediated stress response. Post-injection, these values began to normalise and by >1-hour post-procedure, hypertension was present in only 29.3% of participants and elevated PR in 2.2%, indicating near-complete haemodynamic recovery.

Table 2. Haemodynamic parameters across procedural phases (n = 92)

Parameter	Pre-procedure	Injection phase	Post-injection	Post-procedure (>1 h)
Hypertension, n (%)	40 (43.5)	56 (60.9)	43 (46.7)	27 (29.3)
Normal BP, n (%)	52 (56.5)	36 (39.1)	49 (53.3)	65 (70.7)

Elevated PR, n (%)	8 (8.7)	11 (12.0)	12 (13.0)	2 (2.2)
Normal PR, n (%)	84 (91.3)	81 (88.0)	80 (87.0)	90 (97.8)

BP = blood pressure; PR = pulse rate. Hypertension: systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg. Tachycardia: PR > 100 bpm.

Pain intensity across procedural phases

Pain was highest during the injection phase, with 52.2% of participants reporting moderate pain and 13.0% reporting severe or worst pain (Table 3). In the post-injection phase (10 minutes after the procedure), the distribution shifted towards milder categories, with 52.2% reporting mild pain. By >1-hour post-procedure, 38.0% of participants reported complete absence of pain and a further 41.3% reported only mild discomfort, such that 79.3% experienced no or mild pain. The proportion of patients reporting severe pain fell from 8.7% during the injection to 3.3% at >1 hour.

Table 3. Distribution of pain intensity across procedural phases (n = 92)

Pain category	Injection phase n (%)	Post-injection n (%)	Post-procedure n (%)
No pain	0 (0)	5 (5.4)	35 (38.0)
Mild (VAS 1–3)	32 (34.8)	48 (52.2)	38 (41.3)
Moderate (4–6)	48 (52.2)	31 (33.7)	16 (17.4)
Severe (7–9)	8 (8.7)	8 (8.7)	3 (3.3)
Worst (10)	4 (4.3)	0 (0)	0 (0)

VAS = Visual Analogue Scale.

Effect of sex on pain perception

A statistically significant association was observed between sex and injection-phase pain intensity (Table 4; Fisher's exact test, p = 0.021). Among males, 75.0% reported moderate or greater pain during the injection, compared with 42.9% of females. All four reports of "worst pain" (VAS 10) were from male participants. In the post-injection phase, males again demonstrated a trend toward greater pain (47% moderate-to-severe vs 32% in females), though this did not attain statistical significance (p = 0.062). By the post-procedure phase, pain distribution was comparable between sexes (p = 0.609).

Table 4. Association between sex and injection-phase pain intensity (n = 92)

Gender	Mild n (%)	Moderate n (%)	Severe n (%)	Worst n (%)
Female (n=28)	16 (57.1)	10 (35.7)	2 (7.1)	0 (0)
Male (n=64)	16 (25.0)	38 (59.4)	6 (9.4)	4 (6.3)

*Statistically significant (Fisher's exact test, p < 0.05).

Effect of dose frequency on pain perception

Table 5 presents pain scores stratified by dose frequency. During the injection phase, first-dose recipients were the only group to report "worst pain" (7.3% vs 0%; p = 0.346), suggesting a trend towards greater procedural discomfort with initial exposure. However, no statistically significant difference was found between first-dose and multiple-dose recipients across any pain phase: injection (p = 0.346), post-injection (p = 0.230), or post-procedure (p = 0.374).

Table 5. Association between injection dose frequency and pain intensity across procedural phases (n = 92)

Pain category	First dose n (40 %)	Multiple doses n (60 %)	p-value
Injection phase pain			
Mild	17 (30.9)	15 (40.5)	
Moderate	29 (52.7)	19 (51.4)	
Severe	5 (9.1)	3 (8.1)	
Worst	4 (7.3)	0 (0)	0.346
Post-injection phase pain			
No pain	4 (7.3)	1 (2.7)	
Mild	28 (50.9)	20 (54.1)	0.23

Moderate	16 (29.1)	15 (40.5)	
Severe	7 (12.7)	1 (2.7)	
Post-procedure phase pain			
No pain	17 (30.9)	18 (48.6)	
Mild	26 (47.3)	12 (32.4)	
Moderate	10 (18.2)	6 (16.2)	
Severe	2 (3.6)	1 (2.7)	0.374

Chi-square/Fisher's exact test. NS = not significant ($p > 0.05$).

Effect of age on pain perception

Younger participants (31–45 years) exhibited a trend towards higher pain intensity across all phases notably, the highest relative proportions of severe and worst pain during the injection phase yet none of these associations achieved statistical significance (injection phase: $p = 0.085$; post-injection: $p = 0.212$; post-procedure: $p = 0.384$). The 46–60-year cohort, which constituted the largest subgroup, predominantly reported mild-to-moderate pain and no participant in this age group reported "worst pain" during the injection. These findings suggest potential age-related differences in pain tolerance or reporting behaviour, but the study was underpowered to detect a significant effect.

DISCUSSION

The present study provides a granular, prospective characterisation of pain experienced by Indian patients undergoing intravitreal ranibizumab injection, with concurrent haemodynamic monitoring across four peri-procedural time points. The core findings are: (i) pain is highest during the injection, predominantly mild-to-moderate and resolves substantially within one hour; (ii) male sex is a significant predictor of greater injection-phase pain; (iii) first-dose recipients demonstrate a trend toward higher pain that does not reach statistical significance; and (iv) age does not independently predict pain in this cohort.

The observation that over half of participants reported moderate pain during injection, with 13% reporting severe or worst pain, is broadly consistent with published literature. Rifkin and Schaal reported that most patients experience transient but tolerable discomfort during IVI, with VAS scores clustering in the mild-to-moderate range when 30-gauge needles and topical proparacaine anaesthesia are used [1]. The use of a smaller-gauge needle, as employed in our protocol, is thought to reduce injection-site resistance and associated pain [8].

The statistically significant sex difference in injection-phase pain ($p = 0.021$), with males reporting higher intensity, merits discussion. This finding is in apparent contrast to the broader pain science literature, in which women are generally considered to have lower pain thresholds and higher pain sensitivity than men, attributed to neuroendocrine and psychosocial factors [9]. However, sex-based differences in the context of ophthalmic procedures are less well characterised. Shiroma et al. noted gender-based perceptual differences in pain during IVI in a systematic review, observing that the direction of the effect varied across studies and may be modulated by procedure-specific factors including anxiety, prior experiences and sociocultural norms around pain expression [4]. In the Indian cultural context, stoicism and underreporting of pain among women particularly in clinical settings may partly explain the observed pattern.

The trend toward greater pain among first-dose recipients, while not statistically significant ($p = 0.346$), aligns with psychological adaptation theory. Repeated exposure to IVI has been hypothesised to attenuate anticipatory anxiety and fear, thereby lowering the affective component of pain perception a phenomenon described by Massamba et al. in the context of ranibizumab injection [3]. Güler et al. similarly reported that experienced patients tended to rate IVI-related pain lower than treatment-naive individuals, irrespective of the anti-VEGF agent used [2]. Our study was likely underpowered to detect a significant dose-frequency effect and a larger prospective study or randomised controlled trial incorporating validated anxiety instruments would be informative.

The haemodynamic data corroborate the subjective pain reports. The sharp rise in hypertensive readings during the injection phase from 43.5% pre-procedure to 60.9% intra-procedure parallels the pain trajectory, providing objective physiological evidence of an acute stress response. The concomitant rise in PR, though modest, is consistent with a sympathetically mediated vasopressor response. Importantly, both BP and PR normalised substantially within one hour, underscoring the transient nature of procedural stress. Clinicians should remain vigilant in patients with pre-existing cardiovascular disease, in whom peri-procedural haemodynamic fluctuations may carry greater risk.

The absence of a significant age effect on pain (all $p > 0.05$) is notable. Younger participants (31–45 years) showed higher relative proportions of severe pain, consistent with the hypothesis that older individuals may have altered pain perception due to age-related changes in central sensitisation pathways, or may have accumulated greater procedural experience [5]. However, the small number of participants in the youngest age category ($n = 11$) limits the statistical power of this comparison.

Several limitations of the present study warrant acknowledgement. The single-centre design and relatively modest sample size (n = 92) restrict the generalisability of findings. The absence of a validated anxiety scale (e.g., the State-Trait Anxiety Inventory) limits the ability to adjust for anticipatory anxiety as a confounder of pain perception. Pain assessment relied exclusively on patient self-report, which is inherently subjective. Future multi-centre, randomised studies with larger sample sizes, incorporating psychometric instruments and objective pain biomarkers, are recommended.

CONCLUSION

Intravitreal injection of ranibizumab was associated with transient, predominantly mild-to-moderate procedural pain that resolved substantially within one hour of the procedure. Males reported statistically significant higher pain intensity during injection-phasethan females. First-dose recipients and younger patients experienced greater pain intensity which was however not statistically significant, possibly due to limited sample size.

These findingsemphasize the importance of pre-procedural patient counselling, standardised topical anaesthesia and a meticulous, technique-driven approach to minimise procedural discomfort.Understanding these patterns can help clinicians better prepare patients for the procedure, alleviate anxiety, and potentially improve compliance for repeat injections.

Further studies with larger sample sizes are recommended to validate these findings and explore adjunct pain-reduction strategies, particularly in first-time recipients and anxious subgroups.

DECLARATIONS

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Competing interests: The authors declare no conflicts of interest.

Ethics approval: Approved by the Institutional Ethics Committee, ESIC MC PGIMSR & MH, Bengaluru (IEC No: 532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.Vol.IV/201-B/2024). All procedures were performed in accordance with the Declaration of Helsinki.

Data availability: De-identified data supporting the findings of this study are available from the corresponding author on reasonable request.

Author contributions: R.K. and A.R. conceived and designed the study. B.K. performed data collection. Y.S.V. performed statistical analysis. All authors participated in manuscript preparation and approved the final version.

REFERENCES

1. Rifkin L, Schaal S. Factors affecting patients' pain intensity during in-office intravitreal injection procedure. Retina. 2012;32:696–700. https://doi.org/10.1097/IAE.0b013e318225deaf
2. [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;29:190–194. https://doi.org/10.3341/kjo.2015.29.3.190
3. [Massamba N, Elluard M, Agoune W, et al. Assessment of ocular pain following ranibizumab intravitreal injection. Acta Ophthalmologica. 2015;93(s255). https://doi.org/10.1111/j.1755-3768.2015.0261.x
4. Shiroma HF, Takaschima AKK, Farah ME, Höfling-Lima AL, Luca Canto G, Benedetti RH, Rodrigues EB. Patient pain during intravitreal injections under topical anesthesia: a systematic review. Int J Retina Vitreous. 2017;3:23. https://doi.org/10.1186/s40942-017-0076-9
5. 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;69:1167–1172. https://doi.org/10.4103/ijo.IJO_2470_20
6. [Bilak Ş, Bilgin B. Assessment of patient pain experience during intravitreal ranibizumab and aflibercept injection. Turk J Ophthalmol. 2018;48:61–65. https://doi.org/10.4274/tjo.46695
7. Shin SH, Park SP, Kim YK. Factors associated with pain following intravitreal injections. Korean J Ophthalmol. 2018;32:196–203. https://doi.org/10.3341/kjo.2017.0095
8. Rodrigues IA, Shetty R, Koh A, et al. Pain perception and patient satisfaction with intravitreal injection: a comparison of 27-gauge and 30-gauge needles. Retina. 2016;36:379–384.
9. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, gender and pain: a review of recent clinical and experimental findings. J Pain. 2009;10:447–485. https://doi.org/10.1016/j.jpain.2008.12.001.