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Evaluating the Efficacy of Topical and Subconjunctival Diclofenac in the Improvement of Corneal Alkali Burn in Rabbits

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Abstract

Objective- To compare the effects of topical eye-drop and subconjunctival administration of diclofenac on improvement of experimental corneal alkali wound in rabbits eyes.
Design- Experimental study.
Animal- fifteen rabbits.
Procedures- Alkali wounds were inflicted on the central corneas of 15 rabbits which were divided into three groups, A, B and C. A round 9 mm diameter paper filter that had been soaked in normal NAOH was positioned on all the rabbits' right central cornea, to cause corneal wound. Group A and B were treated with Diclofenac eye-drop and subconjunctival injection of Diclofenac, respectively. And group C was indicated as a control group. After 21 days, all the right eyes were sent to laboratory for pathological analysis.
Result- Comparison between groups showed that groups A, and B, had significantly lower ($P<0.05$) discharge days than the control group. Duration of blepharospasm in groups A and B were significantly shorter than the control group ($P<0.05$). Corneal vascularization revealed significant differences between groups. Pair wise comparison determined that group B had a significantly lower degree of corneal vascularization than the control group. Stromal inflammation was most prominent in group A and control group. Statistical analysis showed significantly less inflammation in group B than the control group ($P<0.05$)
Conclusion and Clinical Relevance- Corneal ulcer is one of the most important and common disease of the anterior segment of the eye. Many drugs have been used to prevent and treat corneal ulcer complication. According to our results, topical usage of Diclofenac is easier and more practical than subconjunctival injection.
Keywords- Diclofenac, Eye drop, Subconjunctival, Cornea.

Introduction

An alkali burn of the cornea causes a recalcitrant keratitis characterized by frequent blister formation, recurrent epithelial breakdown, stromal cell death, inflammatory cell infiltration, and endothelial dysfunction.[25] Several proteinases released from the alkali-injured cornea might account for the ulcerative process. Elevated activities of proteinase and acid glycosidase have been thought to be responsible for the ulcerative process in alkali-injured corneas.[9]

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Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of worldwide medications specifically in treatment of ocular disease.[19] NSAIDs are potent inhibitors of COX enzymes, and thereby the synthesis of PGs. Within the eye, PGs cause vasodilatation, disruption of the blood-ocular barrier, and leukocyte migration. Consequently, their inhibition by cyclooxygenase inhibitors may have therapeutic effects.[13,14,27] Two main isoforms of COX, COX-1 and COX-2, have been identified.[36] COX-1, a constitutive enzyme, synthesizes PGs that regulate physiologic processes. Present in most tissues, COX-2 is an inducible enzyme that is expressed throughout the body, primary during inflammatory responses and in association with pain or fever.[29] Aspirin and other chemically related compounds, used systemically for many decades for their analgesic, antipyretic, and anti-inflammatory properties, have more recently been prepared in topical ophthalmic formulations; they have

been proven to be useful in treatment of ocular inflammation, including control of miosis during surgery, postsurgical inflammation of the anterior segment, cystoid macular edema (CME) and inflammation due to noninfectious conjunctivitis such as allergic conjunctivitis. In addition, they can be used to decrease pain, neovascularization and photophobia after refractive surgery.[12,13,14,34,35] There are some other treatments, including the steroids and anti-allergic drugs, for ocular inflammation; but NSAIDS are preferred because do not produce the classical adverse effects associated with steroids, such as elevation of intraocular pressure (IOP), cataract and aggravation of ocular infection. Although usage of topical NSAIDs is increasing in ophthalmology medicine, scientists worry about their corneal complications. An alternative medicine to suppress ocular inflammation is diclofenac that has been used in this study to evaluate the improvement rate of alkali corneal burnt in rabbit. However, the recent reports of corneal melting is surprising.[12]

Materials and Methods

15 New Zealand adult male and female rabbits with normal eyes were divided into three groups with five animals each. Prior to the study, ophthalmic examinations including, indirect ophthalmoscopy, slit lamp bio microscopy, STT, and fluorescein staining of both eyes were performed. Animals were anesthetized with xylazine (5 mg/Kg, IM) and ketamine (35 mg/Kg, IM). The corneal alkali burn was made by placing a 9-mm diameter; circular piece of filter paper soaked in 1molar NaOH on the central cornea for 30s. Only one eye in each rabbit was treated. The cornea was rinsed with 2 ml of physiological saline immediately after alkali exposure. Then, in group A, topical diclofenac was applied every 8 hours, and in group B, 0.4 cc of diclofenac was administered through subconjunctival injection every 7 days. Duration of treatments was 21 days. Group C, as control group, remained untreated after alkali exposure (Fig.1).

Figure 1. Corneal alkaline burn in the experimental rabbit

The rabbits were maintained in a relatively dark room and only during the time of examination and treatments were the lights turned on. The eyes were examined daily by slit-lamp bio microscopy for 21 days. Clinical outcome was monitored by duration of blepharospasm, duration of ocular discharge, and corneal vascularization.

All rabbits were euthanized by IV injection of sodium pentobarbital in day 21 and the eyes were fixed in 10% buffered formalin and embedded in paraffin. Sections were stained with H&E, PAS, and Gram, and examined by light microscopy (Olympus BX41, Japan). To document the findings, microphotographs were obtained by digital camera (Olympus DP12, Japan). Samples were monitored by evaluating corneal thickness (9µm), numbers of epithelial rows, keratocyte density, stromal vascularization, stromal inflammation, and stromal collagen arrangement.

Statistical analysis for duration of ocular discharge, duration of blepharospasm, and corneal vascularization among the three groups was performed by Kruskal–Wallis test. Pair wise comparison between each group with control group was performed by Mann–Whitney test. P values of <0.05 were considered to be significant. Fisher exact test was used for statistical comparison of microscopic parameters between each group with control group.

Results

Freshly burned corneas became cloudy immediately after burning, and subsequently, turned opaque within 24 hours. All rabbits showed blepharospasm due to pain on the first 2 days following ulcer formation and the eyes were semi-closed. Corneal edema was most prominent during the first week after inducing ulcers in all groups. Comparison between groups showed that groups A and B, had significantly lower ($P<0.05$) discharge days than the control group (Fig.2).

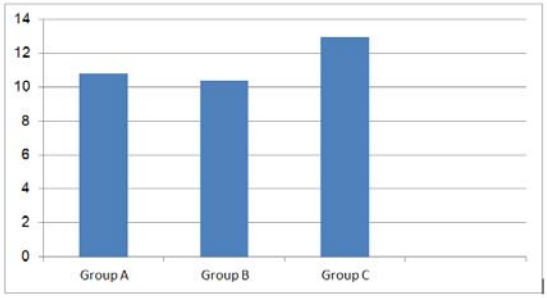

Figure 2. Median days of ocular discharge in groups A, B and the control group.

Duration of blepharospasm in groups A and B were significantly shorter than the control group ($P<0.05$); however, there was no significant difference between

groups A and B (Fig.3). Corneal vascularization revealed significant differences among groups. Pair wise comparison determined that group B had a significantly lower degree of corneal vascularization than the control group (Fig.4). Statistical analysis showed significantly less stromal inflammation in groups A and B than the control group ($P<0.05$) (Fig.5, 6 and 7).

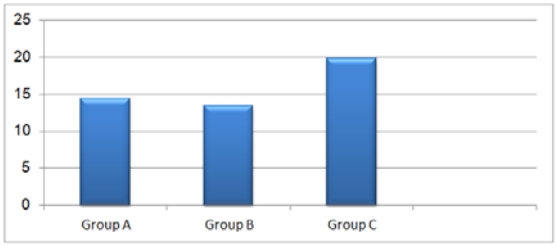

Figure 3- Median days of belphoraspasm in groups A, B and the control group.

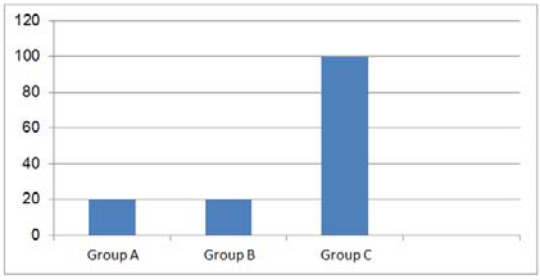

Figure 4. Percentage of corneal neovascularization groups A, B and the control group.

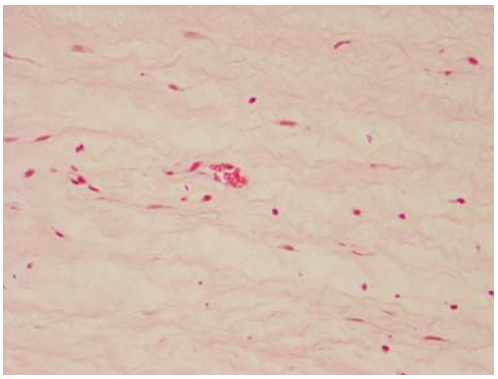

Figure 5. Photomicrograph of a cornea. Loss of keratocytes, site of intrastromal neovascularization and a few inflammatory cells in the stroma can be seen. (H&E x 400).

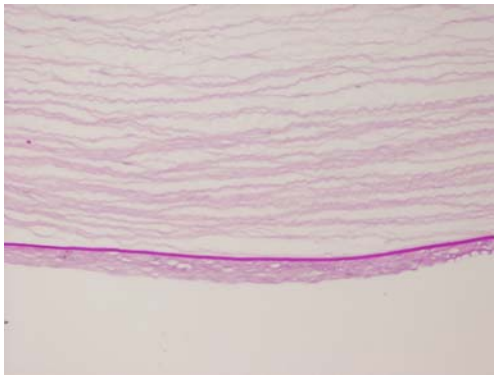

Figure 6. Photomicrograph of a cornea. There is retrocorneal fibrous membrane formation (PAS x 200).

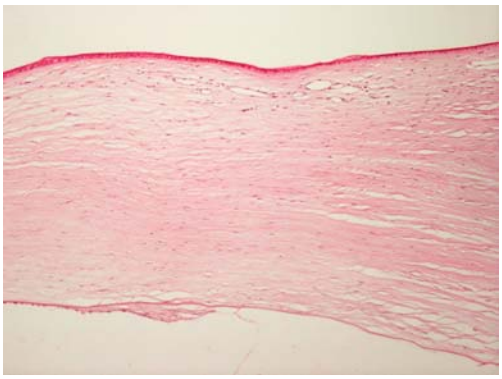

Figure 7. Photomicrograph of a cornea. There is neovascularization with mild inflammatory cells in stromal layer. Formation of retrocorneal membrane can be seen (H&E x 100).

Discussion

The lucent structure of the cornea is easily become opaque by many factors such as trauma, chemical burn, contact lens etc. The opacity blocks the light. All mentioned factors result in hypoxia, infections and finally neovascularization on the cornea.[1,4,8] Alkali burn is one of the most dangerous chemical burnt which have poor prognosis and also the most of serious chemical injuries to the anterior segment of the eye.[26] Many investigations have been performed to prevent and treat chemical burn complications.[33]

Alkaline chemicals cause injuries via two different chemical processes: the saponification of triglycerides found in the cell membranes by the hydroxyl ions, which leads to acute lysis of these cell membranes and the denaturation and hydrolysis of proteins due to the change in PH. The hydrolysis leads to loss of the quaternary, tertiary, and secondary structures of proteins and therefore to loss of function of structural as well as transport proteins and enzymes. Consequences are cell death, reduced mechanical strength, and impaired repair mechanisms. Damage to the corneal epithelial stem cells

at the limbus will particularly influence the corneal healing process and therefore the visual outcome.[10,12] Perilimbal whitening is a useful indicator in humans to judge the extent of corneal stem cell damage and indirectly the damage to the underlying ciliary body and trabecular meshwork.[32] The alkaline molecules may rapidly penetrate the cornea and enter the anterior chamber. This usually destroys the keratocytes of the affected stroma and damages the corneal endothelial cells.[7,31] Damage to intraocular structures including iris, ciliary body, and lens has been reported in humans.[32] A fibrinous uveitis may result from pH-induced cell lysis and release of necrotic debris into the aqueous humor. Acute clinical signs found in our rabbits included blepharospasm, chemosis-ocular discharge and conjunctival hyperemia. Furthermore, there was an extensive destruction of the corneal epithelium exposed to the alkaline substance. Saponification and denaturation of the stroma was visible as fine white opacities, and subsequent mild to moderate corneal edema was present.[6]

The usage of topical NSAIDs is increasing in ophthalmology medicine but scientists are worried about their corneal complications. There are some reports about complications such as stromal infiltrates, punctate keratitis, immune ring, and persistent epithelial defects. The repair of the severely ulcerated cornea is a challenge for ophthalmologists. In this experiment we have evaluated the efficacy of topical and subconjunctival diclofenac on angiogenesis, stromal inflammation and ophthalmic discharge following alkali wound in rabbit's eye. NSAIDs are a chemically heterogenous group of compounds that inhibit the formation of eicosanoids and lack a steroid nucleus biosynthetically derived from cholesterol. A discussion of the pertinent chemistry of NSAIDs including their chemical structures, is available elsewhere.[13] There are six major classes: salicylates, indole acetic acid derivatives, aryl acetic acid derivatives, aryl-propionic acid derivatives, enolic acid derivatives, and fenamates.[19] All NSAIDs inhibit COX enzymes and thereby the formation of excessive endogenous PGs including PGE2, PGD2, PGF2a, and PGI2. These endogenous PGs act on iris smooth muscle to cause miosis, promote vasodilation, disrupt the blood-ocular barrier, increase leukocyte migration, stimulate pain, facilitate allergic responses, and regulate intraocular pressure (IOP).[12,13,14,27,30,38] NSAIDs do not inhibit lipoxygenase (LPO) and thus do not typically prevent generation of leukotrienes. This may explain their decreased anti-inflammatory effects compared to corticosteroids, which inhibit both LPO and COX. However, diclofenac that has been used in our study is notably exception and inhibit LPO by direct and indirect means, respectively.[20,21,23] The topical formulations of NSAIDs are limited to the relatively water soluble classes: Indole acetic, aryl acetic, and aryl propionic acids.[2] Diclofenac 0.1%, as an aryl acetic acid derivative, is FDA approved for reducing inflammation after cataract surgery, decreasing pain after refractive surgery and anti angiogenic effects.[19] According to this truth we evaluated efficacy of topical and subconjunctival diclofenac on angiogenesis.

In another study saberi et al indicated that NSAID and corticosteroids decreased ocular discharge days in all treated groups.[33] Our experiment led to same result with a remarkable decrease in ocular discharge and blepharospasm in treatment groups in comparison with control group.

This could be explained by therapeutic effects of the drugs discussed before. NSAIDs appear to have anti-inflammatory and anti-angiogenic effects independent of their inhibition of COX.[3,13] Results of this study has revealed that neovascularization was meaningfully decreased in groups treated by topical and subconjunctival diclofenac compared with control group; a Pair wise comparison determined that group A had a significantly lower degree of corneal vascularization than group B and control group. In an experimental study, Abdulgani and coworkers used topical and subconjunctival injection of bevacizumab. They showed subconjunctival bevacizumab is effective in reducing corneal neovascularization in animal models in comparison with topical usage of bevacizumab. They said it could be because of low absorption occurred due to more rapid cleaning of the drug.[1]

An investigation has evaluated a positively charged submicron emulsion of piroxicam on the rabbit corneum healing process following alkali burn on 36 rabbits. They measured reepithelization of corneal epithelium and the inhibition of neovascularization and have demonstrated the effectiveness of piroxicam on alkali burn.[18] In 2007, Durrie et al. used topical ketrolac, nepafenac and brofenac to heal the corneal epithelium and lessening pain during recovery in those had Photorefractive keratectomy (PRK). All patients treated with NSAIDs showed positive effects in healing procedure without any complications and pain lessened sooner in the nepafenac group than the other groups.[11] A study was conducted to assess the effects of NSAIDs and corticosteroids on corneal ulcer. Their results justified that NSAIDs had the ability to impede polynuclear leukocytes (neutrophils) via tear flow due to inhibition of cyclooxygenase and lipoxygenase. Hence, there were no adverse effects on corneal reepithelization.[37] After that, in 1995, researchers evaluated the ability of topical diclofenac to decline corneal opacity during recovery of PRK in rabbits. The study confirmed that diclofenac had meaningful effect on corneal ulceration and prevented corneal opaqueness afterward.[28] In the same year, the comparison was conducted between the effect of NSAIDs and corticosteroids on traumatic corneal ulceration in rabbits. They used diclofenac, flubiprofen and prednisolon. Their results showed low-severity scar tissue on cornea due to prednisolone in comparison with

those treated with diclofenac and flubiprofen. Moreover, there was no significant statistical difference between latter groups.[24] Many investigations, particularly in human, have reported that diclofenac induces corneal ulcer and melting. The reasons for these side effects are obscured. To justify reasons, scientists have described the reaction of diclofenac solutions and conservators in eye. They said this reaction could directly or indirectly induce adverse effect on cornea.[5,15,16,17] However, in this study we could not demonstrate any corneal melting in diclofenac treated group. Pharmacological industries have used various adjuvant, conservator and solution in their products. Considering that, this might be the reason of such corneal melting. Moreover, our duration of treatment was less than the other studies. Duration might have important role in inducing corneal melting. Surprisingly, in those treated with subconjunctival injection there were not any of diclofenac side effects.

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چکیده

بررسی مقایسه‌ای داروی دیکلوفناک موضعی با فرم تزریقی آن به صورت زیر ملتحمه‌ای بر روند ترمیم زخم قرنیه القایی با سود در چشم خرگوش

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هدف- هدف از این مطاالعه بررسی مقایسه ای داروی دیکلوفناک موضعی با فرم تزریقی آن به صورت زیر ملتحمه‌ای بر روند ترمیم زخم قرنیه القایی با سود در چشم خرگوش می‌باشد.

طرح مطالعه- مطالعه تجربی.

حیوانات- پانزده عدد خرگوش.

روش کار- زخم قلیایی در مرکز قرنیه چشم راست پانزده خرگوش سالم ایجاد شد که به سه گروه A,B و C تقسیم شده بودند. در این روش با استفاده از کاغذ صافی به قطر ۹ میلی‌متر که به سود نرمال آغشته و در مرکز قرنیه قرار داده شده بود، زخم قرنیه القا شد. سپس گروه A و B به ترتیب تحت درمان با قطره چشمی دیکلوفناک و تزریق زیر ملتحمه‌ای این دارو قرار گرفتند و پس از ۲۱ روز، چشم راست تمام حیوانات جهت بررسی پاتولوژی خارج و به آزمایشگاه هیستوپاتولوژی فرستاده شد.

نتایج- مقایسه آماری بین گروه‌ها حاکی از آن بود که، میزان روزای ترشحات چشمی و التهاب پلکی به صورت معنی‌داری در گروه A و B از گروه کنترل کمتر بود ($p<0.05$). در مقایسه دوتایی گروه‌ها با یکدیگر، گروه B کمترین میزان نوعروق‌زایی قرنیه را در مقایسه با A نشان می‌دهد. شدت التهاب استروما در گروه B به مراتب از گروه A و کنترل کمتر بود.

نتیجه‌گیری و کاربرد بالینی- زخم قرنیه یکی از مهمترین و متداولترین بیماری های بخش قدامی چشم می‌باشد. داروهای بسیاری برای پیشگیری و درمان عوارض ناشی از زخم قرنیه استفاده می‌شود. نتایج بدست آمده از این مطالعه نشان می‌دهد که استفاده از دیکلوفناک موضعی نسبت به تزریق زیر ملتحمه‌ای آن، به مراتب آسان‌تر و با قابلیت انجام پذیری بالاتری می‌باشد.

کلمات کلیدی- دیکلوفناک، موضعی، زیر ملتحمه‌ای، قرنیه، زخم قلیایی.