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Toxic keratolysis from combined use of nonsteroid anti-inflammatory drugs and topical steroids following vitreoretinal surgery

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PURPOSE. *To evaluate the corneal complications associated with the combined use of nonsteroid anti-inflammatory drugs (NSAIDs) and topical steroids following vitreoretinal surgery.*
METHOD. *Description of corneal lesions in three patients after vitrectomy with use of topical ketorolac and prednisolone acetate.*
RESULTS. *Three eyes of three patients developed an atrophic central corneal ulcer with stromal thinning following a pars plana vitrectomy under local anesthesia. Lesions were asymptomatic and were found during a routine examination 2, 3, and 8 weeks after surgery, respectively. Surgical indications were as follows: a preretinal membrane, choroidal neovascularization, and massive uveal effusion following cataract surgery. Topical postoperative treatment was as follows: ketorolac 4 times a day, a combination of prednisolone acetate, polymyxin B, and neomycin 6 times a day, and 1% cyclopentolate 3 times a day. Suspension of ketorolac and ocular occlusion led to the resolution of corneal lesions between 2.5 and 3 months later, yielding a central superficial scarring, which showed no changes after a follow-up of 3 years.*
CONCLUSIONS. *Toxic keratolysis may appear as a secondary effect of the combined use of topical NSAIDs and steroids following vitreoretinal surgery and must be taken into account in the differential diagnosis of postoperative corneal lesions. (Eur J Ophthalmol 2006; 16:582-7)*

KEY WORDS. *Toxic keratolysis, Nonsteroid anti-inflammatory drugs, NSAIDs, Steroids, Vitrectomy, Vitreoretinal surgery*

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INTRODUCTION

Both steroids and nonsteroid anti-inflammatory drugs (NSAIDs) are widely used in ophthalmology. Because they inhibit prostaglandin synthesis, NSAIDs are useful in limiting inflammation and pain (1). Topical ocular NSAIDs have been used to prevent and treat cystoid macular edema (2-5), allergic conjunctivitis (6, 7), intraoperative miosis (8), and inflamed pterygia and pinguecula (9). They are also used to manage pain and inflammatory reactions resulting from corneal abrasions (10, 11), argon laser trabeculoplasty (12), or from surgical procedures for treatment of cataracts (13-15), glaucoma (16), myopia (17, 18), and strabismus (19). Recent studies have reported the effectiveness of NSAIDs in controlling pain following vitreoretinal surgery when they are administered intravenously during surgery (20).

By inhibiting the phospholipase A2, steroids interfere

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with the arachidonic acid metabolism, enabling prevention and treatment of inflammatory conditions when administered topically. Nevertheless, its use has been associated with possible secondary effects such as glaucoma, cataractogenesis, and infections, as well as impairment of healing processes on the corneal surface.

Topically administered NSAIDs are better tolerated than steroids, and, in spite of their widespread use, secondary corneal alterations are infrequent. Among these alterations are the following: reduction of corneal sensitivity (21), persistent epithelial defects (22), superficial punctate keratitis (23), and stromal and subepithelial infiltrates (24, 25). In August 1999, the American Society of Cataract and Refractive Surgery warned of the severe complications associated with the use of topical NSAIDs, such as melting and corneal perforation (26). Since then, new cases have been reported, mainly following cataract surgery. To our knowledge, however, there have been no reports of severe corneal complications related to the use of NSAIDs following vitreoretinal surgery.

This report describes the corneal lesions resulting from ulcerative keratolysis in patients treated with topical NSAIDs and steroids following vitrectomy.

METHODS

This article reviews three patients who developed an asymptomatic atrophic corneal ulcer following combined topical treatment with NSAIDs and steroids during the follow-up of vitreoretinal surgery. We analyze the probable causes and clinical outcome following suspension of NSAIDs.

Patient 1

The right eye of a 69-year-old man was operated on in December 2000. A pars plana vitrectomy was performed to remove a subfoveal choroidal neovascular membrane in the context of age-related macular degeneration. Preoperative visual acuity was 20/400. No intra- or postoperative complications developed. Postoperative topical treatment was undertaken with prednisolone acetate, neomycin, and polymyxin B (Poly-pred®) every 4 hours, ketorolac (Acular®) every 6 hours, and 1% cyclopentolate every 8 hours, in accordance with our postoperative protocol. After 1 week, the frequency of Poly-pred® was reduced to every 8 hours. In an examination 2 months later, a paracentral corneal asymptomatic epithelial defect with stromal thinning was detected (Fig. 1, Left). There was no inflammatory reaction in the anterior chamber. Administration of topical ketorolac and prednisolone was discontinued, and a new treatment regime was begun with topical fluorometholone (Isoptoflucon®) and aureomycin ointment every 8 hours combined with eye occlusion. The corneal epithelial defect slowly improved, resolving 3 months later, leaving a paracentral corneal scar and stromal thinning. Final visual acuity remained unchanged at 20/400 (Fig. 1, Right). Corneal cultures for bacteria and fungi were negative.

Patient 2

A 45-year-old man with no systemic or ophthalmic pathologies other than cataracts underwent phacoemulsification cataract surgery with posterior chamber lens implantation in the right eye in April 2001. At the end of surgery, a massive uveal effusion developed. A treatment regime was undertaken as follows: 60 mg of oral prednisone every 24 hours, 125 mg of acetazolamide (Edemox®) every 8 hours, prednisolone acetate, neomycin, polymyxin B (Poly-pred®) every 6 hours, 1% cyclopentolate every 6 hours, ciprofloxacin (Oftacilox®) every 3 hours, and gentamicin ointment every 24 hours. After 2 weeks, the patient showed a vitreous hemorrhage and persistent uveal effusion. Visual acuity was counting fingers. A pars plana vitrectomy with scleral drainage of the suprachoroidal hemorrhage was performed. A treatment regime was undertaken consisting of topical prednisolone acetate, neomycin, and polymyxin B (Poly-pred®) every 4 hours, ketorolac every 6 hours, 1% cyclopentolate every 8 hours, and 60 mg of oral prednisone every 24 hours. Seven days later, prednisolone acetate was reduced to every 8 hours and prednisone to 30 mg a day, while the rest of the regime remained unchanged. Three weeks after surgery, the patient showed an asymptomatic corneal ulcer with no stromal infiltration, suggesting a toxic keratolysis. The treatment regime was suspended and replaced by eye occlusion, fluorometholone (Isoptoflucon®), and aureomycin ointment every 6 hours. Six weeks later, the corneal defect had completely resolved, leaving a mild, superficial central corneal scarring (Fig. 2). Visual acuity was 20/20.

Patient 3

A pars plana vitrectomy to remove a preretinal macular membrane was performed in June 2002 on the right eye of a 31-year-old woman. Preoperative visual acuity was

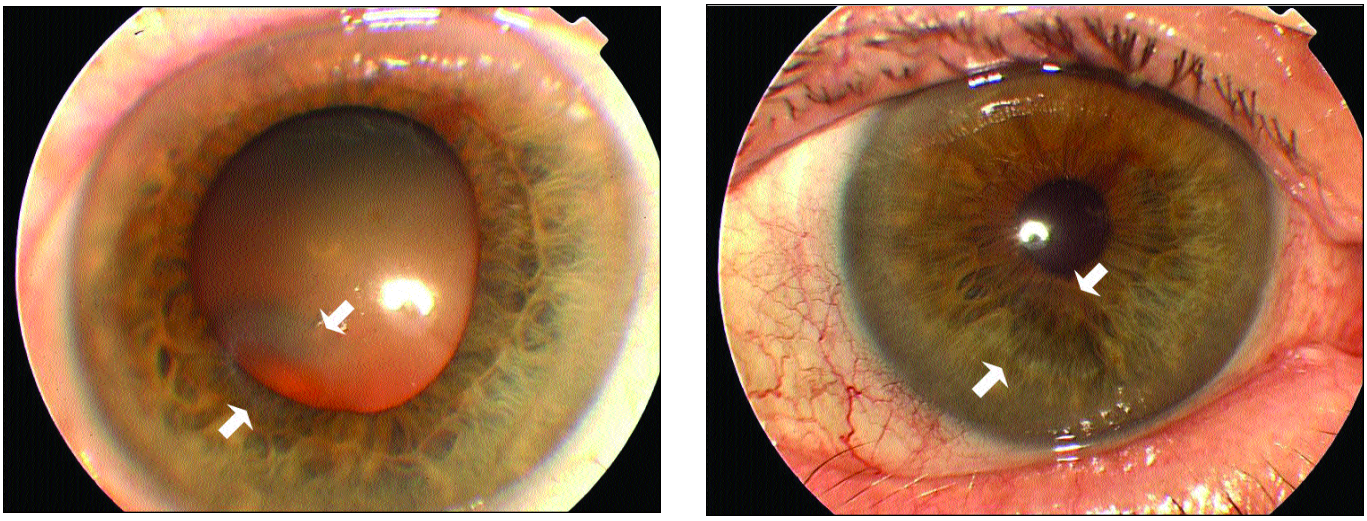

Fig. 1 - *Patient 1. Left: Two months after vitreous surgery. A paracentral corneal asymptomatic epithelial defect with stromal thinning was detected. Right: The corneal epithelial defect resolved 3 months later, leaving a paracentral corneal scar and stromal thinning. Final visual acuity remained unchanged at 20/400.*

20/50. No intra- or postoperative complications developed, except for two asymptomatic central corneal epithelial defects with no stromal infiltration detected 30 days after surgery. Postoperative treatment consisted of prednisolone acetate, neomycin, polymyxin B (Polypred®) every 6 hours, ketorolac every 6 hours, and 1% cyclopentolate every 8 hours for the first week. Seven days after surgery, prednisolone was reduced to every 8 hours, while the rest of the treatment regime remained unchanged. Owing to the suspicion that the corneal defects were the result of toxic keratolysis, administration of ketorolac was suspended, while prednisolone acetate was maintained. Eye occlusion and aureomycin ointment every 8 hours were added to the regime. Two weeks later, the corneal defects had disappeared, with no scarring. Final visual acuity was 20/30.

DISCUSSION

NSAIDs are widely used both in medicine generally and in ophthalmology in particular. The most commonly described secondary effects after topical use are ocular burning and itching (27). Nevertheless, other effects have been described: corneal epithelial toxicity, delayed epithelial healing, subepithelial and stromal infiltrates, toxic keratolysis, and corneal perforation as well as aggravation of asthma attacks (21-28).

In 1999, the American Association of Cataract and Refractive Surgery was the first to warn of the possible involvement of topical NSAIDs in severe corneal lesions. In 2000, Lin and coworkers reported on a series of five patients—four following cataract surgery and one after argon laser trabeculoplasty—who had developed toxic keratolysis following topical postsurgical treatment with diclofenac, which progressed towards a corneal perforation in four of the patients (29). Topical steroids had been administered to three of these patients in conjunction with NSAIDs. In 2001, O'Brien et al described a patient who developed a central corneal ulcer following cataract surgery. This patient received diclofenac and Ocuflox preoperatively, and diclofenac, tobramycin, and dexamethasone postoperatively (30). The same year, Congdon et al reviewed case-reporting records of 140 eyes that had developed corneal or conjunctival pathology in association with the use of topical NSAIDs. An association with a specific topical NSAID was confirmed in 117 cases. Most of the patients developed the complications following ocular surgery, but no one after vitreoretinal surgery. The NSAIDs used were diclofenac and ketorolac, and in 90.7% of surgical procedures, postoperative topical steroids were also administered (26). Guidera and coworkers reported on a series of 18 eyes with similar adverse corneal events following administration of topical NSAIDs. Eleven of these patients developed the complication following cataract surgery, and in nine of them, topical steroids and antibiotics were also administered following surgery (31). In 2001, Flach also reported corneal complications in 11

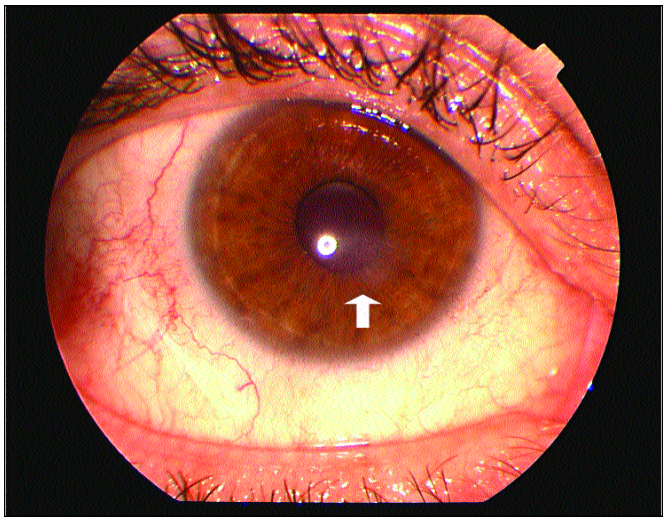

Fig. 2 - *Patient 2. Superficial central corneal scarring 6 weeks following vitreoretinal surgery for a massive uveal effusion.*

postsurgical patients following the administration of topical diclofenac (32). In 2003, Gabison et al published a case of corneal perforation 2 months following photorefractive keratectomy on a patient treated with topical diclofenac (33).

Our series of three patients was, to our knowledge, the first to report corneal complications secondary to topical use of NSAIDs and steroids following vitreoretinal surgery. Corneal ulcers were found 8, 3, and 2 weeks following surgery, respectively, although they may have appeared earlier in the course of the follow-up owing to the asymptomatic nature of this complication. The absence of pain, redness, or an inflammatory reaction in the anterior chamber did not suggest an infectious etiology. This was confirmed in our first case, where the bacteria and fungi cultures were negative. All corneal ulcers were centrally located and resolved more quickly in eyes that had received shorter treatment with topical NSAIDs.

In previous studies, the duration of topical NSAIDs treatment until the development of corneal ulcers ranged from 4 days to 17 months (31, 32). Frequencies and dosages also ranged widely. The most commonly used topical NSAID was diclofenac (either with or without preservatives) and, less frequently, ketorolac. In most patients, topical steroids were also used concurrently (26, 29-32). Corneal ulcers were most commonly found in the upper cornea, generally where a corneal incision had been made for cataract surgery (31). Some patients showed risk factors for developing corneal complications such as dry eye, diabetes, or rheumatic disease (26), in contrast to our patients, who showed no predisposing factors.

NSAIDs inhibit cyclo-oxygenase, an enzyme that converts arachidonic acid into prostaglandins. Lower production of prostaglandins leads to reduced inflammation and pain. At the same time, predominant metabolization of arachidonic acid through the pathway of lipoxygenase increases the production of leukotrienes which augment vascular permeability and neutrophils quimiotaxis, resulting in the release of collagenase. These hydrolytic enzymes could be responsible for keratolysis, which is generally asymptomatic owing to the analgesia secondary to prostaglandins reduction.

Recent research has revealed new pharmacologic properties of NSAIDs that may help explain their relationship to the corneal lesions described. It is known that topical diclofenac reduces substance P concentrations in tears. Substance P is a neuropeptide linked to the conveyance of pain, the depletion of which could cause neurotrophic keratopathy in predisposed patients (34). It has also been suggested that topical NSAIDs lead to a rise in matrix metalloproteinases (MMP), substances that contribute to the degradation of corneal stroma (30, 35). Other studies have shown that NSAIDs inhibit the in vitro proliferation of keratocytes, which delays the healing process, thereby increasing the risk of corneal ulceration (36, 37). It is also known that high doses of NSAIDs cause both apoptosis in different cellular lines, such as monocytes and fibroblast cells (38, 39), and a paradoxical upregulation of the COX-2 enzyme, which mediates in inflammatory processes (39, 40).

The role of topical steroids in ulcerative keratolysis is controversial. On the one hand, there are two mechanisms through which steroids reduce the inflammatory cascade: they inhibit the phospholipase A2 pathway, which causes a reduced production of arachidonic acid, the precursor to numerous inflammatory mediators; corticosteroids also block COX-2 enzymes and therefore would be expected to block some of the paradoxical effect of high nonphysiologic doses of NSAIDs (41). On the other hand, topical steroids play a role in delaying corneal healing processes (36-37), where they may act synergistically with NSAIDs in the development of ulcerative keratolysis, although NSAIDs have a greater deleterious effect.

In the three cases presented herein, topical antibiotics and cyclopentolate were administered, in addition to NSAIDs and steroids. Other studies have also reported combined treatment of topical NSAIDs, artificial tears, an-

tibiotics, and hypotensive drugs (29-32). Further research would be necessary into the role of these drugs and their preservatives in the development of corneal complications when administered in conjunction with topical NSAIDs.

It is important to draw attention to the possible appearance of toxic keratolysis in patients treated with topical NSAIDs and steroids following vitreoretinal surgery. To reduce the occurrence of this complication, both the frequency and the duration of these combined treatments should be reduced as much as possible. Moreover, we recommend frequent monitoring of patients during combined treatment to achieve early detection of these asymptomatic corneal lesions. Discontinuance of topical NSAIDs is sufficient to resolve these lesions, making suspension of treatment with topical steroids unnecessary.

The authors have no proprietary interest.

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