Preemptive analgesia of nepafenac 0.1% in retinal photocoagulation

Emerson Fernandes de Sousa e Castro¹,², Erika Araki Okuda², Vinicius Balbi Amatto², Hirlana Gomes Almeida¹, Marina Gracia¹, Newton Kara-Junior¹

Objective: To evaluate the preemptive effect of nepafenac 0.1% in patients undergoing retinal photocoagulation for the treatment of proliferative diabetic retinopathy. Methods: Thirty patients underwent argon laser photocoagulation in both eyes. The contralateral eye of each patient was the control. The nepafenac and placebo were used 30 minutes before the application of the laser. Both eyes were photocoagulated in the same day. Pain intensity was assessed by visual analog scale and descriptive pain scale. Results: The analysis of the interaction instillation versus nepafenac showed that patients in the placebo group had similar levels of pain in both eyes, and the nepafenac group had significant reduction in pain in the eye that was instilled suspension of 0.1% when compared to the contralateral eye which received placebo (p = 0.023). Conclusion: This study suggests that a suspension of 0.1% nepafenac helpful for preemptive analgesia in patients undergoing retinal photocoagulation compared to placebo.

Keywords: Pain/prevent & control; Analgesia; Anti-inflammatory agents, non-steroidal/administration & dosage; Anti-inflammatory agents, non-steroidal/therapeutic use; Light coagulation; Diabetic retinopathy/drug therapy

Resumo

Objetivo: Avaliar o efeito preemptivo com nepafenaco 0,1% em pacientes submetidos à fotocoagulação da retina para tratamento da retinopatia diabética proliferativa. Métodos: Trinta pacientes foram submetidos à fotocoagulação com laser de argônio em ambos os olhos. O olho contralateral de cada paciente foi o controle. O nepafenaco e o placebo foram utilizados 30 minutos antes da aplicação do laser. Ambos os olhos foram fotocoagulados no mesmo dia. A intensidade da dor foi avaliada por meio da escala analógica visual e da escala descritiva de dor. Resultados: A análise da interação instilação versus nepafenaco mostrou que os pacientes do grupo placebo apresentaram níveis de dor semelhantes em ambos os olhos, e os do grupo nepafenaco apresentaram redução importante do nível de dor no olho em que foi instilado a suspensão de 0,1% quando comparado ao olho contralateral que recebeu placebo (p=0,023). Conclusão: Este estudo sugere que a suspensão de 0,1% nepafenaco foi útil na analgesia preemptiva de pacientes submetidos à fotocoagulação da retina quando comparada ao placebo.

Descritores: Dor/prevenção & controle; Analgesia; Anti-inflamatórios não esteroides/administração & dosagem; Anti-inflamatórios não esteroides/uso terapêutico; Fotocoagulação; Retinopatia diabética/quimioterapia

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INTRODUCTION

Preemptive analgesia aims to reduce the intensity and duration of pain, both during and after procedures, by preventing reflex hyperexcitability in the spinal cord(1).

Analgesic agents are not generally used during argon laser retinal photocoagulation, yet most patients complain of pain during and after the procedure, despite the use of anaesthetic eye drops. General anaesthesia or local anaesthetic block, indicated in cases of intolerable pain, increase the morbidity and mortality of the procedure(2).

Non-steroidal anti-inflammatory drugs (NSAIDs) with local or systemic effect have analgesic and antipyretic properties(3). The only NSAID suitable for topical application is nepafenac 0.1% ophthalmic suspension, which non-selectively inhibits the cyclooxygenase enzyme and presents superior anti-inflammatory properties compared to conventional NSAIDs(3). Nepafenac 0.1% has only been approved for the treatment of pain and inflammation associated with cataract surgery(3).

The aim of this study was to determine whether using an analgesic agent in addition to the anaesthetics commonly used in retinal photocoagulation provides any additional benefit.

METHODS

A prospective, randomised, double-blind case-control study was conducted on 30 consecutive patients diagnosed with proliferative diabetic retinopathy presenting clear ocular media who underwent argon laser photocoagulation in both eyes between June 2011 and May 2012.

The project was approved by the Research Ethics Committee of the São Paulo State Civil Servants Hospital under number 094/10 and was authorised by the hospital manager. All patients provided their free and informed consent.

Exclusion criteria were: presence of retinal abnormalities associated with other systemic diseases, uncooperative patients, pregnancy, use of systemic analgesic or anti-inflammatory agents, and refusal to participate in the study.

The study variables were divided into dependent (pain level) and independent (age, gender, use of placebo or nepafenac 0.1%). Data were collected through a questionnaire using the Visual Analogue Scale (VAS) and the Descriptive Pain Scale (DPS), both frequently used in other studies in the literature(4,5).

Patients were divided into two groups of 15 patients each, who used either nepafenac 0.1% or placebo. The two groups were matched for age and gender. A single drop of anaesthetic eye drops was administered to each patient 5 minutes before laser application. The study medication was administered 30 minutes before laser application. The contralateral eye was used as a control, undergoing photocoagulation the same day. Fifteen minutes after laser application, subjects responded to the VAS and DPS questionnaire.

For all subjects, photocoagulation was carried out using a Visulas 532s Zeiss device set to spot size 100 µm, power setting 0.20 mW, time 0.10 seconds, and approximately 200 burns.

The pain response of patients was analysed using mixed-model ANOVA for multiple factors. This model was chosen due to the study design which combines paired and unpaired samples.

The pain level was assessed in relation to three variables: 1) anaesthetic eye drops administered to one eye versus non-administration to the contralateral eye (paired samples); 2) nepafenac 0.1% administered to one group versus placebo given to the other group (unpaired samples); and 3) gender.

Patient age was included as a covariate and its potential influence was controlled for by the model. The three factors above were assessed both in isolation and combined. A p-value <0.05 was adopted for rejection of the null hypothesis.

RESULTS

As illustrated in Table 1, the results from the DPS show that the effects of age, gender, nepafenac 0.1%, and anaesthetic eye drops were not statistically significant in isolation, nor were the interactions between anaesthetic eye drops and age, gender and nepafenac 0.1%, or anaesthetic eye drops and gender and nepafenac 0.1%. However, the interactions between anaesthetic eye drops and gender, and anaesthetic eye drops and nepafenac 0.1% produced statistically-significant results.

Table 1

<table>
<thead>
<tr>
<th>Isolated effects</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.09</td>
<td>0.1602</td>
</tr>
<tr>
<td>Gender</td>
<td>0.37</td>
<td>0.5470</td>
</tr>
<tr>
<td>Nepafenac 0.1%</td>
<td>2.02</td>
<td>0.1673</td>
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<tr>
<td>Anaesthetic eye drop</td>
<td>0.40</td>
<td>0.5304</td>
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<table>
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<tr>
<th>Interactions</th>
<th>F</th>
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<td>Anaesthetic eye drop x Age</td>
<td>0.11</td>
<td>0.7474</td>
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<tr>
<td>Anaesthetic eye drop x Gender</td>
<td>6.97</td>
<td>0.0141</td>
</tr>
<tr>
<td>Anaesthetic eye drop x Nepafenac</td>
<td>5.85</td>
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<tr>
<td>Gender x Nepafenac</td>
<td>0.85</td>
<td>0.3657</td>
</tr>
<tr>
<td>Anaesthetic eye drop x Gender x Nepafenac</td>
<td>3.59</td>
<td>0.0697</td>
</tr>
</tbody>
</table>

Figure 1 shows that administering nepafenac 0.1% or a placebo to men does not alter the level of pain, whereas in women nepafenac significantly reduces pain perception.
Figure 2 shows that patients in the placebo group had similar pain levels in both eyes. However, patients in the nepafenac group presented a significant reduction of pain perception in the eye that received nepafenac 0.1% compared to the contralateral eye, which received no eye drops.

**DISCUSSION**

Pain perception varies between individuals and is dependent on many factors, including cultural and gender differences, past experience and anxiety levels\(^{(2)}\). Diabetic retinopathy is the most common cause of blindness among the economically active population in the United Kingdom\(^{(3)}\). Argon laser retinal photocoagulation is an effective treatment to reduce severe visual loss in proliferative diabetic retinopathy\(^{(3)}\).

As many patients report some degree of pain both during and after laser treatment\(^{(3)}\), several studies have attempted to identify the best form of analgesia for this procedure\(^{(3)}\).

Invasive procedures such as retrobulbar, peribulbar and subtenon anaesthesia have been suggested, but they can cause serious complications which limit their use\(^{(11)}\). A study carried out on 60 eyes of 30 patients with proliferative diabetic retinopathy concluded that topical ketorolac tromethamine 0.5% is no more effective than artificial tears for relieving pain during photocoagulation\(^{(12)}\).

Preemptive analgesia involves the administration of analgesics before the painful stimulus, thus preventing or reducing the hypersensitivity response and pain memory in the nervous system; this produces long-term benefits for the patient’s quality of life and helps reduce expenses on further treatments\(^{(13)}\).

Another alternative suggested in the literature is to reduce the retina’s time of exposure to laser, which significantly reduces the level of pain\(^{(14)}\).

As shown in Table 1, the results from the DPS show that the effects of age, gender, nepafenac 0.1%, and anaesthetic eye drops were not statistically significant in isolation, nor were the interactions between anaesthetic eye drops and age, gender and nepafenac 0.1%, or anaesthetic eye drops and gender and nepafenac 0.1%. However, the interactions between anaesthetic eye drops and gender, and anaesthetic eye drops and nepafenac 0.1% produced statistically-significant results.

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**CONCLUSION**

This study shows that nepafenac 0.1% ophthalmic suspension was effective for the preemptive analgesia of patients submitted to retinal photocoagulation compared to placebo, particularly in women.

**REFERENCES**


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