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Research Article

Intravitreal Injection Topical Anesthesia with and without 2% Lidocaine Gel

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Abstract

Purpose: Intravitreal injection (IVI) pain is controlled by various methods; none is demonstrably superior. This prospective trial compared pain in patients undergoing IVI with topical anesthesia with or without 2% lidocaine gel.

Methods: Patients over 40 years scheduled for atleast two IVIs in one eye were included. Initial anesthesia was 0.5% proparacaine/hydroxyl propyl methyl cellulose or 0.5% proparacaine/2% lidocaine gel. Patients answered questionnaires about discomfort during blepharostat positioning and IVI pain from 0-10. Thirty days later, patients received the other anesthesia for the second IVI. Corneal and conjunctival staining with lissamine green and fluoresce in was evaluated on the first post operative day using the Oxford scale.

Results: Forty patients were included, comprising 18 men and 22 women (mean age, 68.15±10.38 years). There was no significant difference in age (p=0.880) or sex (p=0.635); significance was shown between diagnostic frequencies (p < 0.001). Mean pain scores during blepharostat placement were 0.75±0.98 and 0.50±0.75 in the placebo and lidocaine groups, respectively (p=0.040); during IVI, they were 1.35±1.09 and 0.95±0.96, respectively (p=0.017). The placebo and lidocaine groups differed significantly in satisfaction; 45% and 70% were very satisfied, respectively (p=0.031). There was no significant difference between groups in regard to keratitis mean score (p=0.897) and lissamine green staining (p=0.397).

Conclusion: Lidocaine gel has important benefits over standard topical anesthetics and relieves IVI pain.

Introduction

Intravitreal injection (IVI) is used to deliver pharmacologic drugs at high doses to the posterior segment of the eye. Neovascular Age-related Macular Degeneration (AMD) remains among the leading causes of blindness in the developed world [1]. After the advent of anti-Vascular Endothelial Growth Factor (anti-VEGF), intravitreal therapy became one of the most frequently performed vitreoretinal procedures.

As the IVI procedure usually can be performed very safety, 75% of ophthalmic procedures are performed using topical anesthesia [2]. Patients should be cooperative with a low grade of anxiety, because discomfort at the time of injection can lead to sudden movement and can cause complications such as hemorrhage, lens damage, and retinal tears. Numerous local anesthesia methods for IVI have been compared, including anesthetic drops, lidocaine gel, anesthetic-soaked cotton pledgets, and subconjunctival and peribulbar blocks [3-5], but there is a lack of evidence to support which method is the best, because the total pain experience is equivalent regardless of the anesthetic method used [6]. Friedman and Margo published a prospective study of 120 patients comparing topical lidocaine gel and subconjunctival lidocaine. They found no significant difference in pain between the groups. Kozak et al. [7] Found similar results, but with high incidences of hyposphagma and chemosis in the subconjunctival group.

In 2008, the Food and Drug Administration (FDA) approved Akten™ (lidocaine 3.5% gel; Akorn, Buffalo Grove, IL, USA) for all ophthalmic procedures. Until then, only proparacaine was approved for ocular surgery [8]. Many countries typically use lidocaine gel (2%) preparations, even though it is considered an off-label use, because many ophthalmic studies have demonstrated positive findings. Thus, lidocaine gel has become a popular method of anesthesia for IVI. There are various methods used to control pain during IVI. However, there has been no method repeatedly shown to be superior in controlling pain [9]. This clinical trial aimed to compare comfort and pain in patients undergoing IVI with topical anesthesia with or without 2% lidocaine gel, and to provide guidance for ophthalmologists in their choice of anesthesia.

Methods

After evaluation and approval by the Hospital Ethical Committee of the Federal University of Sao Paulo (CEP 0705/10), a prospective, randomized, double-blinded, single-center clinical trial was conducted from January 2015 to April 2015. All patients received a thorough explanation of the study design. Written informed consent was obtained before inclusion in the study. The

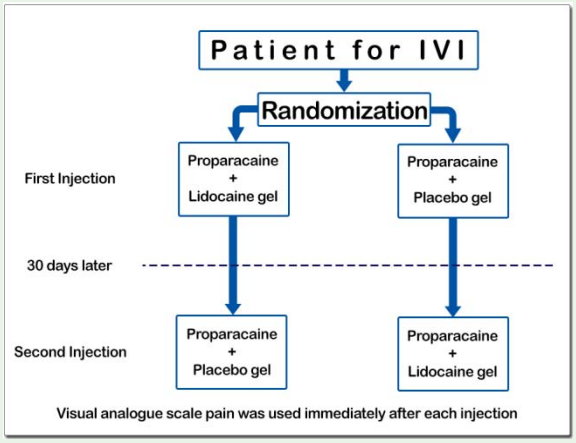

Figure 1: Flow diagram.

protocol adhered to the tenets of the Declaration of Helsinki. Consecutive patients older than 40 years who were scheduled to undergo at least two intravitreal ranibizumab (Lucent is; Genentech, Inc., San Francisco, CA, USA) or aflibercept (Bayer; Germany) injections only in one eye for the treatment of neovascular AMD, diabetic macular edema, or central vein occlusion were evaluated for inclusion in the study. Patients were excluded if they were older than 90 years, underwent any surgery within the previous 30 days, had a history thromboembolic events, psychological and mental disorders, a reported allergy to the topical anesthetic agent, inability to understand the pain scale used to grade discomfort, deafness, and if they used any analgesic medication, because it could influence the evaluation of pain. Prior to arrival in the operating room, the patients were randomized using opaque envelopes. Each patient selected an envelope arranged in sequential order to start treatment with either 0.5% proparacaine hydrochloride (Anestalcon; Alcon Inc. Fort Worth, TX, USA) plus 2% Hydroxyl Propyl Methyl Cellulose (HPMC) (Vista gel, Vistatek Produtos Opticos, Sao Paulo, Brazil) (control group) or

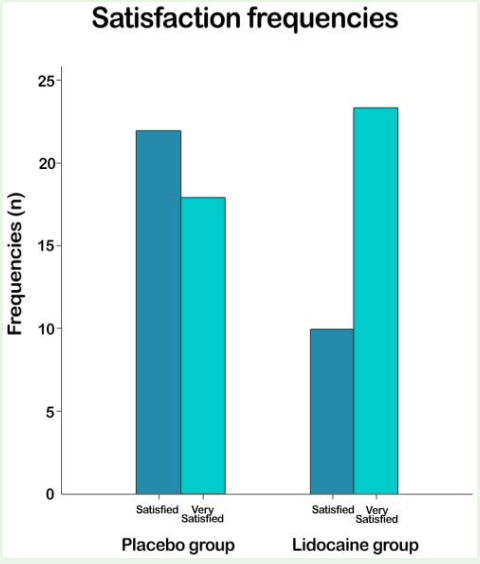

Figure2: Satisfaction Frequencies.

0.5% proparacaine hydrochloride plus an ophthalmic anesthetic gel of 2% lidocaine sterile was produced with physiologic characteristics for the ocular surface tissue, with an appropriate viscosity (1400 mP to get homogeneous dispersion) and neutral pH, by one research assistant experienced with the technique.

Description of the procedure

Drops of 0.5% proparacaine hydrochloride and 5% povidone iodine were placed on the eye. Five minutes before the procedure, 0.3 mL of 2% HPMC or 2% lidocaine gel was placed over the ocular surface and into the inferior fornix to allow enough time for the lidocaine to take effect. A cotton tip soaked in proparacaine was placed on the injection site for 30 seconds in all patients (Figure 1).

All injections were performed by the same the retinal specialist (S. N.) Who was blinded to which anesthetic was used. He placed a sterile eyelid speculum and rinsed the anterior segment with sterile 0.9% NaCl before the IVI was performed with a 30-gauge disposable needle. The IVI was 3.5 mm posterior to the superior-temporal limbus for pseudophakic patients, and 4 mm posterior for phakic patients. After the procedure, he asked the patient about discomfort during the positioning of the eyelid speculum and the pain felt during the procedure. The answer was reported using the Visual Analog Scale (VAS) for pain, and was graded on a scale of 0 to 10, where 0 represents "no pain at all" and 10 represents "the most intense pain that one could ever feel." Corneal and conjunctival staining with lissamine green and fluoresce in was evaluated on the first postoperative day using the Oxford scale.

Statistical analysis

Statistics were performed with SPSS for Windows (SPSS for Windows version 17, Chicago, IL, USA). Nonparametric and parametric statistical methods were performed for analysis. One-way binomial tests were used to compare sex and eye frequencies. The chi-squared test of association was performed to compare groups with respect to sex and eye (right or left). Wilcoxon's signed rank tests were performed to compare related samples with respect to pain during blepharostat placement and pain during injection. Tests were used to compare patient satisfaction. A 0.05 significance level was used for all statistical tests. Means are presented as the mean±SD.

Results

In total, 40 patients were included in this study. The subjects comprised 18 men (45%) and 22 women (55%) with a mean age of 68.15±10.38 years. Patients who had their right eye treated represented 65% of the total. There was no significant difference in age (p=0.880) or sex (p=0.635) between the right and left eyes. There was a significant difference in indications for IVI frequencies ($p < 0.001$), as shown in (Table 1).

Forty patients completed the study. All patients underwent two IVIs within a30-day interval. The procedures were successfully performed with good patient cooperation and no complications.

There was no statistically significant difference between the groups with respect to age (p=0.27) or sex (p=0.23). The mean age was 68.15±10.38 years (range, 41–87 years).

Table 1: Baseline Characteristics and Demographic Data.

Baseline Characteristics and Demographic Data	
Age	68.15±10.38 years
Gender	Male: 18 (45%) Female: 22 (55%)
Pathology	AMD: 65% DM: 17.5% CRVO: 10% Myopia: 2% BRVO: 2.5%
Eyetreated	Right: 65% Left: 35%

Pain during blepharostat placement

The mean pain score during blepharostat placement was 0.75±0.98 in the control group and 0.50±0.75 in the lidocaine group (p=0.040).

Pain during intravitreal injection

The mean pain score during IVI was 1.35±1.09 in the control group and 0.95±0.96 in the lidocaine group (p=0.017).

Patient satisfaction

In the control group, 55% were satisfied with their anesthesia, and 45% were very satisfied. In the lidocaine group, 30% were satisfied and 70% were very satisfied. The frequencies are shown in Figure 2. There was a significant difference between the groups (p=0.031) (Figure 2).

Incidence of keratitis

There was no significant difference between groups in regard to keratitis mean score (p=0.897) and lissamine green staining (p=0.397)

Discussion

Since the introduction of anti-VEGF agents for the treatment of CRVO, diabetic macular edema and other maculopathies, the number of IVI procedures has been growing exponentially. Thus, an understanding of the pain associated with the injection, as well as methods to optimize patient comfort, is invaluable [11]. The purpose of this study was to evaluate if augmentation with lidocaine gel provided more comfort than a single topical anesthetic in patients who underwent IVI. From the results of this study, we observed that the augmentation of proparacaine with lidocaine gel provided more comfort for patients both during placement of a blepharostat and an IVI, and the majority of patients were very satisfied (70%) when we used the gel, versus 45% in the control group.

Topical proparacaine drops provide very effective and cost-effective anesthesia during office-based IVI [12]. Some studies support the advantages of the anesthetic gel, because its viscosity causes it tore main on the eye for a longer duration than drops, resulting in better anesthesia at lower drug concentrations [9]. Gel provided prolonged lubrication, facilitating surgery, [13] and avoided corneal epithelial damage and surface irregularities that would reduce the need for artificial tear lubrication. In a study evaluating pain during phacoemulsification under topical anesthesia with tetracaine 0.5% augmented with lidocaine 2% gel; there was not a better analgesic result than with a single instillation [14]. Page and frauenfelder [15] published a review of 26 references about the safety and efficacy of lidocaine gel, and concluded that it was at least as effective for pain control as alternative therapies in all studies, with a longer duration of action than topical drops. Lidocaine gel is a potentially underutilized tool in ophthalmic surgery. Patients who were treated bilaterally simultaneously, one eye with topical lidocaine gel, and the other injected with subconjunctival lidocaine, preferred subconjunctival anesthesia for their next treatment [16]. Antiangiogenic treatment is usually performed over more than 6 months; therefore, the retinal specialist should offer various anesthesia options to their patients, and determine which one they prefer for treatment compliance. This information should be included in the medical records of the patient to measure pain, we typically use a VAS. It is a subjective perception, and can be influenced by many factors: improved vision from the previous injection, sex, and age over 65 years [17]. In this study, we should have used a 100-point VAS rather than a 10-pointscale to determine the amount of pain more accurately. To the best of our knowledge, this study is the first to compare topical anesthesia with and without augmentation with lidocaine gel to determine if it increased the anesthetic effects. We used the same patients in a crossover study design to create the best scenario in which to make unbiased comparisons. Strengths of this study include comparisons of a consecutive series of patients receiving randomized topical anesthesia to confirm if this association was positive in patients. A weakness of this study is that some patients already underwent an IVI before this study. In the literature, patients have a reduced perception of pain after their first IVI [18]. Nevertheless, this bias is minimized with a crossover design. The crossover design also improves our power and reduces our effect size. In our study, a power of 76% and an effect size of 0, 38 were achieved. The power would be smaller if we compare 80 injections divided into 2 independent groups. The effect size is considered between small and medium by the conventional values proposed by Cohen (1969).

In conclusion, we consider topical anesthesia with drops the optimal choice for most patients scheduled for IVI, but in cases of stressed and anxious patients, we can augment anesthesia with an anesthetic gel, subconjunctival in filtration, and even sedation. Lidocaine gel appears to have significant benefits over standard topical ocular anesthetic agents when employed appropriately without adverse effect son cornea and conjunctiva. We conclude that topical anesthesia augmented with 2% lidocaine gel relieved pain caused by IVI.

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