

# 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

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## 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.<sup>1</sup> 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.<sup>1,2</sup> Nevertheless, none

of these medications are risk free. Topical steroids can induce elevated intraocular pressure.<sup>3</sup> Similarly, the use of topical NSAIDs may cause corneal melt and impaired corneal wound healing.<sup>3</sup> 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.

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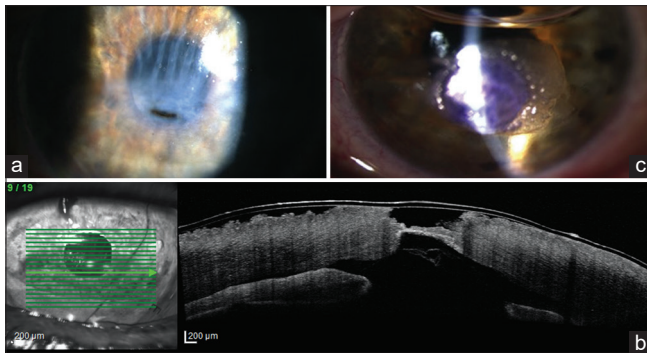
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## CASE REPORT

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 Ketorolac 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 Ketorolac 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



**Figure 1:** (a) Corneal melt with perforation noted on day 5 following cataract surgery and prophylactic use of topical nonsteroidal anti-inflammatory drugs in conjunction with steroid/antibiotic combination. (b) Anterior segment ocular coherence tomography showing the amniotic membrane and the bandage contact lens with perforation and shallow anterior chamber. (c) Corneal melt with glue and bandage contact lens *in situ*

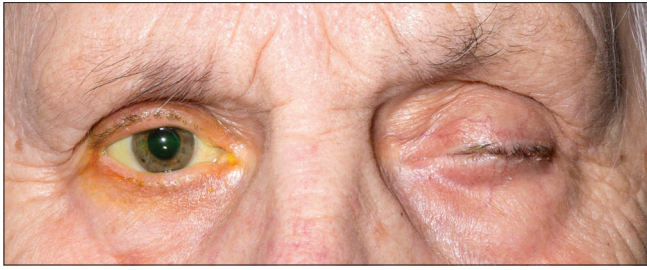
she was discharged home with BCVA of counting fingers (CF) on oral Moxifloxacin and topical Guttate cefuroxime and gentamicin 6 times a day.

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 medially 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, neurotrophin, 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



**Figure 2:** Eye with permanent subtotal tarsorrhaphy

and Refractive Surgery survey, in which generic diclofenac was most associated with either corneal melting or punctate epitheliopathy.<sup>2</sup> 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.<sup>4</sup> 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.<sup>5</sup>

Corneal melt has been reported with various types of NSAIDs like diclofenac,<sup>6</sup> bromfenac,<sup>7</sup> 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<sup>18</sup> 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 keratotomomy, 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.<sup>18</sup> 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.*,<sup>19</sup> 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.<sup>19</sup> Gueudry *et al.*<sup>20</sup> reported 8 cases of corneal melt secondary to topical indomethacin (Indocollyre 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.<sup>8</sup> 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.<sup>21</sup> 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.<sup>9</sup> 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].<sup>10-17</sup> 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.<sup>4</sup> 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.<sup>4</sup> 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 <sup>8</sup>	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. <sup>7</sup>	74	Male	Cataract surgery	Neomycin-polymyxin B -dexamethasone (maxitrol®) 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. <sup>6</sup>	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. <sup>6</sup>	66	Female	Cataract surgery	Apraclonidine hydrochloride drops QDS, diclofenac QDS	4 weeks	Epithelial defect and stromal melt	Inferior cornea	Lubrication and antibiotic	Nil	Nil	20/40
Lin et al. <sup>6</sup>	77	Female	Cataract surgery	Tobramycin-dexamethasone (tobradex®) QDS, diclofenac drops four times a day	2.5 weeks	Corneal perforation	Supero-nasal cornea	Glue, BCL, corneal patch graft	Nil	Nil	Unknown
Lin et al. <sup>6</sup>	71	Male	Cataract surgery	Prednisolone acetate 1% 6 times a day, diclofenac QDS	10 days	Epithelial defect followed by perforation	Superior cornea	Corneo-scleral patch graft	Nil	Nil	20/200
Lin et al. <sup>6</sup>	79	Male	Argon laser trabeculoplasty	Diclofenac QDS, glaucoma medications:(latanoprost, brimonidine, timolol, dorzolamide)	5 weeks postoperative and 2 weeks postcommencing diclofenac	Epithelial defect with descemetocoele	Infero-central cornea	Glue and BCL followed by PK	POAG	Nil	Unknown
Cabourne et al. <sup>4</sup>	85	Male	Cataract surgery	Neomycin-polymyxin B -dexamethasone (maxitrol®) QDS, ketorolac QDS	20 days	Epithelial defect and stromal melt	Not mentioned	Preservative free dexamethasone and chloramphenicol	POAG	Nil	20/120
Cabourne et al. <sup>4</sup>	94	Female	Cataract surgery	Neomycin-polymyxin B -dexamethasone (maxitrol®) 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. <sup>4</sup>	78	Male	Cataract surgery	Neomycin-polymyxin B -dexamethasone (maxitrol®) QDS, ketorolac QDS	6 days	Epithelial defect + 80% melt	Not mentioned	Preservative free dexamethasone and chloramphenicol + oral doxycycline and oral prednisolone	Nil	Nil	CF
Cabourne et al. <sup>4</sup>	81	Female	Cataract surgery	Neomycin-polymyxin B -dexamethasone (maxitrol®) 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. <sup>4</sup>	72	Female	Cataract surgery	Neomycin-polymyxin B -dexamethasone (maxitrol®) QDS, ketorolac QDS	8 days	Stromal melt and perforation followed by endophthalmitis	Central cornea	Corneal Gluing followed by tectonic graft	Nil	OA	PL

Contd...

**Table 1: Contd...**

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
Mohamed-Noriega <i>et al.</i> <sup>9</sup>	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 to 20/60 with pinhole
Jesus <i>et al.</i> <sup>10</sup>	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 prosthetic hypertension	HM
Wolf <i>et al.</i> <sup>11</sup>	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
Harada <i>et al.</i> <sup>12</sup>	21	Male	Cataract surgery	Betamethasone sodium phosphate 0.1%, levofloxacin 1.5% and nevanac 0.1% QDS	10 days	Corneal melt and perforation	Paracentral	Emergency keratoplasty	GVHD and dry eye	Acute myelogenous leukemia	Not mentioned
Harada <i>et al.</i> <sup>12</sup>	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
Harada <i>et al.</i> <sup>12</sup>	70	Female	Cataract surgery	Betamethasone sodium phosphate 0.1%, loxofloxacin 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
Prasher <sup>13</sup>	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	20/30
Khalifa and Miffin <sup>14</sup>	52	Female	Conductive keratoplasty	Ketorolac tromethamine TDS, gatifloxacin QDS	5 days	Corneal melt at the site of previous keratoplasty	Superior cornea	Prednisolone acetate 1% hourly	MGD	Nil	Not mentioned
Mian <i>et al.</i> <sup>15</sup>	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
Feiz <i>et al.</i> <sup>16</sup>	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

*Contd...*

**Table 1: Contd...**

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
Asai <i>et al.</i> <sup>17</sup>	71	Male	Pterygium surgery	Bromfenac sodium BD, ofloxacin fluorometholone 0.1%	40 days	Corneal melt	Nasal limbal	Ofloxacin, Fluorometholone 0.1%	Nil	Not mentioned	Not mentioned
Ashena <i>et al.</i> (this report)	84	Female	Cataract surgery	Tobradex QDS and ketorolac tromethamine QDS	5 days	Corneal melt and perforation	Paracentral	Preservative free topical antibiotics, Omnilenz, glue, PK, permanent tarsorrhaphy	Dry eye	Diabetes, acne rosacea, COPD	PL

BD: Twice daily, TDS: Three times daily, QDS: Four times daily, MGD: Meibomian gland dysfunction, PED: Persistent epithelial defect, BCL: Bandage contact lens, PK: Penetrating keratoplasty, POAG: Primary open angle glaucoma, RA: Rheumatoid arthritis, CF: Counting fingers, HM: Hand movement, PL: Perception of light, OA: Osteoarthritis, GVHD: Graft versus host disease, COPD: Chronic obstructive pulmonary disease

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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