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Efficacy of Sublingual Use of Ketorolac Tromethamine in Reducing Pain During Treatment with Laser Photocoagulation in Patients with Diabetic Retinopathy Double Blind, Randomized, Sham-Controlled Study

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Abstract

Objective: To evaluate the analgesic effect of sublingual ketorolac tromethamine during argon laser photocoagulation in patients with diabetic retinopathy.

Methods: A double blind, randomized, sham - controlled study, was conducted in 60 patients with diabetic retinopathy, referred for argon laser panretinal photocoagulation (PRP). For the evaluation of pain intensity, a numerical scale from zero to ten was used. The trial sample was divided into two groups. Group 1 consisted of 27 patients who used one 10 mg tablet of ketorolac tromethamine and group 2 comprised of 33 patients who used a sham, both with the same method of administration, 30 minutes before application of the laser.

Results: Of the 27 patients in Group 1, 20 (74%) felt pain in the first stage, 5 (19%) experienced pain in the second stage and 2 (7%) felt no pain at any time. Of the 33 patients in Group 2, 27 (82%) felt pain in the first stage, 3 (9%) experienced pain in the second stage and 3 (9%) felt no pain at any time. There was no statistically significant difference between the groups (p=0.65 and 0.33).

Conclusion: Ketorolac tromethamine was not able to reduce pain during panretinal photocoagulation in patients with proliferative diabetic retinopathy.

Keywords Laser photocoagulation; Pain management; Ketorolac tromethamine; Diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is an ocular manifestation of diabetes and is a leading cause of blindness in people between the ages of 20 and 74 in the USA [1]. The proliferative form of the disease is the most feared by their visual complications, due to its ocular manifestations such as retinal ischemia, which leads to a retinal neovascularization.

It is estimated that in eyes with untreated proliferative DR, the rate of progression to blindness is 50% at 5 years [2-4] and that about 80% of diabetics with over 25 years of the disease will have some sign of retinopathy [5,6]. One of the treatments performed for the proliferative form of the disease is argon laser photocoagulation. A study such as the Retinopathy Diabetic Study (RDS) proved that panretinal photocoagulation (PRP) is effective and reduces severe visual loss in patients with this disease [7]. It is known that when the patient is subjected to photocoagulation the feeling of pain can range from mild to severe intensity during the procedure [8]. Pain during PRP is thought to result from photocoagulation the ciliary nerves running in the suprachoroidal space [9]. In order to reduce pain, analgesia can be performed with a injection of anesthetic, retrobulbar, peribulbar, or subtenonian, however, all these procedures have risks of complications, limiting their applicability. Oral analgesics may be an alternative to reduce the discomfort felt by the patient during a session of laser therapy.

Ketorolac tromethamine is a nonsteroidal anti-inflammatory potent analgesic, available in sublingual form and is a drug indicated for short-term treatment of acute moderate to severe pain.

The purpose of this study is to evaluate the analgesic effect of sublingual ketorolac tromethamine during argon laser photocoagulation in patients with diabetic retinopathy.

Materials and Methods

The Ethics Committee of the Agamemnon Magalhães Medical Research Hospital approved this study. A double-blind, randomized, sham-controlled study, was conducted, at the Santa Luzia Hospital/ Santa Luzia Foundation, in the city of Recife (HOSL/FSL), from March 2012 to February 2013, where 60 patients suffering from diabetic retinopathy were examined, referred from the outpatient retinal clinic of Santa Luzia Foundation for PRP laser. The patients had already done a clinical history and complete examination with binocular indirect ophthalmoscopy under mydriasis.

A research questionnaire was used which contained: Identification, sex, type of treatment for diabetes mellitus (oral medication and/or insulin therapy), prior treatment with laser photocoagulation for diabetic retinopathy.

Unidimensional pain scales were used for assessment of pain: Numerical Rating Scale (NRS) and the Faces Pain Scale (FPS) with 6 faces. The NRS evaluate the pain on a scale of 0 to 10, or a scale from 0 to 5 categories with 0 representing no pain and 10 indicating worst pain. The FPS evaluates the pain according to which face drawn represents, the expression of happiness rating corresponds to no pain and the expression of sadness corresponds to the maximum pain [10,11].

Inclusion criteria were: over 18 years of age; a consent form freely signed by the patient or his guardian; diagnosed with diabetic retinopathy by clinical and/or additional eye exams; being monitored at the Retinal Department of the Santa Luzia Foundation.

Exclusion criteria were: corneal opacities or cataracts that prevented adequate visualization of the retina; retinal disease other than diabetic retinopathy; and refusal by the patient to participate in the study.

The study sample was divided into two groups. Group 1 consisted of 27 patients who used one 10 mg tablet of sublingual ketorolac tromethamine 30 minutes before laser application. Group 2 consisted of 33 patients who used a sham (pill manufactured with a corn starch base), with the same route of administration, 30 min before laser application. Patients were divided into the two groups randomly. In each patient just only one eye could be treated (Figure 1).

The pupillary dilatation was performed using 1% tropicamide (Mydriacyl; Alcon Inc.) and phenylephrine hydrochloride 10% (Allergan).

The photocoagulation was performed using an argon laser (VISULAS 532s, Zeiss): an average of 500 pulses with 200 micron spot size, and pulse duration of 0.2 seconds were performed, maximum treatment time of 30 minutes and on average 15 minutes.

Immediately after the session, patients were questioned about the presence and intensity of pain felt during the procedure. Pain assessment was carried out using NRS and FPS scales. Fifteen minutes after the procedure, patients were again asked about the pain (Figure 1). The questions were taken immediately after and 15 minutes after photocoagulation so that acute pain was evaluated.

The same ophthalmologist always performed the photocoagulation procedure and another professional performed the pain assessment, on both occasions, in order to avoid technical and collection errors.

The volunteers were responsible for the randomization of patients, the distribution of the drug and sham as well as the application of pain assessment scales through.

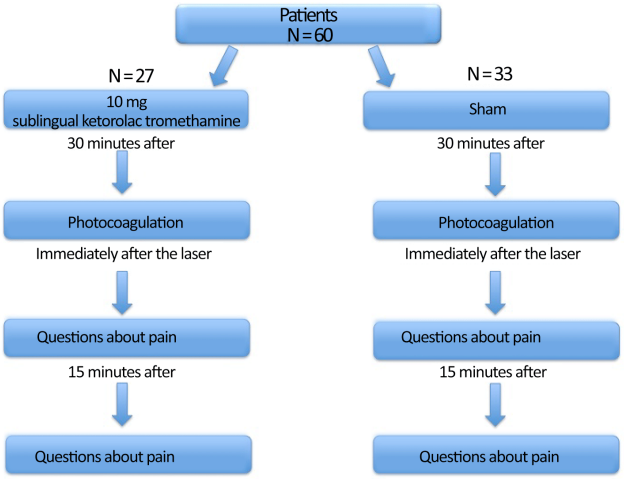

Figure 1: Flowchart of Study Methodology.

Statistical analysis

The data was evaluated using Excel through the MYSQL database (Microsoft Corp., Red-mond, WA). Statistical analysis was performed using STATA/SE 12.0 for Windows, using Two-sample Wilcoxon rank-sum (Mann-Whitney) test for comparisons between groups. We considered p=0.05 to be significant.

Results

Were studied 60 patients (60 eyes) with a mean age of 58 years. Of the patients, 26 (43%) were male, 46 (77%) were insulin therapy dependent and 42 (70%) had already undergone laser photocoagulation on another occasion. Within the sample studied, in Group 1, 27 patients (45%) used ketorolac tromethamine for evaluation of analgesia and in Group 2, 33 patients (55%) used the sham.

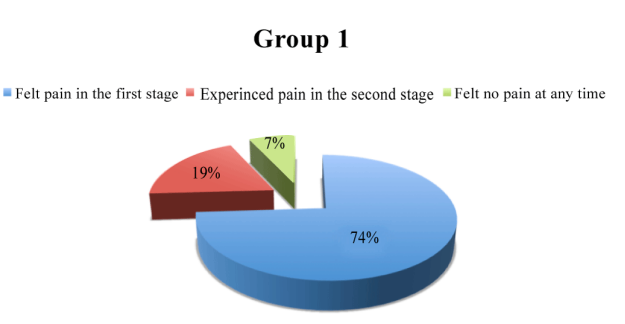

Figure 2: Response to pain in group 1.

In Group 1, of the 27 patients, 20 (74%) felt pain in the first stage and 5 (19%) experienced pain in the second stage and 2 (7%) felt no pain at any time (Figure 2). In Group 2, of the 33 patients, 27 (82%) felt pain in the first stage, 3 (9%) experienced pain in the second stage and 3 (9%) felt no pain at any time (Figure 3).

There was no statistically significant difference between the groups (p=0.65 and 0.33).

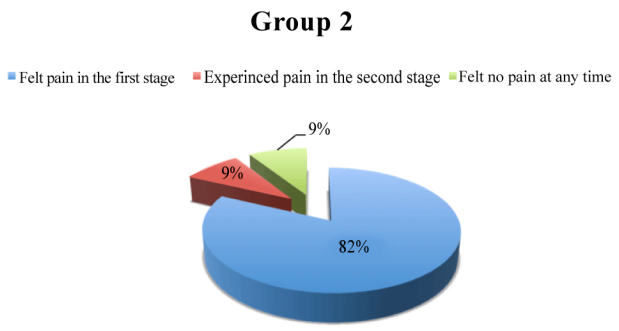

Figure 3: Response to pain in group 2.

Discussion

This study showed no difference of pain reduction in patients who received the sham and ketorolac tromethamine after laser photocoagulation. This result corroborates previous published studies related to the evaluation of pain after laser therapy [9].

The literature shows different ways of trying to reduce pain in patients undergoing laser therapy. The study by Techa and colleagues concluded that a subconjunctival injection of 2% lidocaine significantly reduces the incidence of pain [12].

Not all methods of reducing the pain were effective. Studies have concluded that both the intramuscular injection of ketorolac tromethamine and the use of diazepam, mefenamic acid and acetaminophen (alone or in combination with each other) are not effective in reducing pain perception. Only peribulbar block was effective in reducing pain for this procedure [13]. However, one should take into consideration the risk/benefit of this technique. The risks posed by these types of analgesia such as perforation of the eye, retrobulbar hemorrhage, traumatic optic neuropathy, central nervous system as well as cardiorespiratory depression have been reported complications of this form of anesthesia [13]. In addition to the risks of retrobulbar anesthesia, it induces akinesia making it a disadvantage when you need to direct the patient's eye movements during treatment.

Conclusion

Ketorolac tromethamine was not able to reduce pain during argon laser photocoagulation in patients with proliferative diabetic retinopathy.

The study has some limitations. We considered patients who had undergone photocoagulation and this can interfere somehow, in pain assessment. Studies with patients without prior laser treatments should be performed to confirm the results with greater fidelity.

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