

The Role of Topical NSAIDs in Keratolysis

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Abstract

The main purpose of this article is to report three clinical cases of corneal melting secondary to topical NSAIDs from different commercial laboratories, with different indications, time intervals, and clinical indications. After reviewing available sources, we conclude that the use of topical NSAIDs should be under very controlled monitoring, and possibly limit its application to a very precise group of indications taking into account patient risk factors that may exacerbate this complication.

Keywords: Corneal Melting; Topical NSAIDs; Keratolysis; Use of Topical NSAIDs

Abbreviations

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; FDA: Food and Drug Administration; BAK: Benzalkonium Chloride; MMPs: Metalloproteinases; PRK: Photorefractive Keratectomy; LASIK: Laser *In Situ* Keratomileusis

Introduction

During the recovery of ophthalmological surgeries, whether intraocular or surface, the management of inflammation is a cornerstone to obtain the expected results. For this purpose, different therapeutic options of topical non-steroidal anti-inflammatory drugs are available in the market, however side effects that may be brought about by its inappropriate use must be known, one of the main ones is keratolysis or “corneal melting” (Melting).

We present the report of three cases of keratolysis secondary to the inappropriate use of topical NSAIDs, a review of the literature regarding its mechanism of action and pharmacodynamics, in order to understand the mechanism by which corneal melting occurs.

Description of Cases

Case No. 1 (See attached photos): A 32-year-old female patient who, prior to undergoing - LASEK (Laser-Assisted Sub Epithelial Keratomileusis), is prescribed ketorolac ophthalmic solution at 0.45% every 6 hours 4 days before surgery and up to 8 days postoperatively, at which time the patient consulted for acute pain 8/10, sensation of foreign body and tearing. Physical examination included visual acuity of 0.40, hyperemia, upper corneal leucoma with corneal thinning at 12 o'clock in OD.

Case No. 2 (See attached photos): A patient in early postoperative period of pterygium who used for 20 days diclofenac sodium solution 0.1% every 8 hours in the operated eye, as an analgesic and anti-inflammatory. In the control of the postoperative month, she reported a foreign body sensation and persistent lachrymation. The biomicroscopy presented 30% corneal thinning located in the temporal region adjacent to a pterygium scar, that extended towards the visual axis and the upper quadrant.

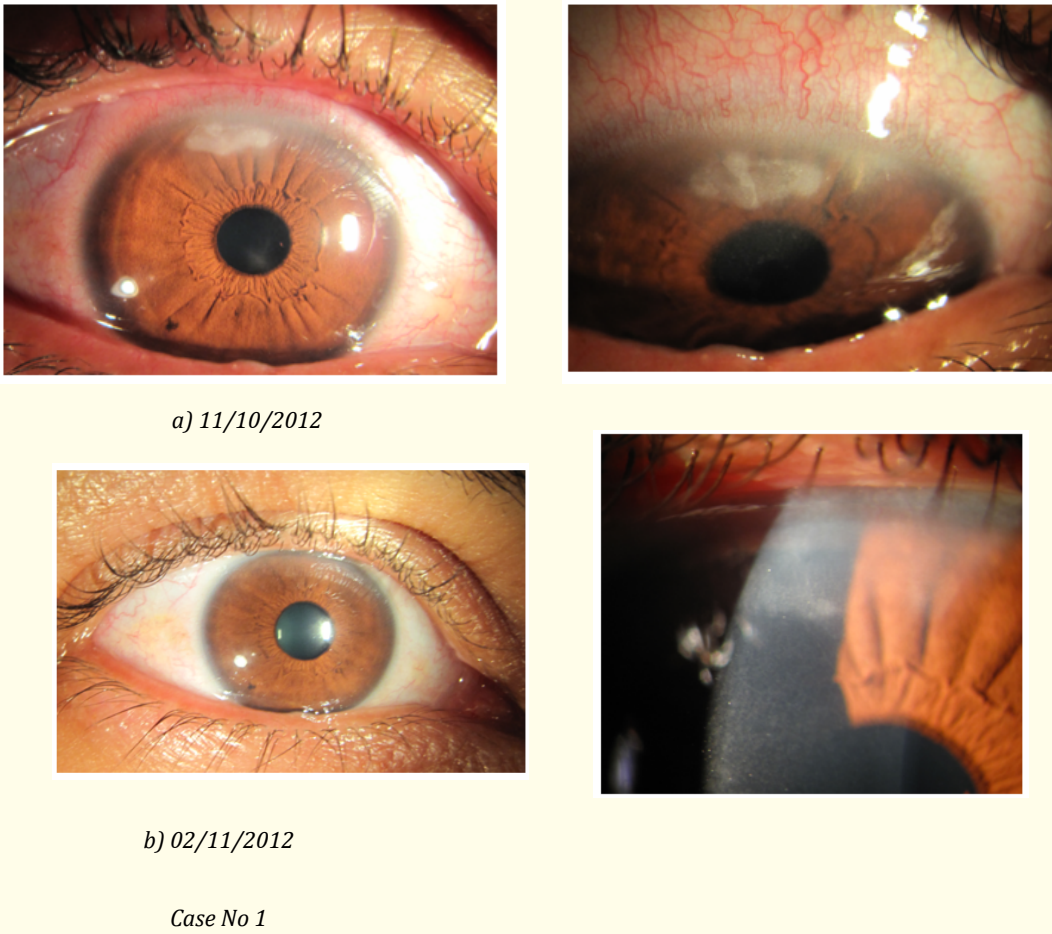
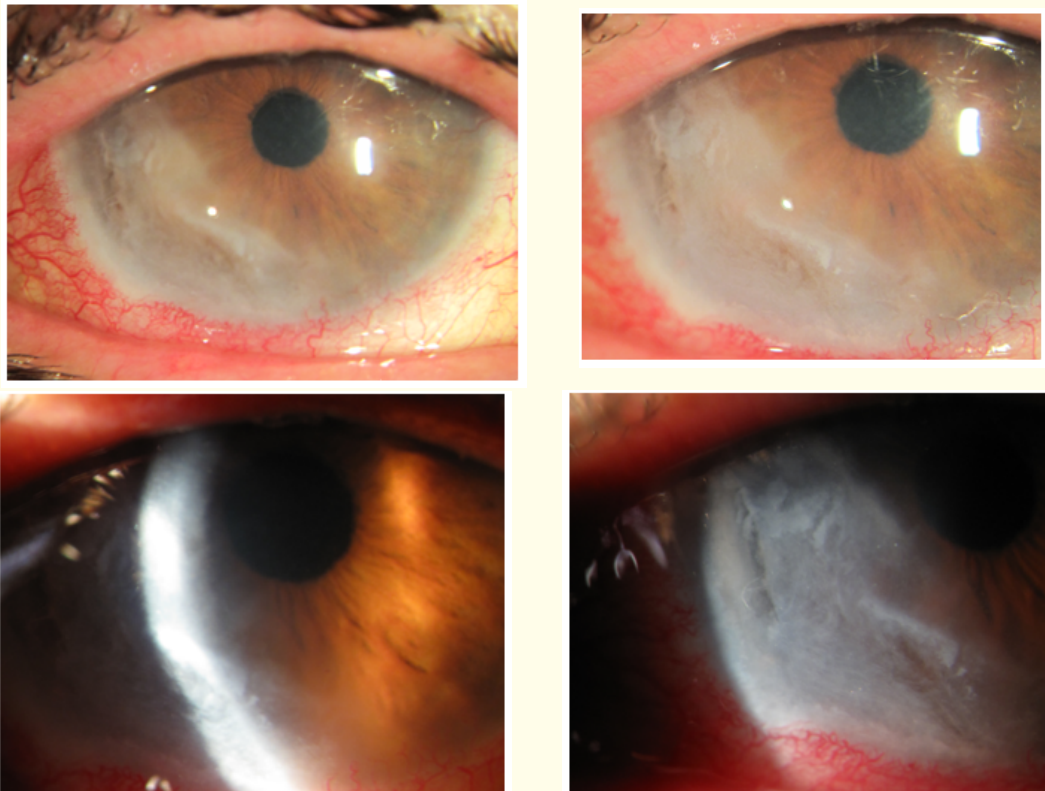


Figure 1

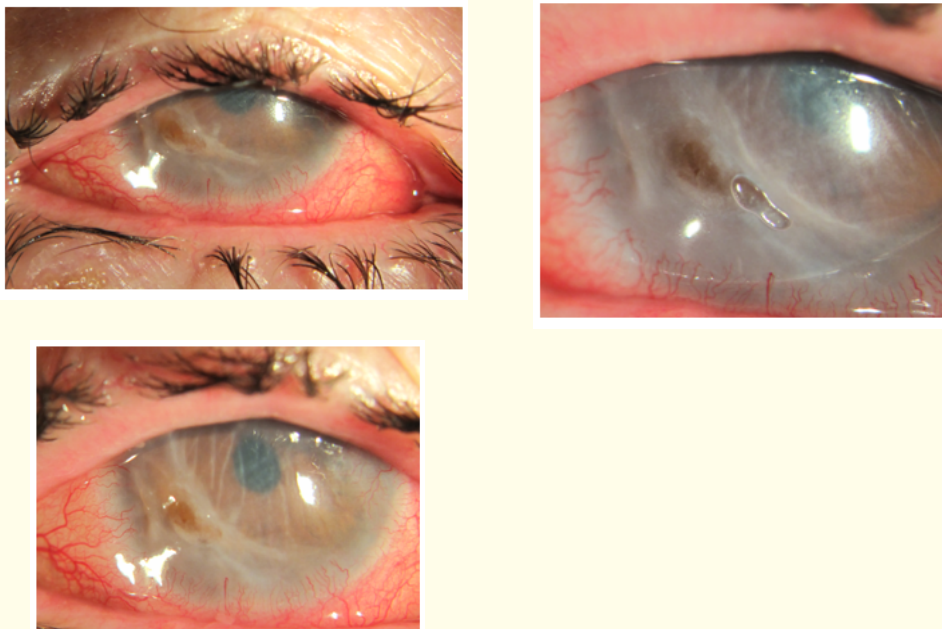


Figure 2

Case No. 3: A 76-year-old female patient with a history of keratoconjunctivitis and herpetic uveitis who, after extraction of cataract by phacoemulsification, is prescribed with Prednisolone acetate 1% + phenylephrine hydrochloride 0.12% ophthalmic solution 2 times per day, ciprofloxacin 0.3% + dexamethasone 0.1% ophthalmic solution 3 times a day and Nepafenac ophthalmic suspension at 0.1% every 12 hours, the latter was suspended by the attending physician but the patient despite the recommendation persistent with this dose more than a month, presenting keratolysis with 2 months of use.



a) 10/01 2013



b) 23/02/ 2013

Case No 3

Figure 3

In general, all cases were treated with suspension of the treatment of topical NSAIDs, artificial tears without preservative, intramuscular Dexamethasone phosphate and therapeutic contact lens, some cases were also managed with oral tetracycline with partial clinical improvement (See annex - Case No. 3).

Discussion

Topical non-steroidal anti-inflammatories are a useful tool for the management of postoperative ophthalmologic surgery patients, mainly in the treatment of symptoms of discomfort, photophobia, decreased inflammation and pain, as well as prevention of macular edema, maintenance of intraoperative mydriasis, among others [1,5].

Some of the topical NSAIDs associated with keratolysis that have been reported in the literature are: generic sodium diclofenac, ketorolac trometamol with or without preservatives, bromfenac sodium, Nepafenac [3,5-7].

Mechanism of action - pharmacokinetics

- NSAIDs are anti-inflammatory drugs that inhibit the activity of cyclooxygenases (COXs), decreasing the synthesis of prostaglandins (PGE₂, PGD₂, PGF₂ α and PGI₂), and reducing pain and postoperative inflammation [1,3]. These endogenous PGs act on the smooth muscle of the iris causing miosis, promote vasodilation, alteration of the ocular blood barrier, increase in leukocyte migration, facilitate the allergic response and regulate the intraocular pressure [3].
- NSAIDs do not inhibit lipoxygenase (LPO) and therefore do not prevent the generation of leukotrienes, generating a lower anti-inflammatory potency in comparison with corticosteroids, which inhibit both COX and LPO. However, celecoxib and diclofenac are exceptions and inhibit LPO by direct and indirect means, respectively [3,4].
- La FDA (Food and drug administration) approves the use of NSAIDs as a postoperative anti-inflammatory treatment in cataract surgery [4,5]. Different studies have compared the role of NSAIDs and corticosteroids, without finding consistent differences related to reduction of intraocular inflammation after a cataract surgery [4,5]. However, it has been shown that NSAIDs are more effective in restoring the blood-gas barrier, as observed by means of the evaluation of proteins in the anterior chamber in a slit lamp or in the quantitative measurement with ocular fluorophotometry. Therefore, there is a good evidence that topical NSAIDs can be used in place of or in addition to topical corticosteroids after a cataract surgery to prevent excessive inflammation, improve visual recovery, and as prevention and treatment of macular edema [4].

Side effects

Some of the complications related to the use of NSAIDs are: ocular burning, hyperemia, punctate keratitis, sub epithelial infiltrates, stromal infiltrates, immune rings, persistent corneal defects, decreased corneal sensation and in severe cases keratolysis, decrease in corneal sensation, delaying early corneal wound healing and re epithelialization [2-4,6].

Keratolysis

It has not been possible to clarify which is the exact mechanism by means of which the keratolysis is generated, however it has been possible to establish possible associated factors:

- Inhibition of keratocyte proliferation by NSAIDs, upregulation and overexpression of a family of proteases known as matrix metalloproteinases [5,7,10]. Increased MMP production by invading inflammatory cells and resident corneal cells leads to overexpression of interstitial collagenase MMP-1, PMN leukocyte collagenase MMP-8, and gelatinase A MMP-2. This disrupts the balanced interaction among MMPs, MMP inhibitors, prostaglandins, and cytokines and destroys newly deposited extracellular matrix. Interruption of the healing process may contribute to the keratolysis seen with topical NSAIDs [6].
- Decreased corneal sensitivity, with delayed healing mediated by MMP8 [6].
- Associated Risk Factors: Ocular surface pathology: keratoconjunctivitis sicca, limbal deficiency, neurotrophic keratitis, exposure, dry eye syndrome, neurotrophic keratopathy, absence or defects of epithelialization, concomitant use with other topical steroids, or collagen diseases (Syndrome Sjögren, rheumatoid arthritis) [3-6,10,11].

- It was also postulated that a vitamin E (Solubilizer present in the generic form of diclofenac) played a role producing effects such as inhibited epithelial proliferation and an aberrant up regulation of collagenase and gelatinase [8].
- By selectively blocking cyclooxygenase activity, NSAIDs shunt arachidonic acid to the lipoxygenase pathway, which results in the formation of leukotrienes in higher than normal levels. leukotrienes are potent neutrophil chemo attractants as well as stimulators of neutrophil degranulation. The neutrophil granules contain powerful collagenases that may play a crucial role in the development of NSAID-related to corneal melts and perforations [3,9].
- The onset of keratolysis may be observed after as few as 4 days or as many as 17 months of uninterrupted instillation photorefractive keratectomy (PRK), and laser in situ keratomileusis (LASIK).
- A strong association of keratolysis and corneal ulcers associated with NSAIDs has been described with the concomitant application of topical steroids and quinolone-like high-spectrum antibiotics, situations in which an increase in metalloproteinase production has been demonstrated *in vitro* [7].

Conclusion

With regard to the cases presented, we believe that corneal melting could be produced by the following factors:

- BAK: It is important to remember that the epithelial corneal toxicity of benzalkonium chloride (which is found as a preservative in several topical NSAIDs), is a factor that can predispose even more to corneal melting [2].
- A deficient tear film has been associated with corneal melting. In addition, abnormal tear production may contribute to enhanced corneal toxicity from topical therapy, particularly if preservatives are present [2].
- Corneal surface alteration: A cornea with a compromised epithelium is resistant to the collagenolysis poorly, and any delay in re epithelialization can favor corneal melting [8].
- Pterygium Chronic inflammation at the limbus predisposes the cornea to postoperative stromal melting [8].
- Prolonged use of topical NSAIDs [8].

After reviewing sources and with experience in the cases presented, we may conclude that the use of NSAIDs is not a direct cause of keratolysis but must be formulated taking into account the risk factors and determining conditions in each of them. Clinical scenarios to avoid the potential risk of a corneal keratolysis.

Among the factors reported, more important are the adequate integrity of the corneal epithelium, history of ocular surface pathologies and collagen pathologies, duration and dose of anti-inflammatory treatment. Furthermore, the importance of a strict follow-up of the patient to be alert at the onset of signs suggestive of corneal melting and thus its early management with suspension of the NSAID and medications focused on recovery of the integrity of the corneal antigen should be remembered.

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Conflict of Interest

We declare that there is no financial interest or conflict of interest in the development of this article.

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