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Peribulbar versus topical anesthesia for pain during panretinal photocoagulation in proliferative diabetic retinopathy: a randomized controlled trial

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Abstract

Purpose

To compare pain control with peribulbar anesthesia versus topical tetracaine alone during panretinal photocoagulation (PRP) in patients with proliferative diabetic retinopathy (PDR), and to assess its safety.

Methods

In this single-center, prospective, within-person, randomized, controlled superiority trial at a tertiary eye hospital in Mexico City, adults with PDR scheduled for their first PRP session were enrolled. Using block randomization, one eye of each patient was assigned to peribulbar anesthesia (1.5 mL of 2% lidocaine and 1.5 mL 0.5% bupivacaine) and the fellow eye to topical 5% tetracaine with a sham injection; both eyes were treated in the same session. Patients were masked to allocation; the outcome assessor was not. The primary outcome was pain on the numerical rating scale (NRS) at 1, 5, 10, and 15 minutes during PRP. Secondary outcomes were heart rate, respiratory rate, blood pressure and SpO2 at the same time points, and the presence of adverse events.

Results

Fifty patients (100 eyes) were randomized, and all 50 eyes in each group were analyzed. Peribulbar anesthesia produced significantly lower median pain scores: 3 vs. 4.5 at 1 minute ($P = 0.01$), 4 vs. 6 at 5 minutes ($P = 0.01$), and 6 vs. 7.5 at 15 minutes ($P < 0.01$), but not at 10 minutes (6 vs 7; P = 0.05). Additionally, respiratory rate dispersion was lower in this group at 15 minutes: 18 (16–18) vs. 18 (18–20) ($P < 0.01$). Heart rate, blood pressure, and SpO2 did not differ between groups. No anesthesia-related complications occurred; two patients had hypotension and one vomited during PRP of the control eye.

Conclusion

Our findings suggest that peribulbar anesthesia using lidocaine and bupivacaine significantly reduced pain during PRP compared with topical anesthesia alone, with no anesthesia-related complications observed. Trial registration: ClinicalTrials.gov NCT07640256, 2026-06-01, retrospectively registered. Funding: none.

Background

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus (DM), affecting 30–40% of patients, and is the leading cause of vision loss among the working-age population [1–4]. In Mexico, DM affects about 13.6 million adults, and DR has an estimated prevalence of 31.5% among them [1, 5]. Proliferative diabetic retinopathy (PDR) affects approximately 7% of all patients with DM [3, 6]. Since the 1970s, panretinal photocoagulation (PRP) has been the standard treatment for PDR, supported by evidence from the Diabetic Retinopathy Study (DRS), which showed that PRP reduces the risk of severe visual loss by more than 50% [7]. Subsequently, the Early Treatment Diabetic Retinopathy Study (ETDRS) confirmed the benefit of PRP for high-risk PDR and suggested considering earlier treatment in severe nonproliferative diabetic retinopathy [8]. Although newer treatments such as intravitreal anti-angiogenic drugs have shown slightly better visual outcomes than PRP, the latter remains essential. Studies suggest that combining these drugs with PRP is as effective and offers additional benefits, such as lower costs and fewer required ophthalmic visits and injections, thereby improving treatment adherence [9–11].

However, PRP is painful, with studies reporting pain in more than 70% of patients [12]. This discomfort can lead to fewer burns and suboptimal treatment, increasing the risk of vision loss [13, 14]. Topical anesthetics, such as lidocaine and tetracaine, are commonly used in ophthalmic procedures but often provide insufficient pain relief during PRP [15, 16]. Pain during PRP is thought to arise from thermal stimulation of the choroid and of the long and short ciliary nerves that run through the suprachoroidal space [17]; these nerves lie beyond the reach of topical anesthetics but can be blocked by local anesthetic that spreads into the intraconal space after a peribulbar injection [18]. Although many studies have evaluated less invasive strategies such as topical or oral analgesics, their effectiveness in PRP pain management has been limited. A network meta-analysis by Arruda et al. of 15 randomized controlled trials and four crossover trials found that only peribulbar 2% lidocaine significantly reduced pain compared with placebo. Other

interventions, including NSAIDs, topical anesthetics, pregabalin, opioids, and acetaminophen, did not yield statistically significant results [16]. In a randomized trial by Wu et al., peribulbar 2% lidocaine was the only intervention that significantly lowered pain scores compared with the control group. In this study, both systolic and diastolic blood pressure increased significantly after laser treatment, but patients treated with peribulbar anesthesia exhibited the smallest post-PRP increase among all groups [12]. Additional studies comparing peribulbar anesthesia with topical agents confirmed superior pain control, particularly during the PRP session, though not at the 48-hour follow-up [20]. Subconjunctival lidocaine has also demonstrated efficacy in lowering pain scores, reducing session duration, and increasing the number of laser burns applied [21, 22]. However, it has not been compared directly with peribulbar anesthesia. Most of these studies relied solely on subjective pain ratings. Because pain perception is influenced by genetic, psychological, cultural, and social factors [23], sympathetic responses to pain, such as changes in heart rate, respiratory rate, blood pressure, and oxygen saturation, may provide a useful objective complement [24].

The potential benefits of regional anesthesia must be weighed against its risks. Retrobulbar blocks are highly effective due to their rapid onset and complete akinesia and analgesia, but they carry risks such as retrobulbar hemorrhage, optic nerve injury, and cardiorespiratory complications [19, 25, 26]. Peribulbar anesthesia achieves a similar efficacy through communication between the extraconal and intraconal spaces, with a lower risk of serious complications such as globe perforation [18]. Although complications such as ptosis, optic nerve injury, brainstem anesthesia, and retrobulbar hemorrhage have been reported with peribulbar blocks, these are rare and often related to technical errors, such as unintended retrobulbar placement [18, 27]. Combining short-acting lidocaine with long-acting bupivacaine may optimize both rapid onset and prolonged anesthesia [25], but previous PRP trials have evaluated peribulbar lidocaine alone, and the combination has not been assessed using both subjective and physiological measures of pain. A within-person design controls for the inter-patient variability in pain perception.

The objective of this randomized trial was to determine whether peribulbar anesthesia with 2% lidocaine and 0.5% bupivacaine reduces pain during PRP compared with topical 5% tetracaine alone, the standard of care at our institution, in patients with PDR. The primary outcome was pain intensity on the numerical rating scale (NRS) at the 1-, 5-, 10-, and 15-minute marks while undergoing PRP application in each eye. Secondary outcomes were heart rate, respiratory rate, blood pressure, and oxygen saturation during PRP, and safety, assessed as ocular and systemic adverse events. We hypothesized that peribulbar anesthesia would be superior to topical anesthesia.

Methods

Trial design

This was a single-center, prospective, within-person (fellow-eye) randomized controlled superiority trial with a 1:1 allocation ratio. The unit of randomization was the eye: one eye of each participant was randomly assigned to peribulbar anesthesia and the fellow eye to topical anesthesia with a sham injection, and both eyes were treated in the same session. The Institutional Review Board of Asociación Para Evitar la Ceguera en México, I.A.P., approved the study under approval number RE-23-05. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, as well as with the regulation of health research under the General Health Law and the Mexican policy for the execution of research projects in humans (NOM-012-SSA3-2012). Written informed consent was obtained from all participants. This trial adheres to the CONSORT 2025 statement guidelines.

The trial was registered retrospectively on ClinicalTrials.gov (NCT07640256; https://clinicaltrials.gov/study/NCT07640256) on 1 June 2026. The trial protocol and statistical analysis plan are available as supplementary file “Study Protocol and Statistical Analysis Plan”. Trial results have been submitted to the registry and are pending quality-control review.

Changes to the trial protocol

There were no changes to the trial protocol after the trial commenced.

Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of this trial.

Setting and participants

The trial was conducted at a single site, the Department of Retina and Vitreous of the Asociación Para Evitar la Ceguera en México, I.A.P., a tertiary-care ophthalmology hospital in Mexico City, Mexico. Consecutive patients referred for their first PRP session in the retina clinic were recruited between July 2023 and June 2024.

Adults aged 18 years or older with bilateral proliferative diabetic retinopathy who were scheduled to undergo their first PRP session and were able to maintain the required posture at the slit lamp throughout the procedure were included. Exclusion criteria were a history of phobic anxiety disorder related to needles or injections; known allergies or hypersensitivity to lidocaine, bupivacaine, or tetracaine; use of analgesics within 24 hours prior to treatment; media opacities that precluded adequate PRP; and cognitive or motor impairments that could hinder effective communication of pain.

All peribulbar and sham injections were performed by one retina fellow with 4 years of experience in regional ocular anesthesia, and all PRP sessions were performed by one retina fellow with 4 years of experience in PRP administration.

Interventions

Topical 5% tetracaine is the standard anesthesia for PRP at our institution. Both eyes of each participant received a single drop of topical 5% tetracaine, followed by a two-minute observation period.

In the eye assigned to peribulbar anesthesia, a mixture of 1.5 mL of 0.5% bupivacaine and 1.5 mL of 2% lidocaine was prepared in a 3 mL syringe. The peribulbar injection was administered using a 25G needle inserted horizontally through the inferior palpebral conjunctiva, directed axially over the infraorbital rim, and then angled upward to deliver the anesthetic into the orbit. After a five-minute latency period, the eyes assigned to the control group received a sham injection, consisting of a 3 mL syringe filled with normal saline, without a needle, used to simulate insertion by applying pressure at the same site as the peribulbar injection.

Five minutes after the sham injection, the participants underwent PRP using a double-frequency Nd:YAG 532-nm laser (PUREPOINT®, ALCON) following the standard PRP protocol, starting with the right eye always, regardless of allocation. Each eye received between 1,200 and 1,500 burns, with spot sizes ranging from 200 µm to 500 µm. Pulse durations were set between 100–200 ms. Power was titrated before initiating treatment to obtain a gray-whitish burn, and adjusted throughout the procedure in order to avoid under- or over-treatment. A 10-minute interval was provided between the right- and left-eye PRP sessions.

No systemic analgesics, sedatives or other concomitant treatments were administered before or during the procedure, and no rescue analgesia was permitted. All procedures followed a standardized written protocol and were supervised by a resident, who served as the outcome assessor.

Outcomes

The primary outcome was patient perception of pain during PRP administration in each eye, measured using the numerical rating scale (NRS). The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends the use of this scale due to its simplicity, patient preference, and high completion rates, especially among elderly individuals. The NRS measures pain intensity on a scale of 0 to 10, where 0 corresponds to the absence of pain and 10 represents the worst pain imaginable [28]. Pain was self-reported by the participant and recorded by a resident who served as the outcome assessor at 1, 5, 10, and 15 minutes of PRP in each eye. The primary analysis was the NRS score at each time point, summarized as the median (IQR) for each group. The proportion of eyes with moderate to very severe pain (NRS score ≥ 4) was also recorded.

Secondary outcomes were heart rate, respiratory rate, oxygen saturation (SpO_2), and blood pressure measured with the Aquarius Vital Sign Monitor (Shenzhen Northern Meditec Limited, Shenzhen, China) at baseline before PRP, and at the 1-, 5-, 10-, and 15-minute marks while undergoing PRP application in each eye, summarized as the median (IQR) or mean (SD) for each group at each time point.

Harms

Adverse events were assessed systematically by the resident who served as the outcome assessor, who was not masked to allocation, from the time of injection until the end of a 45-minute observation period after PRP. Ocular adverse events assessed included chemosis, retrobulbar hemorrhage, ptosis, globe perforation, and extraocular movements were evaluated after the peribulbar injection. Systemic adverse events assessed included hypersensitivity reactions, hypotension, defined as systolic blood pressure (BP) below 90 mmHg or diastolic BP below 60 mmHg, bradycardia, defined as a heart rate lower than 60 beats per minute, nausea, and vomiting. Events occurring after discharge were not recorded. Because both eyes were treated in the same session, systemic adverse events were attributed to the eye, and therefore the intervention, undergoing treatment at the time of onset.

Sample Size

The sample size was estimated using the formula for the comparison of two means. Data previously published by Zakrzewski et al. [29] were used as a reference, which report a mean pain score on the visual analog scale of 25.7 ± 19.9 versus 41.3 ± 31.0 between the treatment and control groups. This study reported a difference of 15 points on the visual analog scale. Assuming an α of 0.05 and a power of 80% (β = 0.20), and using Fleiss's formula, a minimum of 44 eyes was required to find statistically significant differences. An estimated loss of 20% during follow-up was anticipated, so the calculation was adjusted to 53. Recruitment ended after 50 patients had been enrolled, at the end of the planned recruitment period (June 2024); as no participants were lost, this exceeded the minimum of 44 required.

No interim analyses were planned or performed, and no stopping guidelines were used.

Randomization and allocation concealment

Randomization was performed using balanced (permuted) blocks of four, without stratification, to determine which eye of each participant received peribulbar anesthesia. Based on the calculated sample size of 44 patients per group, 11 blocks were created, each consisting of one of the six possible permutations of the two allocations (AABB, ABAB, ABBA, BAAB, BABA, and BBAA), where A indicated that the right eye received peribulbar anesthesia and B that the left eye received it, with the fellow eye assigned to the control group. The blocks were numbered randomly from 1 to 11 by the primary investigator using a computer random number generator, and participants were assigned sequentially according to the order of the blocks. Participants were enrolled by a research fellow who had no access to the allocation sequence. The allocation sequence was kept by the primary investigator, who was not involved in enrollment, and who informed the retina fellow performing the injections of each participant's allocation only after the participant had been enrolled, immediately before the procedure. After the injections, PRP was performed by a second retina fellow who had not observed them.

Masking

Participants were masked to the allocation of their eyes. The fellow who performed the injections and the evaluator who recorded the NRS scores and vital signs were not masked, whereas the fellow who performed PRP, who was not present during the injections, and the data analyst were masked. Masking of participants was attempted by applying the same topical anesthetic to both eyes and by performing a sham injection at the same site with a needleless syringe.

Statistical analysis

All randomized eyes were analyzed in the group to which they were allocated. The Shapiro-Wilk test was used to assess normality. Descriptive statistics were used to analyze the baseline population characteristics. Data from normally distributed variables is presented as mean (SD), and data from non-normally distributed variables as median (IQR). The grouped quantitative variables had a normal distribution; however, when the treatment groups were separated, all the variables had a non-normal distribution. Repeated measurements of related groups with a non-normal distribution were analyzed using the Friedman test. Group comparisons of unrelated groups with a non-normal distribution were performed using the Mann-Whitney U test. The two groups were treated as independent samples, as each eye received a different treatment. The measurements of vital signs, NRS score, and laser parameters were registered in a coded Excel spreadsheet (Microsoft Corporation), and statistical analysis was performed using SPSS software (version 29.0, IBM, Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant. There were no missing data, and no subgroup or sensitivity analyses were performed.

Results

Participant flow and recruitment

Between July 2023 and June 2024, 505 patients were assessed for eligibility, of whom 455 were excluded: 306 did not meet the inclusion criteria, 67 declined to participate, and 82 were excluded for other reasons (48 had media opacities that precluded adequate PRP, 25 had uses of analgesics within 24 hours before treatment, and 9 had hypersensitivity to lidocaine. A total of 100 eyes of 50 patients with type 2 diabetes mellitus (DM) and proliferative diabetic retinopathy (PDR) were randomized: one eye of each patient to peribulbar anesthesia (n = 50 eyes) and the fellow eye to topical anesthesia with a sham injection (n = 50 eyes) (Fig. 1). All eyes received the allocated intervention, and all participants completed the PRP sessions and the 45-minute observation period. No participants were lost to follow-up or excluded after randomization, and all 50 eyes in each group were included in the analysis of the primary outcome. Recruitment ended in June 2024, at the end of the planned recruitment period.

Delivery of the interventions

All peribulbar and sham injections were performed by a retina fellow, and all PRP sessions were performed by a separate retina fellow. The interventions were administered to all participants. Laser power had to be reduced because of intolerable pain in one eye (2%) in the peribulbar group and three eyes (6%) in the control group. No systemic analgesics, sedatives, or other concomitant treatments were administered before or during the procedure.

Baseline characteristics

Baseline characteristics are summarized in Table 1 and include mean (SD) diabetes duration (18 [6.4] years), baseline heart rate (78.8 [10.3] beats per minute), systolic blood pressure (141.4 [25.6] mmHg), diastolic blood pressure (75.8 [12.5] mmHg), and respiratory rate (16, IQR 16–18 breaths per minute). All eyes had untreated PDR prior to the study.

Table 1
Baseline characteristics in patients undergoing panretinal photocoagulation

n = 50 (100 eyes)	**Total**
Age, years, mean (SD)	59.2 (9.7)
Gender, female, n (%)	24 (48)
Diabetes duration, years, mean (SD)	18.0 (6.4)
Arterial hypertension, present, n(%)	32 (64)
Duration of hypertension, years, median (IQR)	3 (0–15)
Baseline capillary blood glucose level, mg/dL, median (IQR)	178 (130–218)
Baseline heart rate, bpm, mean (SD)	78.8 (10.3)
Baseline respiratory rate, breaths/min, median (IQR)	16 (16–18)
Systolic BP, mmHg, mean (SD)	141.4 (25.6)
Diastolic BP, mmHg, mean (SD)	75.8 (12.5)
Baseline SpO_2, %, median (IQR)	95 (93–96)
Baseline NRS, points, median (IQR)	0 (0–0)

SD = standard deviation; IQR = interquartile range; bpm = beats per minute; BP = blood pressure; SpO_2 = oxygen saturation; NRS = numerical rating scale.

Primary outcome

NRS scores, heart rate, respiratory rate, blood pressure, and SpO_2 at each time point are shown for each group in Tables 2 and 3, and the between-group comparisons in Table 4. All 50 eyes in each group had NRS data at every time point. Most participants reported

experiencing pain during PRP (49 out of 50 eyes experienced some degree of pain in both groups). There was a statistically significant difference in median pain scores between the groups at most time points: 3 vs. 4.5 at the 1-minute mark ($P = 0.01$); 4 vs. 6 at 5 minutes ($P = 0.01$); and 6 vs. 7.5 at 15 minutes ($P < 0.01$). Notably, 46 eyes (92%) in the control group reported moderate to very severe pain (NRS score ≥ 4), compared to 37 eyes (74%) in the treatment group (risk difference, − 18 percentage points; 95% CI, − 32 to − 4; relative risk, 0.80; 95% CI, 0.67 to 0.97).

Table 2
Comparing clinical parameters in response to pain during panretinal photocoagulation in the treatment group

Parameter	1 minute	5 minutes	10 minutes	15 minutes	*P* value
HR, bpm, median (IQR)	78 (70–87)	79 (72–89)	80 (70–90)	80 (71–87)	0.57
RR, breaths/min, median (IQR)	18 (16–18)	18 (16–18)	18 (16–20)	18 (16–18)	0.04*
Systolic BP, mmHg, mean (SD)	156.3 (28.2)	155.0 (25.2)	154.8 (25.0)	149.8 (25.9)	0.67
Diastolic BP, mmHg, mean (SD)	82.2 (12.8)	82.0 (12.0)	83.0 (12.3)	79.2 (15.7)	0.66
SpO_2, %, median (IQR)	95 (93–96)	95 (94–96)	95 (94–97)	95 (95–96)	< 0.01*
NRS, points, median (IQR)	3 (1–5)	4 (2–7)	6 (3–8)	6 (3–7)	< 0.01*

Table 4
Comparing clinical parameters in response to pain during panretinal photocoagulation among treatment and control groups

Parameter	1 minute			5 minutes			10 minutes			15 minutes		
	T	C	*P* value	T	C	*P* value	T	C	*P* value	T	C	*P* value
HR, bpm, median (IQR)	78.0 (70.0–87.0)	79.0 (69.0–90.0)	0.77	79.0 (72.0–89.0)	78.0 (69.0–91.0)	0.94	80.0 (70.0–90.0)	79.5 (71.0–91.0)	0.76	80.0 (71.0–87.0)	77.5 (70.0–92.0)	0.87
RR, breaths/min, median (IQR)	18 (16–18)	18 (16–18)	0.09	18 (16–18)	18 (17–20)	0.051	18 (16–20)	18 (18–20)	0.06	18 (16–18)	18 (18–20)	< 0.01*
Systolic BP, mmHg, mean (SD)	156.3 (28.2)	153.0 (23.3)	0.12	155.0 (25.2)	153.4 (25.4)	0.87	154.8 (25.0)	155.4 (25.0)	0.82	149.8 (25.9)	149.0 (26.6)	0.83
Diastolic BP, mmHg, mean (SD)	82.2 (12.8)	80.2 (13.2)	0.77	82.0 (12.0)	82.4 (11.6)	0.98	83.0 (12.3)	83.3 (12.5)	0.86	79.2 (15.7)	81.4 (14.4)	0.96
SpO_2, %, median (IQR)	95 (93–96)	95 (94–96)	0.37	95 (94–96)	95 (94–96)	0.72	95 (94–97)	95 (94–96)	0.88	95 (95–96)	95 (94–96)	0.60
NRS, points, median (IQR)	3 (1–5)	4.5 (2–7)	0.01*	4 (2–7)	6 (3–8)	0.01*	6 (3–8)	7 (5–8)	0.05	6 (3–7)	7.5 (5–9)	< 0.01*
T = treatment group; C = control group; HR = heart rate; bpm = beats per minute; IQR = interquartile range; RR = respiratory rate; BP = blood pressure; SD = standard deviation; SpO_2 = oxygen saturation; NRS = numerical rating scale.												
*P < 0.05.												

HR = heart rate; bpm = beats per minute; IQR = interquartile range; RR = respiratory rate; BP = blood pressure; SD = standard deviation; SpO_2 = oxygen saturation; NRS = numerical rating scale.

*P < 0.05.

Table 3
Comparing clinical parameters in response to pain during panretinal photocoagulation in the control group

Parameter	1 minute	5 minutes	10 minutes	15 minutes	*P* value
HR, bpm, mean (SD)	79.5 (12.6)	79.3 (12.9)	80.0 (13.2)	79.6 (13.1)	0.99
RR, breaths/min, median (IQR)	18 (16–18)	18 (17–20)	18 (18–20)	18 (18–20)	< 0.01*
Systolic BP, mmHg, mean (SD)	153.0 (23.3)	153.4 (25.4)	155.4 (25.0)	149 (26.6)	0.66
Diastolic BP, mmHg, mean (SD)	80.2 (13.2)	82.4 (11.6)	83.3 (12.5)	81.4 (14.4)	0.67
SpO_2, %, median (IQR)	95 (94–96)	95 (94–96)	95 (94–96)	95 (94–96)	0.03*
NRS, points, median (IQR)	4.5 (2–7)	6 (3–8)	7 (5–8)	7.5 (5–9)	< 0.01*

HR = heart rate; bpm = beats per minute; SD = standard deviation; RR = respiratory rate; IQR = interquartile range; BP = blood pressure; SpO_2 = oxygen saturation; NRS = numerical rating scale.

*P < 0.05.

[Insert Table 4 here]

Secondary outcomes

Heart rate, blood pressure, and SpO_2 did not differ between groups at any time point (Table 4). The mean (SD) systolic blood pressure at 15 minutes was similar in both groups: 149.8 (25.9) mmHg in the treatment group and 149 (26.6) mmHg in the control group. The median SpO_2 also remained comparable at 95% (IQR 95–96%) in the treatment group and 95% (IQR 94–96%) in the control group. The median respiratory rate was 18 breaths per minute in both groups at all time points; at 15 minutes, its distribution differed between groups (IQR 16–18 in the peribulbar group vs 18–20 in the control group; $P < 0.01$), whereas the differences at earlier time points were not statistically significant.

Harms

No anesthesia-related complications, such as hypersensitivity reactions, globe injury, or hemorrhage from peribulbar injections, were observed after the 50 peribulbar injections, and no PRP-related adverse events were observed during the observation period. Two patients (4%) experienced hypotension and one patient (2%) vomited during PRP of the control eye; all events resolved with observation. No participants withdrew because of adverse events.

Ancillary analyses

No subgroup or sensitivity analyses were performed.

Discussion

Since PRP remains a cornerstone treatment for PDR, effective pain control is essential to improve treatment completion [19, 30]. In this randomized trial, peribulbar anesthesia using a 50:50 mixture of 2% lidocaine and 0.5% bupivacaine produced significantly lower NRS pain scores compared with topical 5% tetracaine alone at 1, 5, and 15 minutes of PRP; the difference at 10 minutes did not reach statistical significance (Table 4). Although some pain was still reported in the peribulbar group at all time points, the pain scores were consistently lower than those in the control group (Table 4).

These findings are consistent with previous evidence. In the meta-analysis by Arruda et al. [16] and the trial by Wu et al. [12], peribulbar lidocaine was the only intervention that significantly reduced pain during PRP; Raman et al. [20] likewise found better pain control with peribulbar anesthesia than with topical anesthesia during the session. Subconjunctival lidocaine has also been shown to reduce pain and allow more burns to be applied [21, 22]. However, more research is needed to directly compare this technique with peribulbar anesthesia.

The physiological measurements remain as an area of opportunity for future research. Wu et al. reported that patients who received peribulbar anesthesia had the smallest post-PRP increase in blood pressure [12], whereas we found no differences between groups

in heart rate, blood pressure, or SpO_2 at any time point. The only between-group difference was in respiratory rate dispersion at 15 minutes, with identical medians in both groups. However, since vital signs are influenced by factors other than pain, such as anxiety, and the treatment of the fellow eye in the same session could increase sensitivity to pain, these findings should be interpreted with caution. Standardized objective measures of pain are still needed.

No anesthesia-related complications, such as hypersensitivity reactions, globe injury, or hemorrhage, occurred after 50 peribulbar injections. Two patients experienced hypotension and one vomited during PRP of the control eye; these events resolved with observation and were likely autonomic responses to the pain induced by PRP administration. Serious complications of peribulbar blocks, such as globe perforation, optic nerve injury, and brainstem anesthesia, are rare and often related to technical errors [18, 26, 27], so a trial of this size cannot exclude them. The benefit of peribulbar anesthesia should therefore be weighed against the invasiveness and the small risk of serious complications that may occur with a peribulbar injection.

This study has several limitations. The evaluator administering the NRS scale was not blinded to treatment allocation. While all PRP sessions were completed, the laser power had to be reduced in one treatment eye and three control eyes due to intolerable pain. An additional limitation is that both eyes were treated on the same day, with PRP always initiated in the right eye. This fixed order may have influenced pain perception in the second eye, either by increasing sensitivity due to anticipation or decreasing it due to adaptation. The sample size was small, limiting the precision of the effect estimates. Finally, this was a single-center study of patients undergoing their first PRP session with a single-spot 532-nm laser, so the results may not apply to retreatment sessions, other laser systems, or other settings.

In conclusion, our findings suggest that peribulbar anesthesia using lidocaine and bupivacaine significantly reduced pain during PRP compared with topical anesthesia alone, with no anesthesia-related complications observed. Future research should focus on standardizing objective pain measurements using serial monitoring of vital signs while comparing various anesthetic techniques to determine the safest and most effective approach for improving outcomes in patients with PDR.

Declarations

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Competing interests: Gerardo García-Aguirre has received consultant and lecture honoraria from Alcon, Abbvie, Bayer, and Nidek; speaker, consultant, and lecture honoraria from Roche Genentech; and consultant honoraria from Astellas. The remaining authors declare no competing interests.

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Kingston Ureña-Wong, Salvador Hernandez-Castellanos, Rodolfo Rivas-Ruiz, Maria M. Solbes Gochicoa, Gerardo Garcia-Aguirre, and Ramses Rosales-Diaz. The first draft of the manuscript was written by Kingston Ureña-Wong, Gerardo Garcia-Aguirre, and Maria M. Solbes Gochicoa, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Asociacion Para Evitar la Ceguera en Mexico, I.A.P.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable

Data availability statement: De-identified individual participant data, a data dictionary, and the statistical analysis code will be available after publication from the corresponding author (jerry_gar_md@yahoo.com) upon reasonable request from qualified researchers, subject to a data-sharing agreement. The trial protocol and statistical analysis are available as supplementary file “Study Protocol and Statistical Analysis Plan” on ClinicalTrials.gov (Identifier: NCT07640256).

Use of artificial intelligence: The authors declare that AI-assisted tools (Claude, Anthropic) were used to support specific aspects of this work, including grammar and language editing, improving readability, formatting, and summarising author-written text. These tools were not used to generate the research question or study design, interpret the findings, or formulate the conclusions. All AI-assisted output was directed, reviewed, verified, and revised by the authors, who take full responsibility for the final manuscript.

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Figures

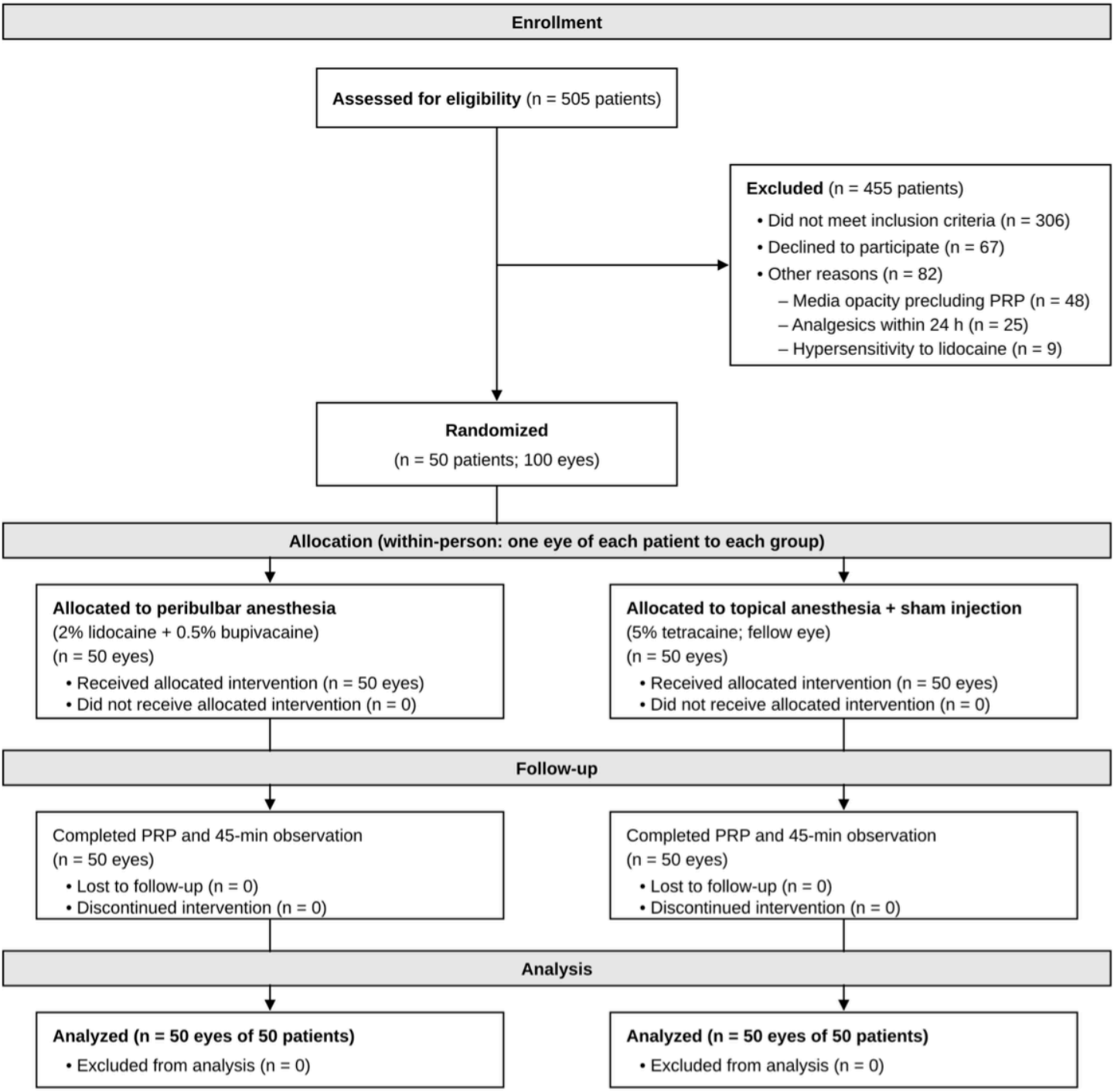

Figure 1

CONSORT flow diagram of our within-person randomized trial. Each patient contributed one eye to each group, so both groups include the same 50 patients. PRP = Panretinal photocoagulation