Case Report

Prophylactic Use of Nonsteroidal Anti-Inflammatory Drugs after Cataract Surgery and Corneal Melt

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Abstract

Purpose: To describe a case where prophylactic use of nonsteroidal anti-inflammatory drugs (NSAID) eye drops lead to recurrent corneal melt with loss of vision and a brief literature review.

Methods: This is a case report of an 84-year-old diabetic female with chronic dry eye, operated by two different surgeons on each eye at different time intervals. She received topical NSAID prophylaxis after the second surgery only, which led to blindness due to recurrent corneal melt and chronic choroidal effusions. We also present a brief literature review.

Results: This lady presented with corneal melt and perforation 5 days following the use of topical NSAIDs prophylaxis after a routine cataract surgery in the second eye. Unfortunately, all efforts to save her vision and eye were unsuccessful as she developed repeated complications in spite of corneal gluing, amniotic membrane, penetrating keratoplasty, and tarsorrhaphy. She also had chronic choroidal effusions. She ended up with an opaque cornea and a subtotal tarsorrhaphy, with no other option to improve her vision as she did not qualify for sedation or general anesthesia due to her poor systemic health.

Conclusion: Although it is a common practice for diabetic patients to have topical NSAIDs prophylaxis in combination with steroid eye drops to reduce the risk of cystoid macular edema after cataract surgery, the elderly diabetic patients with concomitant dry eyes should be considered high risk for corneal melt and should be closely monitored. This case highlights the rare but serious complication of topical NSAIDs prophylaxis in the vulnerable cornea, which warrants careful consideration.

Keywords: Cataract surgery, Corneal melt, Dry eyes, Nonsteroidal anti-inflammatory drugs, Phacoemulsification

INTRODUCTION

Pseudophakic cystoid macular edema is considered the most important cause of reduced vision postoperatively and patients with diabetes mellitus are at higher risk of developing this complication.1 Studies and systematic reviews have demonstrated strong evidence that a combination of topical nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids can significantly reduce the prevalence of pseudophakic cystoid macular edema in these patients.1,2 Nevertheless, none of these medications are risk free. Topical steroids can induce elevated intraocular pressure.3 Similarly, the use of topical NSAIDs may cause corneal melt and impaired corneal wound healing.3 There has been reports of cases with corneal melt and perforation secondary to topical NSAIDs in the literature with good outcomes. We report a case of an elderly diabetic female presenting with recurrent corneal melt after receiving topical NSAIDs with steroids prophylactically postcataract surgery in one eye (second eye surgery) with eventual loss of vision.
**Case Report**

An 84-year-old diabetic female presented in early 2018, had her right eye (first eye) cataract surgery a couple of years ago and she did not receive any prophylaxis for cystoid macular edema postoperatively. She had the routine steroid and antibiotic combination (Guttate Tobradex®, Alcon Laboratories, USA) in a 4-week tapering regime starting 4 times a day. She settled well with the best corrected visual acuity (BCVA) of 20/20 in her right eye. Her past history included acne rosacea, Type 2 diabetes, asthma, chronic obstructive pulmonary disease, hypothyroidism, hiatus hernia, and chronic dry eyes. She presented with reduced BCVA of 20/60 in the left eye. She underwent an uncomplicated cataract surgery in her left eye (second eye) in May 2018. This time the surgery was performed by a different surgeon and she was prescribed Guttate Tobradex® QID tapering over 4 weeks along with Guttate Ketonolac tromethamine 0.5% (Acular® Allergan Laboratories, USA) eye drops QID postoperatively. Five days later she presented to the eye casualty with reduced BCVA to hand movement. Examination showed inferior para-central corneal melt with positive Seidel test and shallow anterior chamber [Figure 1a]. Her inflammatory markers (ESR and CRP) were normal and auto-immune profile (ANA, CANCA, P ANCA, Rheumatoid factor) were within normal limits. She was referred to the corneal service. Guttate Ketonolac tromethamine 0.5% was immediately discontinued, and she was started on topical Guttate Chloramphenicol preservative free. Moreover, amniotic membrane Omnigen® (NuVision, UK) was placed on the cornea with Omnilenz® (NuVision, UK) to promote healing. However, this did not help [Figure 1b], and she required corneal glue to seal the perforation 2 days later as the anterior chamber continued to remain shallow [Figure 1c]. The patient was admitted on intensive preservative-free lubricants and hourly topical Guttate cefuroxime 5% and Guttate gentamicin 1.5%. In spite of treatment, she developed endophthalmitis within 2 days for which intravitreal tap with intravitreal antibiotic injection was performed. This controlled the infection and she was discharged home with BCVA of counting fingers (CF) on oral Moxifloxacin and topical Guttate cefuroxime and gentamicin 6 times a day.

Her condition remained stable after corneal gluing only for 3 months, when she presented with recurrence of keratitis, corneal melt, and positive Seidel test in August 2018. She underwent urgent penetrating keratoplasty with 8.25 mm donor graft and aqueous tap with intracameral antibiotic injection as further gluing was not possible due to the large area of corneal melt. The aqueous humor culture proved negative for any organism. Two weeks later, she was noticed to have a small epithelial defect on the inferior part of the graft, which progressed to a larger epithelial defect and stromal thinning within a week despite topical lubricants and antibiotics. She was admitted with intensive preservative-free lubrication and underwent temporary tarsorrhaphy. The epithelial defect healed, and she remained stable until November 2018 when she presented with inferonasal corneal graft melt and positive Seidel test. Omnigen® and Omnilenz® were used with topical preservative free lubricants, chloramphenicol, and dexamethasone. At this stage, she underwent permanent temporal and central tarsorrhaphy. Her epithelial defect healed, and she remained stable with BCVA of 20/20 in her right eye and CF in the left eye with a bandage contact lens in place and prophylactic preservative free chloramphenicol. The bandage contact lens was replaced every 4 weeks through the medi ally open palpebral fissure. She was followed up at 4–6 weekly intervals.

Unfortunately, she presented in August 2019 with purulent discharge, severe keratitis, and recurrence of corneal melt in the graft. Bandage contact lens was removed, and she was admitted on hourly cefuroxime and gentamicin eye drops and Moxifloxacin tablets. Seidel test was negative. This controlled the infection; however, left her with a scarred failed corneal graft, shallow anterior chamber, and very poor vision of perception of light in the left eye. Moreover, she was also noted to have large choroidal effusion on B scan. The patient was keen on further procedures to restore her vision. However, she was counseled about poor visual prognosis due to her history of chronic dry eyes, neurotrophia, recurrent corneal melt, and presence of chronic large choroidal effusion. She was unhappy with the cosmetic appearance of her left eye and asked for a reversal of tarsorrhaphy and prosthetic eye. However, due to the risk of further corneal melt and perforation, reversal of tarsorrhaphy was not an option without evisceration at the same time. Nonetheless, due to her poor respiratory health, she was deemed unsuitable for any further general anesthetic procedure. She remains under regular follow-up with the plan to maintain her comfort in the left eye with subtotal tarsorrhaphy [Figure 2].

**Discussion**

The association of topical NSAIDs use and corneal melt was first reported in 1999 in the American Society of Cataract
and Refractive Surgery survey, in which generic diclofenac was most associated with either corneal melting or punctate epitheliopathy. The use of topical NSAIDs reduces corneal sensation through their effect on the corneal nociceptor response, which reduces postoperative pain and results in delayed wound healing and reepithelialization. This has been demonstrated in animal models. NSAIDs have been implicated in delaying wound healing and in decreasing the migration of corneal epithelial cells in rabbits.

Corneal melt has been reported with various types of NSAIDs like diclofenac, bromfenac, indomethacin, and ketorolac. Diclofenac has been frequently linked with corneal melt. However, in the past few years use of ketorolac in prophylaxis or management of CMO has increased. Prophylactic topical ketorolac may be administered during second eye surgery if there is a history of CMO in the first eye following cataract surgery or in all patients prone to CMO regardless of previous involvement. However, some surgeons use the prophylaxis in all diabetic patients regardless of the previous history of CMO. In our case, the surgeries were performed on both eyes by two different surgeons couple of years apart. The first surgeon did not use the prophylaxis for the first eye, but the second surgeon used it as it was their routine practice to prescribe prophylaxis in all diabetic cases undergoing cataract surgery.

Several case reports [Table 1] have been published on corneal melting secondary to topical NSAIDs use following a surgical intervention, with a range of reasonable to poor outcome. However, our case highlights the worst outcome out of all reported. Topical diclofenac has been implicated in several case series too. Flach reported 11 cases with corneal melting following use of topical diclofenac (Voltaren® Ciba Vision, Georgia, USA and Falcon® Alcon Laboratories, Texas, USA) alone or in combination with topical steroid in patients after cataract surgery, photorefractive keratectomy, radial keratotomy, Argon laser trabeculoplasty, or for treatment of cystoid macular edema. Seven out of 11 patients did not have any coexisting ophthalmic or systemic diseases. Corneal melt occurred 4 days to 10 months after starting the treatment. The inconsistent and variable dose-toxicity relationships reflected in these 11 cases of corneal melting suggested that coexisting factors other than a simple drug toxicity are implicated. Likewise, in a series by Guidera et al., severe keratopathy in association with topical use of Ketorolac or Diclofenac was reported in 18 eyes (16 patients), of which 12 eyes developed corneal melt with or without perforation. Most of these patients had underlying ophthalmic or systemic diseases affecting the health of the ocular surface including Sjogren syndrome, glaucoma, uveitis, diabetes, rheumatoid arthritis, and rosacea. This suggested that topical NSAIDs may act as trigger for the onset of melting in a cornea predisposed to melt. Gueudry et al. reported 8 cases of corneal melt secondary to topical indomethacin (Indocurryle 0.1%, Chauvin, Bausch and Lomb, Montpellier, France). They suggested the cautious use of topical NSAIDs, including indomethacin 0.1% ophthalmic solution, in patients with predisposing conditions to corneal melting such as coexisting epithelial defects, epithelial irregularity in the immediate postoperative period or in conjunction with topical steroids.

Surprisingly, 50%–60% of patients undergoing cataract surgery have dry eye disease and cataract surgery can exacerbate or even cause dry eye postoperatively. To reduce the risk of corneal melt and perforation, meticulous assessment, and management of preexisting ocular surface disease prior to cataract surgery is important. It was already known that patients who have dry eye secondary to a rheumatological condition are at an increased risk of corneal melt with the use of preservative containing drops. Moreover, in the setting of cataract surgery, in addition to their anti-inflammatory effect NSAIDs may also act as mild anesthetics, decrease corneal sensation and impede corneal healing. Avoidance of preservative in drops and cautious use of topical NSAIDs were suggested in patients prone to corneal epithelial breakdown. Our patient had two important risk factors, i.e., dry eye and diabetes. It is already known that diabetes increases the risk of corneal melt via nerve damage and neuropathy, delayed reepithelialization, and delayed wound healing. Subsequent use of ketorolac tromethamine on an already weak cornea, may have caused toxicity leading to melting and perforation.

Looking at the literature, corneal melt secondary to topical NSAIDs may happen as early as 3 days and as late as 17 months after starting the eye drop [Table 1]. They also tend to occur in para-central (mainly inferior) cornea, are sterile in nature and mainly associated with rheumatoid arthritis and Sjogren syndrome [Table 1]. This is compatible with our patient’s corneal picture. With regards to the topical antibiotics, it is reported that topical gentamicin and neomycin are significantly more toxic than tobramycin. Also, with regards to preservatives, benzalkonium chloride (BAK) is more toxic. Some studies [Table 1] used a combination of Acular® (contains both ketorolac and BAK) with Maxitrol®. The combined use of topical NSAIDs and other agents such as neomycin and benzalkonium should be considered with added caution, especially in populations at risk, in order to prevent the rare event of corneal melting and associated permanent visual morbidity. From the literature evidence [Table 1], it is now shown that most cases of corneal melt have occurred in patients with preexisting ocular surface disease or systemic conditions like autoimmune conditions and diabetes which leads to dry eye syndrome. However, it is interesting to note that in our patient with diabetes and chronic dry eye syndrome, the only
### Table 1: Summary of published case reports on corneal melts following a surgical intervention and use of topical nonsteroidal anti-inflammatory drugs

| Report | Age (years) | Gender | Procedure                  | Topical medications                                                                 | Presentation with complication of topical medications | Signs                                                                 | Location of melt                          | Final management       | Associated ocular disease | Co-existing systemic disease | Final visual outcome |
|--------|-------------|--------|-----------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------|-------------------------|--------------------------|-----------------------------|-------------------------|
| Ting and Ghosh* | 80 | Male | Cataract surgery            | Prednisolone 1%, ketorolac tromethamine 0.5%, chloramphenicol each TDS            | 1 week                                                | Corneal perforation with positive Seidel test                       | Infero‑nasal cornea                      | Cyanoacrylate glue        | MGD with dry eye            | Nil, moderately raised rheumatoid factor | 20/30                   |
| Murtagh et al.* | 74 | Male | Cataract surgery            | Neomycin-polymyxin B-dexamethasone (maxitro®) QDS, bromfenac BD                  | 8 days postoperative and 11 days postcommence of bromfenac | PED, stromal melt and eventually perforation                     | Infero‑temporal cornea                   | Glue followed by tectonic graft | Undiagnosed Sjogren’s syndrome | Positive RF, anti-Ro and anti-La, positive parotid biopsy | 20/120                  |
| Lin et al.* | 76 | Female | Cataract surgery          | Diclofenac QDS                                                                  | 3 months postoperative and 2 weeks postdiclofenac     | Epithelial defect, stromal melt and perforation                   | Infero‑temporal cornea                   | Glue                    | Nil                       | Nil                          | 20/400                  |
| Lin et al.* | 66 | Female | Cataract surgery          | Apraclonidine hydrochloride drops QDS, diclofenac QDS                          | 4 weeks                                               | Epithelial defect and stromal melt                               | Inferior cornea                          | Lubrication and antibiotic glue, BCL, corneal patch graft | Nil                         | Nil                         | 20/40                   |
| Lin et al.* | 77 | Female | Cataract surgery          | Tobramycin-dexamethasone (tobradex®) QDS, diclofenac drops four times a day     | 2.5 weeks                                             | Corneal perforation                                              | Supero‑nasal cornea                       | Glue                    | Nil                       | Nil                          | Unknown                  |
| Lin et al.* | 71 | Male | Cataract surgery           | Prednisolone acetate 1% 6 times a day, diclofenac QDS                          | 10 days                                               | Epithelial defect followed by perforation                         | Superior cornea                          | Corne‑scleral graft          | Nil                       | Nil                          | 20/200                  |
| Lin et al.* | 79 | Male | Argon laser trabecuoplasty | Diclofenac QDS, glaucoma medications (latanoprost, brimonidine, timolol, dorzolamide) | 5 weeks postoperative and 2 weeks postcommencing diclofenac | Epithelial defect with descemetocele                           | Infero‑central cornea                    | Glue and BCL followed by PK | POAG                      | Nil                          | Unknown                  |
| Cabourne et al.* | 85 | Male | Cataract surgery           | Neomycin-polymyxin B-dexamethasone (maxitro®) QDS, ketorolac QDS               | 20 days                                               | Epithelial defect and stromal melt                               | Not mentioned                            | Preservative free dexamethasone and chloramphenicol | POAG                      | Nil                         | 20/120                  |
| Cabourne et al.* | 94 | Female | Cataract surgery          | Neomycin-polymyxin B-dexamethasone (maxitro®) QDS, Ketorolac QDS               | 11 days                                               | Epithelial defect and stromal melt                               | Not mentioned                            | Preservative free dexamethasone and chloramphenicol + moxifloxacin | Nil                      | RA, Raynaud’s disease      | 20/200                  |
| Cabourne et al.* | 78 | Male | Cataract surgery           | Neomycin-polymyxin B-dexamethasone (maxitro®) QDS, ketorolac QDS               | 6 days                                                | Epithelial defect + 80% melt                                     | Not mentioned                            | Preservative free dexamethasone and chloramphenicol + oral doxycyclin and oral prednisolone | Nil                      | Nil                         | CF                       |
| Cabourne et al.* | 81 | Female | Cataract surgery          | Neomycin-polymyxin B-dexamethasone (maxitro®) drops four times a day for 4 weeks ketorolac drops four times a day for 4 weeks | Day 4                                                  | Epithelial defect + stromal melt                                 | Not mentioned                            | As above + topical ganciclovir and oral aciclovir | Blepharitis and filamentary keratitis | Nil                      | CF                       |
| Cabourne et al.* | 72 | Female | Cataract surgery          | Neomycin-polymyxin B-dexamethasone (maxitro®) QDS, ketorolac QDS               | 8 days                                                | Stromal melt and perforation followed by endophthalmitis         | Central cornea                           | Corneal Gluing followed by tectonic graft | Nil                       | OA                         | PL                       |

Contd...
| Report                      | Age  | Gender | Procedure                        | Topical medications                                                                 | Presentation with complication of topical medications | Signs                        | Location of melt | Final management | Associated ocular disease | Co-existing systemic disease | Co-existing ocular disease | Co-existing systemic disease | Final visual outcome |
|-----------------------------|------|--------|----------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------|-------------------|-------------------|-----------------------|------------------------|------------------------|------------------------|------------------------|
| Mohamed-Noriega et al.19    | 50   | Female | Corneal cross-linking            | Moxifloxacin 0.5%, nepafenac 0.1% QDS                                              | 6 weeks                                                | Corneal melt and perforation | Paracentral       | Emergency keratoplasty | Keratoconus          | Diabetes               |                        |                        | 20/200 improved         |
| Jesus et al.20              | 81   | Male   | Cataract surgery                 | Combined dexamethasone and gentamycin 5 times a day + ketorolac tromethamine TDS   | 15 days                                                | Corneal perforation          | Paracentral cornea | BCL with prophylactic Ofloxacin and preservative free lubricants-awaiting penetrating keratoplasty | Nil                    | Hypertension, benign prostatic hypertension |                        | HM                     |
| Wolf et al.11               | 56   | Female | Cataract surgery                 | Prednisolone QDS, moxifloxacin QDS, nepafenac TDS                                  | 14 days                                                | Corneal melt and perforation | Central           | Emergency keratoplasty | GVHD, no further information on ocular symptoms | GVHD                   | Not mentioned          | Not mentioned          | 20/200                 |
| Harada et al.12             | 21   | Male   | Cataract surgery                 | Betamethasone sodium phosphate 0.1%, levofloxacin 1.5% and nepafenac 0.1% QDS    | 10 days                                                | Corneal melt and perforation | Paracentral       | Emergency keratoplasty | GVHD and dry eye | Acute myelogenous leukemia | Not mentioned          | Not mentioned          | Not mentioned          | 20/200                 |
| Harada et al.13             | 67   | Male   | Cataract surgery                 | Fluorometholone 0.02%, chloramphenicol 0.25%, bromfenac 0.1%                      | 14 days                                                | Corneal melt                | Paracentral       | BCL, lubricants, punctal plugs | Nil                    | Interstitial pneumonia, dermatomyositis | Not mentioned          | Not mentioned          | Not mentioned          | 20/200                 |
| Harada et al.12             | 70   | Female | Cataract surgery                 | Betamethasone sodium phosphate 0.1%, levofloxacin 1.5%, diclofenac 0.1% four times a day | 7 days                                                | Corneal melt                | Paracentral/ peripheral | Lubricants, BCL and punctal plugs | Dry eye                | Hypertension, hyperlipidemia | Not mentioned          | Not mentioned          | Not mentioned          | 20/200                 |
| Prasher13                   | 61   | Male   | Combined cataract and pterygium surgery | Bromfenac, combined dexamethasone and ofloxacin 6 times a day, timolol BD         | 5 days                                                | Corneal melt                | Not known         | Lubricants, BCL, prophylactic topical antibiotics | Dry eye                | Not known              | Not known              | 20/30                  |
| Khalifa and Mifflin14        | 52   | Female | Conductive keratoplasty          | Ketorolac tromethamine TDS, gatifloxacin QDS                                      | 5 days                                                | Corneal melt at the site of previous conductive keratoplasty | Superior cornea | Prednisolone acetate 1% hourly | MGD                   | Nil                    | Not mentioned          | Not mentioned          | 20/100                 |
| Mian et al.15               | 31   | Male   | PRK                              | Ketorolac QDS, ciprofloxacin QDS, prednisolone acetate 1% QDS, but the patient used ketorolac hourly | 5 days                                                | Corneal melt and perforation | Central cornea | PK                | Moderate myopia | Not mentioned          | 20/50                  | Not mentioned          | Not mentioned          | 20/100                 |
| Feiz et al.16               | 35   | Male   | PRK                              | Tobradex and nepafenac QDS (patient used them 2 hourly)                           | 4 days                                                | Corneal melt and perforation | Central cornea | PK                | Nil                    | Not mentioned          | 20/100                 | Not mentioned          | Not mentioned          | 20/100                 |
difference in the postoperative regime between the two eyes was the use of topical NSAID drops in the second eye. Otherwise, both eyes received preserved Guttate Tobradex® (combination of tobramycin and dexamethasone, Alcon Laboratories, Fort Worth, Texas) which has BAK as a preservative. This means that it is not just the use of preservative which may lead to the melt but the combination of NSAID drops.

From our case, it can be concluded that although most cases with corneal melt following the use of NSAIDs prophylaxis post-cataract surgery in the literature have achieved reasonable outcomes after corneal gluing, tectonic graft, and tarsorrhaphy with the maintenance of globe integrity, some can lead to worse outcomes as they become refractory to the medical and surgical management leading to complete loss of vision.

To prevent this rare, but catastrophic, side effect of topical NSAIDs prophylaxis during routine cataract surgery we recommend the following:

• Careful pre-assessment to diagnose and treat the underlying ophthalmic diseases, in particular dry eye disease, prior to anterior segment surgeries

• Judicious prescription of topical NSAIDs in patients with compromised ocular surface healing, i.e., patients with dry eye, Sjogren, rheumatoid arthritis, rosacea and diabetes mellites

• Reduction of epithelial toxicity by prescribing preservative free eye drops where combined steroid or antibiotic use is required with topical NSAIDs

• Close monitoring of patients at risk of corneal melt following ophthalmic procedures.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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