Which Intravitreal Injection Site Results in the Least Pain? - A Prospective, Randomized, Six-Armed, Clinical Trial

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Abstract

Background: Intravitreal injection is the most commonly performed procedure in outpatient retina clinics. However, the optimal injection site for intravitreal injection has not been determined.

Objective: To identify the least painful intravitreal injection site.

Materials and Methods: Prospective, randomized, six-armed clinical trial. One hundred ninety-two patients who were treated with intravitreal injection were randomized into 6 groups according to the injection site: superonasal (SN), superior (S), superotemporal (ST), inferotemporal (IT), inferior (I), and inferonasal (IN). The pain score (visual analog scale), anxiety score (visual analog scale), visual experience during injection, and baseline demographic data were recorded.

Results: The overall median (interquartile range, IQR) pain score across all groups was 2 (2). By injection site, the median pain scores were SN 3 (3), S 2 (2), ST 2 (2), IT 2 (2), I 2 (2), and IN 1 (2). The lowest pain scores were observed in the IN group, whereas the highest were in the SN group. Statistically significant differences were observed between the IN and S sites ($p=0.021$) and between the IN and SN sites ($p<0.001$), at a significance level of 0.05. Further analysis comparing the upper and lower halves of the eye showed significantly higher pain scores in the upper half ($p<0.001$). Pain scores were positively correlated with anxiety scores, with a low correlation observed (Spearman's rank correlation coefficient of 0.399, $p<0.01$). The three most common visual experiences during injection were water flow (47.6%), bright light (32.5%), and shadow of the needle object (12.6%).

Conclusion: The site of injection that gave the minimum pain score and anxiety score was IN. The pain and anxiety scores seem to be less when the injection was performed in the inferior half of the eye.

Keywords: Intravitreal injection; Visual analog scale; Pain; Bevacizumab; Anxiety

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Intravitreal injection is the most common procedure performed in retinal outpatient ophthalmology clinics[1,2]. It is currently considered a standard treatment. The medications most frequently used include bevacizumab, aflibercept, and ranibizumab[3-5]. Diseases treated with this method include age-related macular degeneration, proliferative diabetic retinopathy, diabetic macular edema, choroidal neovascularization, retinal vein occlusion, and neovascular glaucoma[5-9].

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Currently, there is no consensus on the injection site for intravitreal injections. Specialists typically inject medication at a distance of 3.5-4 mm from the limbus in eyes with a natural lens and 3-3.5 mm in eyes with a prior artificial lens implantation. However, the exact injection site is typically selected by the specialist based on preference and ease of access, which may vary depending on the patient's specific condition. In the past, only a limited number of studies have compared the level of pain and discomfort

What is already known about this topic?

Existing evidence suggests that the injection site significantly affects the level of pain experienced by the patient during intravitreal injections.

Somewhere in the lower half of the eye or the upper inner quadrant may represent optimal sites for minimizing pain during these procedures.

Pain experienced during injections impacts patient cooperation in future treatments and affects follow-up compliance, especially when multiple injections are required.

What does this study add?

This study confirms that the IN site of the eye is associated with less pain and anxiety for patients during intravitreal injections.

The findings support adopting the IN site as the preferred injection site to reduce patient pain and anxiety.

between different injection sites[10,11]. Karimi et al.[10] conducted a prospective, randomized, four-armed clinical trial to compare different intravitreal injection sites in 1,004 eyes (from 1,004 patients). The scleral conjunctiva was divided into four quadrants: superonasal (SN), superotemporal (ST), inferonasal (IN), and inferotemporal (IT), to evaluate differences in visual analog scale (VAS) pain scores. The study found that injections at the ST site had the highest average pain score with a mean ± standard deviation (SD) of 4±2, while the SN site had the lowest average pain score with a mean of 1.5±1.7. Females had significantly higher pain scores than males ($p<0.001$). Additionally, there was a negative correlation between the number of previous injections and the average pain score ($p=0.03$). The study by Moisseiev et al.[11], conducted in 218 patients, found that the average pain score (VAS) showed no significant differences across baseline factors such as age, sex, indication for injection, number of injections, diabetes status, lens status, or the injection site (with the injection site divided into four quadrants). However, there was a study by Tewari et al.[12] found that the pain experienced during the injection influenced the patient's cooperation in future intravitreal injections and affected their follow-up compliance in cases where multiple injections were required. To enhance the specificity of the test area division by clearly distinguishing the upper, lower, and lateral regions, this study was designed to assess pain and anxiety levels associated with injections at six different sites. These sites were defined as areas encompassing 60-degree sectors measured from the center of the pupil. Based on a review of the literature, this approach has not been explored in previous studies. To minimize potential sources of bias, such as selection bias, and to ensure an even distribution of injections across the study sites rather than relying on physician preference, the study was designed as a prospective, randomized, six-armed clinical trial. This design was chosen to provide the most accurate assessment of the research questions.

Material and Methods

The prospective randomized comparative study was conducted on 192 patients who received treatment at the retinal clinic of Priest Hospital between October 2020 and June 2021. The study adhered to the principles of the Declaration of Helsinki and was registered with the Thai Clinical Trials Registry (TCTR20210719007). It was reviewed and approved by the Human Research Ethics Committee of Priest Hospital (Approval number 20/2563). All patients scheduled to receive intravitreal injections, aged between 20 and 90 years, who do not have diseases or conditions that could affect the interpretation of pain from the injection, including herpes infection, severe dry eye disease, corneal diseases (including corneal degeneration), uveitis, episcleritis, scleritis, closed-angle glaucoma, or a history of surgery involving the conjunctiva such as pterygium surgery or retinal surgery, will be informed about the study and provided with consent forms for participate. To achieve 90% power to detect a 1.5-point difference in pain VAS scores, with a Type I error of 0.05 and a standard deviation of 2.2 (as reported in a previous study[10]), a total of 1,004 samples were required, with 27 eyes per group. To compensate for missing data, the target was set to collect data from 32 eyes in each group, resulting in a total sample size of 192 eyes. The randomization sequence was generated using Microsoft Excel (RAND function), whereby each participant was assigned a random number, sorted in ascending order, and then allocated sequentially to one of six groups. Participants entering the study in different sequences were randomly allocated to one of the groups, each corresponding to a different injection site, according to a predetermined randomization plan (Figure 1). The injection site areas and groups are as follows:

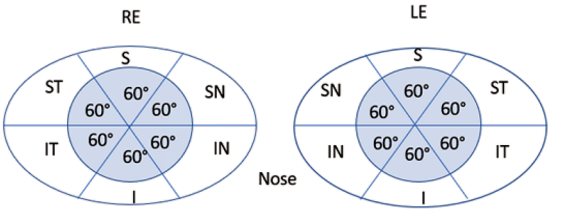

Figure 1. Injection sites of both eyes.

RE=right eye, LE=left eye, ST=superotemporal, S=superior, SN=superonasal, IT=inferotemporal, I=inferior, IN=inferonasal

Group 1: SN – the zone measured 60 degrees upward from the horizontal line toward the nasal side.

Group 2: S – the zone 60 degrees in between SN and ST.

Group 3: ST – the zone measured 60 degrees upward from the horizontal line toward the temporal (outer) side of the eye.

Group 4: IT – the zone measured 60 degrees downward from the horizontal line toward the temporal (outer) side of the eye.

Group 5: I – the zone 60 degrees in between IT and IN.

Group 6: IN – the zone measured 60 degrees downward from the horizontal line toward the nasal side.

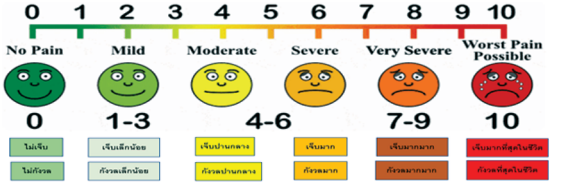

Figure 2. Visual analog scale and the standardized wording used to explain the procedure to patients before the injection.

The randomization process was concealed by a research assistant who was not involved in the treatment procedure or data collection. The assistant performed the group allocation and stored each participant's assignment sequentially in sealed envelopes. The envelopes were opened individually for the physician at the time of administering the injection. The physician responsible for the eye examination and history-taking was unaware of the participant's group until the injection process. Additionally, the staff responsible for preparing the eye drops, providing instructions on the VAS, and conducting post-injection interviews were blinded to the participants' group allocation.

Before receiving the injection, all participants underwent a detailed ophthalmic examination by a retinal specialist. Baseline data, including age, sex, diagnosis, diabetes status, lens status, number of previous injections, and best-corrected visual acuity, were recorded. Participants were briefed on the use of the VAS and shown a sample image (Figure 2). Subsequently, 0.5% tetracaine hydrochloride (Alcon Laboratories Inc.) was administered to the inferior cul-de-sac in four doses: one drop every five minutes for three doses while the patient was seated, with instructions to close the eyes and move them in a circular motion after each drop, followed by a final drop one minute before the procedure while lying on the procedure table, just prior to antiseptic preparation. According to previous studies, the use of topical anesthesia has been proven to be both effective and safe for this type of procedure[13,14]. Tetracaine hydrochloride has been found to be equally effective as other topical anesthetic agents. The antiseptic process involves applying 10% povidone-iodine to the skin around the injection site, followed by rinsing the eye with 5% povidone-iodine. A sterile drape is then placed, and an eyelid speculum is applied. The injections were performed by two retinal specialists according to the assigned injection site. The research assistant opened the envelope to reveal the allocated site at the time of the procedure. The medications injected into the participant's eyes were bevacizumab and aflibercept. Both drugs were administered using a 30-gauge needle at a dosage of 0.05 mL (1.25 mg of bevacizumab or 2 mg of aflibercept) at room temperature. The injection site was located 3.5 mm from the corneal limbus, according to the assigned location for each group. Within two minutes after the injection, patients were interviewed outside the procedure room by a nursing assistant regarding their pain levels, assessed using the VAS, where 0 represents no pain, and 10 represents the worst pain imaginable. Anxiety during the injection was also evaluated using a VAS, with 0 representing no fear or anxiety and 10 representing the highest level of fear or anxiety imaginable.

The use of the VAS interview method was based on the study by Bilgin et al.[15], including assessment of patients' visual experiences during the injection. The interviewer, a nurse assistant stationed in front of the procedure room, was blinded to the injection site. If a patient received injections in both eyes on the same day, only data from the first eye injected were included in the analysis. The eye selected for the first injection was determined by coin flip; if heads, the right eye was injected first.

The primary outcome measure was the pain score (VAS), which is the most widely used method in pain assessment statistics[16,17]. The anxiety measurement used the VAS for anxiety, which has been validated in previous studies[18]. However, assessment of data distribution using the Shapiro-Wilk test indicated non-normality; therefore, comparisons among groups were performed using the non-parametric Kruskal-Wallis test. Post hoc pairwise comparisons were conducted using Dunn's test with Bonferroni correction. A p-value less than 0.05 was considered statistically significant. Spearman's rank correlation coefficient was used for the correlation between variables. For the analysis of categorical data, the chi-square test was used. Descriptive statistics were employed to present the baseline data. All analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 192 participants, aged between 20 and 90 years, participated in the study; however, one participant left the clinic before the evaluation and was excluded from the study. The baseline characteristics, including age, sex, diagnosis, and lens status, are presented in Table 1.

Baseline demographic and clinical characteristics, including age, sex, diagnosis, lens status, diabetes status, and type of medication, were comparable across injection site groups (all p>0.05).

Table 1. Basic demographic data

Variable	Total n (%)	Injection site (%)						p-value
		SN	S	ST	IT	I	IN	
Number of patients	191 (100)	32	32	32	32	31	32	
Age (years); mean±SD		64.9±11.9	61.9±14.1	61.8±16.9	66.8±11.7	59.9±15	65.7±12.4	0.581[1]
Age; n (%)								
<50 years	22 (11.5)	6.5	16.6	15.6	8.8	13.3	8.8	
51-70 years	116 (60.7)	58.0	60.0	50.0	70.6	66.7	58.8	
>71 years	53 (27.7)	35.5	23.4	34.4	20.6	20.0	32.4	
BCVA; LogMAR		0.328	0.44	0.383	0.433	0.481	0.443	
Sex								
Male	175 (91.6)	83.9	96.7	96.9	88.2	90.0	94.1	
Female	16 (8.4)	16.1	3.3	3.1	11.8	10.0	5.9	
Diagnosis group								0.390[2]
AMD & PCV	82 (42.9)	48.4	46.7	50	35.3	26.7	50.0	
PDR & DME & NV	109 (57.1)	51.6	53.3	50	64.7	73.3	50.0	
Lens status								0.303[2]
Phakic	101 (52.9)	67.7	53.3	50	55.9	40.0	50.0	
IOL	90 (47.1)	32.3	46.7	50	44.1	60.0	50.0	
Diabetes								0.150[3]
DM	116 (60.7)	51.6	66.7	56.3	61.8	80.0	50.0	
No DM	75 (39.3)	48.4	33.3	43.7	38.2	20.0	50.0	
Drug								0.736[2]
Bevacizumab	181 (94.7)	96.8	93.3	93.5	94.1	100	91.2	
Aflibercept	10 (5.3)	3.2	6.7	6.5	5.9	0.0	0.8	

SD=standard deviation; BCVA=best-corrected visual acuity; AMD=age-related macular degeneration; PCV=polypoidal choroidal vasculopathy; PDR=proliferative diabetic retinopathy; DME=diabetic macular edema; NV=neovascularization; IOL=intraocular lens; DM=diabetes mellitus; SN=superonasal; S=superior; ST=superotemporal; IT=inferotemporal; I=inferior; IN=inferonasal

[1] Kruskal-Wallis test, [2] Fisher's exact test, [3] Pearson's chi-square test

The overall median (interquartile range, IQR) pain score across all groups was 2 (2). When stratified by injection site, the median pain scores were as follows: SN 3 (3), S 2 (2), ST 2 (2), IT 2 (2), I 2 (2), and IN 1 (2). The IN group had the lowest pain scores, whereas the SN group had the highest (Figure 3). Differences in pain scores among the six groups were analyzed using the Kruskal-Wallis test, which demonstrated a statistically significant difference. Post hoc pairwise comparisons were performed using Dunn's test with Bonferroni correction. Statistically significant differences were observed between the IN and S sites (adjusted p=0.021) and between the IN and SN sites (adjusted p<0.001), at a significance level of 0.05. Further analysis comparing the upper and lower halves of the eye showed significantly higher pain scores in the upper half, as determined by the Mann-Whitney U test (p<0.001). The mean rank was 110.34 (sum of ranks=10,262.00) for the S group and 82.39 (sum of ranks=8,074.00) for the I group.

The distribution of patients with pain scores <4 (zero to mild pain) and ≥4 (moderate pain, severe pain, and worst pain) according to injection site was presented in Table 2. There was a statistically significant difference in pain distribution across injection sites (Pearson's chi-square test, p=0.029).

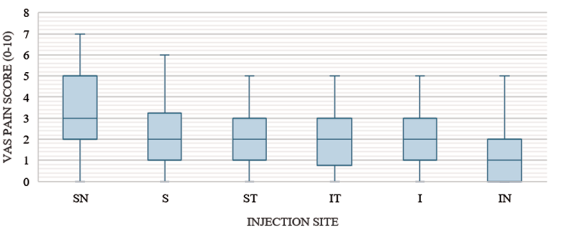

Figure 3. The median pain score with interquartile range (IQR), categorized by injection site. Boxplot showing VAS pain scores by injection site, the central line represents 50th percentile. Bottom of each box represent 25th percentile, top of each box represent75th percentile. The interquartile range is the difference between the 75th and 25th quartiles. The bottom whisker below the box is the minimum value and the per whisker above the box is the minimum value up. The median pain score was highest at the superior nasal (SN) site and lowest at the inferior nasal (IN) site. Differences among groups were statistically significant (Kruskal-Wallis test, p<0.05).

Table 2. Distribution of patients by pain severity category according to injection site

Pain category	Total n (%)	Injection site (%)					
		SN	S	ST	IT	I	IN
<4 (no to mild pain)	148 (77.5)	18 (56.3)	24 (75.0)	27 (84.4)	26 (81.3)	25 (80.6)	28 (87.5)
≥4 (moderate to worst pain)	43 (22.5)	14 (43.7)	8 (25.0)	5 (15.6)	6 (18.7)	6 (19.4)	4 (12.5)

SN=superonasal; S=superior; ST=superotemporal; IT=inferotemporal; I=inferior; IN=inferonasal

Table 3. Mean and mean rank of pain and anxiety for each injection site

	Injection site						p-value[1]
	SN	S	ST	IT	I	IN	
Pain							<0.001
Median (IQR)	3 (3)	2 (2)	2 (2)	2 (2)	2 (2)	1 (2)	
Mean rank	125.35	108.93	97.13	88.15	94.95	65.54	
Anxiety							0.089
Median (IQR)	1 (5)	0 (2)	0 (1)	0 (2)	0 (4)	0 (1)	
Mean rank	115.6	94.4	86.64	91.14	93.57	83.4	

IQR=interquartile range; SN=superonasal; S=superior; ST=superotemporal; IT=inferotemporal; I=inferior; IN=inferonasal
[1] Kruskal-Wallis test

Table 4. Number of patients experiencing various visual perceptions during injection

Experience	Total n (%)	Injection site; n (%)					
		SN	S	ST	IT	I	IN
Water	91 (47.6)	21 (65.6)	20 (62.5)	15 (46.8)	9 (28.1)	16 (51.6)	10 (31.2)
Needle	24 (12.6)	4 (12.5)	4 (12.5)	4 (12.5)	6 (18.7)	3 (10.0)	3 (9.3)
Light	62 (32.5)	6 (18.7)	3 (9.1)	11 (34.4)	15 (46.9)	9 (30.0)	18 (56.2)
Others	14 (7.3)	1 (3.0)	5 (16.0)	2 (6.2)	2 (6.2)	3 (9.6)	1 (3.0)

IQR=interquartile range; SN=superonasal; S=superior; ST=superotemporal; IT=inferotemporal; I=inferior; IN=inferonasal

Pairwise comparison showed a significant difference between the SN and IN groups. The proportion of patients experiencing moderate to severe pain was highest at the SN site (Table 2). No patient reported the worst pain in this study.

For the anxiety VAS scores, there was no statistically significant difference among the injection sites, as shown in Table 3. Pain scores were positively correlated with anxiety scores, with a low correlation observed (Spearman's rank correlation coefficient=0.399, p<0.01).

Regarding patient-reported experiences during the injection, 47.6% reported seeing swirling water, 32.5% reported seeing lights, 12.6% reported seeing the shadow of a needle, and 7.3% reported other visual phenomena (such as the doctor's face). These experiences, categorized by injection site, are presented in Table 4.

In this study, no statistically significant differences were found when comparing the pain scores between diabetic and non-diabetic groups (p=0.294), between the diseases leading to the injection groups (p=0.583), between the lens conditions (p=0.364), and between two types of medications used for the injection (p=0.307), as shown in Table 5.

Table 5. Mean rank pain scores by clinical subgroups

Variable	Category	n	Mean rank	p-value
Diabetes	DM	116	99.31	0.294[a]
	Non-DM	75	90.88	
Lens status	Phakic	101	97.78	0.364[a]
	IOL	90	90.69	
Diagnosis	AMD & PCV	82	93.52	0.583[a]
	PDR & DME & NV	109	97.87	
Medication	Bevacizumab	181	96.94	0.307[a]
	Aflibercept	10	78.95	

DM=diabetes mellitus; IOL=intraocular lens; AMD=age-related macular degeneration; PCV=polypoidal choroidal vasculopathy; PDR=proliferative diabetic retinopathy; DME=diabetic macular edema; NV=neovascularization
(a) Mann-Whitney U test

This study was conducted using a cross-sectional design; therefore, continuous patient follow-up was

not required. Data from one patient were unavailable because the patient left the clinic immediately after the injection. Additionally, anxiety scores were not obtained from five patients due to their inability to report anxiety levels. These cases were recorded as "not applicable". Despite these missing data, the final sample size exceeded the minimum required; therefore, the missing data were not included in the statistical analysis.

Discussion

Intravitreal injections are commonly performed at regular intervals, such as monthly or every two months, to treat various retinal diseases. Minimizing patient discomfort during these procedures is important, as it supports better adherence to follow-up and ultimately improves treatment outcomes. Previous studies have explored the relationship between pain during injections and various factors, such as the type of anesthetic used, injection site, type of medication, and needle size[1,3,12,19] in an effort to determine methods that minimize patient discomfort.

In this study, the median pain score was 2 (IQR 2), which is lower than that reported in previous studies, including Blaha et al. (mean 4.1)[20], Karimi et al. (mean 2.8)[10], and Tewari et al. (mean 3.2)[12]. Factors that may contribute to this difference include sex and age. In this study, 91.6% of the patients were male, due to the hospital's service policy, which primarily serves priests. Previous studies, such as Karimi et al.[10], found that males generally report lower average pain scores than females. Additionally, this study included participants over the age of 70, accounting for 27.7% of the sample. Previous research by He et al.[21] found that individuals over 70 years old have reduced corneal nerve density. The results of this study are consistent with the hypothesis that each injection site results in different levels of pain. Specifically, the site with the least pain was IN, which differed significantly from the site with the most pain, SN. Post hoc pairwise comparisons using Dunn's test with Bonferroni correction demonstrated that pain scores at the IN site were significantly lower than those at the SN site (adjusted $p<0.001$. Compared to a previous study by Moisseiev et al.[11], which involved 218 patients, no significant differences in pain or experience were found across all bevacizumab injection sites. However, their results suggested that injections in the lower half of the eye tended to cause slightly less pain. This differs from the study conducted by Karimi et al.[10], which examined 1,004 patients and categorized the injection sites into four positions based on the 90-degree quadrants of the eye. The findings indicated a statistically significant difference between each injection site and sex, with the least painful site being the SN quadrant and the most painful site being the ST quadrant. Additionally, females reported more pain than males[10].

When considered from a clinical perspective, the approximately 2-point difference on a 0-10 pain scale in this study supports that the IN site is both statistically and clinically less painful than the SN site[22].

All previous studies have categorized the injection sites into four quadrants: ST, SN, IT, and IN, with each zone consisting of areas measured at 90 degrees from the center of the cornea. In contrast, this study refines the injection zones into six areas, with each position encompassing 60 degrees from the center of the cornea. Accordingly, the paralimbal region was divided into six sectors rather than four quadrants to provide greater anatomical resolution and better reflect variations in scleral and conjunctival nerve distribution, allowing more precise localization of injection sites and improved detection of site-specific differences in pain perception.

This study found that the lowest pain scores were observed at the IN and IT sites; moreover, injections in the lower half of the eye were less painful than those in the upper half. This may be explained by the distribution of topical anesthetic drop, which tends to accumulate in the inferior conjunctival sac and drain via the nasolacrimal system. In some cases, gravitational flow and eyelid anatomy may facilitate pooling of the anesthetic drop toward the inferior and lateral aspects of the eye, resulting in higher local anesthetic exposure in the IN and IT regions compared with other areas. This pattern was observed despite the protocol requiring patients to move the eye in a circular manner during anesthetic instillation.

In this study, 22.9% of patients experienced moderate or higher pain (score ≥ 4). Among these patients, 60.5% received injections in the upper half of the eye. The mean rank of anxiety was slightly lower for injections in the lower half compared with the upper half; however, this difference was not statistically significant ($p=0.136$). Spearman's correlation analysis demonstrated a low positive correlation between anxiety and pain scores ($p<0.01$). This finding is consistent with Chen et al.[23], who reported that pre-injection anxiety is positively correlated with pain during intravitreal injection.

Potential confounding factors were addressed through several methodological approaches. Randomization was used to allocate participants to injection site groups, facilitating the distribution of

both known and unknown confounders. Baseline demographic and clinical characteristics, including age, sex, diagnosis, lens status, diabetes status, and type of medication, were comparable across groups, suggesting minimal confounding from measured variables. In addition, standardized procedures were applied to all participants, including the same anesthetic regimen, injection technique, and needle size, to reduce procedure-related variability. Masking of outcome assessors further minimized measurement bias. Nevertheless, residual confounding cannot be entirely excluded, particularly from subjective factors such as individual pain perception and anxiety, as pain and anxiety were assessed using VAS, which rely on self-reporting and are subject to individual variability. In addition, complete blinding of participants was not feasible, as patients were required to fixate in specific directions during the injection procedure.

This study has several limitations. It was conducted at a single center with a predominantly male population, which may limit generalizability. Although the distribution of pain-sensing nerves in the sclera and conjunctiva is not known to differ by sex, previous studies have reported higher pain scores in females. In addition, two anti-VEGF agents, aflibercept and bevacizumab, were used. However, given their similar pH ranges (aflibercept pH 6.05, bevacizumab pH 5.9-6.2), a clinically significant difference in pain related to pH is unlikely.

No severe complications, other than sub-conjunctival hemorrhage, were observed following intravitreal injections in this study.

Conclusion

This study demonstrated that pain scores from intravitreal injections differed significantly according to injection site. Anxiety during the injection was significantly correlated with the pain experienced. In addition, patients receiving injections in the lower half of the eye reported lower pain scores than those in the upper half, with the IN site being the least painful.

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Author Contributions

The author meets the International Committee of Medical Journal Editors (ICMJE) authorship criteria. AN: Conceptualization, methodology, investigation, data curation, formal analysis, interpretation of data, writing-original draft preparation, writing-review and editing, supervision, and final approval of the manuscript.

Clinical Trial Registration

This study was registered with the Thai Clinical Trials Registry (TCTR20210719007).

Conflicts of Interest

The author declares no conflict of interest.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. Data containing personal identifiers are not publicly available in order to protect participant confidentiality.

Ethics Approval and Consent to Participate

This study was approved by the Human Research Ethics Committee of Priest Hospital, Department of Medical Services, Thailand (Approval No. 20/2563). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study.

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Use of Artificial Intelligence

ChatGPT (OpenAI, GPT-5.5) was used solely for English language editing and grammatical refinement during manuscript preparation. The author reviewed and verified all generated text and takes full responsibility for the accuracy, integrity, and originality of the manuscript. Artificial intelligence tools were not involved in study design, data collection, data analysis, interpretation of results, or scientific decision-making.

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