Safety and Efficacy of Peribulbar Anesthesia for Pain Management in Patients With Proliferative Diabetic Retinopathy During Panretinal Photocoagulation

Principal investigator: José Gerardo García-Aguirre

Department of Retina and Vitreous, Asociación para Evitar la Ceguera en México I.A.P. Vicente García Torres

San Lucas, Coyoacán, Ciudad de Mexico 04030, Mexico

Phone: +52 55 1084 1400

Email: jerry_gar_md@yahoo.com

Associated investigators:

Kingston Ureña-Wong

Rodolfo Rivas-Ruiz

Ramses Rosales-Diaz

Salvador Hernandez-Castellanos

Maria M. Solbes-Gochicoa

Institution: Asociación Para Evitar la Ceguera en México, I.A.P.

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Theoretical framework

Diabetic retinopathy (DR) is a microangiopathy caused by chronic hyperglycemia and is one of the most common complications of diabetes mellitus (DM), affecting 30-40% of patients.[1-3] Notably, some studies suggest that up to 75% of individuals with DM develop DR within 15 years of diagnosis.[4] DR is the leading cause of vision loss among the working-age population and was the fifth most common cause of avoidable blindness worldwide in 2020, following cataracts, glaucoma, refractive errors, and age-related macular degeneration.[5,6] By 2045, projections indicate that approximately 160 million people will develop some degree of DR.[7] In Mexico, DM affects about 13.6 million adults, with an expected increase to 19.9 million by 2050.[8] Among Mexican patients with DM, DR has an estimated prevalence of 31.5%[1]

DR is classified as either nonproliferative or proliferative, with the former further divided into mild, moderate, and severe stages.[9] The progression from mild nonproliferative diabetic retinopathy (NPDR) to severe NPDR or proliferative diabetic retinopathy (PDR) occurs in about 6% of cases.[10] PDR, characterized by neovascularization, vitreous hemorrhage, or preretinal hemorrhage, affects approximately 7% of all patients with DM.[3,11] Since the 1970s, panretinal photocoagulation (PRP) with argon laser 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%.[12] Subsequently, the Early Treatment Diabetic Retinopathy Study (ETDRS) confirmed the benefit of PRP for high-risk PDR, and suggested consideration of earlier treatment in severe NPDR.[13]

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.[14–16] However, PRP is often painful, with studies reporting pain in more than 70% of patients.[17] This discomfort can result in the application of fewer burns and suboptimal treatment, increasing the risk of vision loss.[18,19] Thus, effective pain management during PRP is critical for reducing patient discomfort, therefore improving patient adherence and treatment efficacy. Topical anesthetics, such as lidocaine and tetracaine, are commonly used in ophthalmic procedures but often provide insufficient pain relief during PRP.[20,21] Studies have shown that regional interventions, such as peribulbar injections or the combination of topical anesthesia with subconjunctival injections, reduce pain perception and improve procedural outcomes.[17,22-23]

Among invasive anesthesia techniques, retrobulbar blocks are highly effective due to their rapid onset and complete akinesia and analgesia,[24,25] but they carry risks such as retrobulbar hemorrhage, optic nerve injury, and cardiorespiratory complications.[24,26] Peribulbar anesthesia offers similar efficacy by leveraging communication between the extraconal and intraconal spaces while reducing the risk of serious complications such as globe perforation.[27] Our anesthetic approach combines short-acting lidocaine with long-acting bupivacaine, optimizing both rapid onset and prolonged analgesia.[25] Although many studies have evaluated less invasive strategies such as topical or oral analgesics, their effectiveness in PRP pain management has been limited. A meta-analysis by Arruda et al.[21] 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. 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.[28] Subconjunctival lidocaine has also demonstrated efficacy in lowering pain scores, reducing session duration, and increasing the number of laser burns applied.[22,23] However, more research is needed to compare this technique to peribulbar anesthesia directly.

Despite supporting evidence for several anesthetic approaches, the pain measurements in these studies were predominantly subjective. Pain perception is influenced by various factors—genetic, psychological, cultural, and social[29]—making objective indicators a valuable complement. Sympathetic responses to pain, such as changes in heart rate, respiratory rate, blood pressure, and oxygen saturation, provide measurable markers.[30] Wu et al.[17] compared different anesthetic techniques and found that only peribulbar 2% lidocaine significantly lowered pain scores compared with the control group.

This study aimed to evaluate the efficacy of peribulbar anesthesia using 2% lidocaine and 0.5% bupivacaine compared with topical 5% tetracaine in reducing pain during laser PRP in patients with PDR, using pain rating as a subjective parameter and vital signs as objective parameters.

Research question

What is the analgesic effect of peribulbar anesthesia compared to topical anesthesia in patients with diabetic retinopathy undergoing PRP with argon laser?

Objectives and hypotheses

General objective

To determine the reduction in the NRS scale between eyes of patients undergoing PRP following an injection of peribulbar anesthesia with 2% lidocaine + 0.5% bupivacaine versus those eyes receiving a sham injection.

Specific objectives

- To determine the pain score using the NRS scale between the eyes of patients undergoing PRP following the application of a sham injection vs transeptal anesthesia with 2% lidocaine + 0.5% bupivacaine.
- To measure and compare the frequency of adverse effects and complications associated with the transeptal anesthesia intervention versus those of patients receiving a sham injection.
- To measure heart rate before and after the application of panretinal photocoagulation.
- To measure respiratory rate before and after the application of panretinal photocoagulation.

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- To measure systolic and diastolic blood pressure pre- and post-application of panretinal photocoagulation.
- To measure oxygen saturation pre- and post-application of panretinal photocoagulation.

General hypothesis

In patients who received panretinal photocoagulation, eyes undergoing peribulbar anesthesia will present a lower pain score on the NRS scale than eyes that received a sham injection.

Specific hypotheses

- In patients who received panretinal photocoagulation, eyes undergoing peribulbar anesthesia will present a pain score on the NRS scale 20% lower than eyes that only received a sham injection.
- The incidence of adverse effects and complications of peribulbar anesthesia is similar to that of the sham injection.
- In eyes undergoing intervention with prior peribulbar anesthesia, the post-procedure increase in heart rate will be 10% lower than the increase observed in eyes receiving a sham injection.
- In eyes undergoing intervention with prior peribulbar anesthesia, the post-procedure increase in respiratory rate will be 10% lower than the increase observed in eyes receiving a sham injection.

- In eyes undergoing intervention with prior peribulbar anesthesia, the post-procedure increase in systolic and diastolic blood pressure will be 10% lower than the increase observed in eyes receiving a sham injection.

Methods

Study design

Prospective, randomized, single-masked, controlled trial

Patients

Patients were recruited from the Asociación Para Evitar la Ceguera en México, I.A.P. Retina department according to specific eligibility criteria. Adults aged 18 years or older with 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; and cognitive or motor impairments that could hinder effective communication of pain.

Study design

A block randomization scheme was created to ensure a balanced allocation of the eyes across the study groups. Eleven blocks containing four possible permutations for the two groups were created. The intervention group received peribulbar anesthesia and the control group received topical anesthesia. The blocks were numbered randomly from one to 11, and one eye of each participant was assigned to the treatment or control group according to the permutation, with the contralateral eye assigned to the corresponding alternative.

The eyes assigned to the treatment group received a single drop of topical 5% tetracaine to improve patient comfort during the peribulbar injection, followed by a two-minute observation period. 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, which also received 5% tetracaine, were administered a sham injection. In this group, topical 5% tetracaine was applied, followed by a two-minute observation period. The sham injection consisted 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. Each eye received between 1,200 and 1,500 burns, with sizes ranging from 200 µm to 500 µm. Pulse durations were set between 100-200 ms. The 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 period of 10 minutes was provided between the right- and left-eye PRP sessions.

Variables and Measurements

The primary variable assessed in this study 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.[24] The evaluator administering the NRS was not masked to the treatment allocation. The secondary variables assessed in this study were heart rate, respiratory rate, oxygen saturation (SpO_2), and blood pressure measured before and after the application of PRP in each eye. All vital signs were measured with the Aquarius Vital Sign Monitor (Shenzhen Northern Meditec Limited, Shenzhen, China) at baseline before the start of PRP, and at the 1-, 5-, 10-, and 15-minute marks while undergoing PRP application in each eye.

Safety was evaluated by monitoring for ocular and non-ocular adverse events, assessing extraocular movements after peribulbar injection, and conducting a 45-minute observation period after the PRP session.

Standardized methods

A) Topical anesthesia with 0.5% Tetracaine

1. Patient seated in a comfortable position.
2. 1 drop of 0.5% tetracaine will be applied onto the ocular surface to be treated and the conjunctival fornices.
3. Any excess residue will be cleaned with a cotton swab.

B) Peribulbar injection of 3 mL of 2% lidocaine + 0.5% bupivacaine

1. Patient in a comfortable position.
2. 2 drops of 0.5% tetracaine will be applied to the conjunctival fornices 10 minutes prior to the administration of anesthesia.
3. A Mixture of 1.5 mL of 2% lidocaine and 1.5 mL of 0.5% bupivacaine will be prepared in a 5 mL syringe.
4. Lower eyelid skin will be cleaned with 97% alcohol.

5. Palpation of the orbital notch with the index finger or thumb, located at the junction of the outer 1/3 and the inner 2/3 of the orbital rim.
6. The patient will be asked to look upward (supraversion).
7. Using a 5 mL syringe, a 25G needle will be inserted, bevel up, through the skin, entering near the bony margin, lateral to the notch.
8. Aspiration prior to injecting the medication will be performed.
9. 3 mL of 2% lidocaine + 0.5% bupivacaine will be injected
10. Extraocular movements will be evaluated.

Sham peribulbar injection

1. Patient in a comfortable position.
2. 2 drops of 0.5% tetracaine will be applied to the conjunctival fornices 10 minutes prior to the administration of anesthesia.
3. Lower eyelid skin will be cleaned with 97% alcohol.
4. Palpation of the orbital notch with the index finger or thumb, located at the junction of the outer 1/3 and the inner 2/3 of the orbital rim.
5. With a 5 ml syringe filled with normal saline without a needle, a peribulbar injection will be simulated near the bony margin, lateral to the notch.
6. Extraocular movements will be evaluated.

Statistical Analysis Plan

The sample size was calculated using a two-sample t-test to compare two means, based on previous results reported by Zakrzewski et al.[31] Assuming an alpha risk of 0.05 and a beta risk of 0.2, a minimum of 44 patients was required to find statistically significant differences. 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 measurements of vital signs, NRS score, and laser parameters were registered into 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.

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