Graefe's Arch Clin Exp Ophthalmol
(2005) 243: 780–784

CLINICAL INVESTIGATION

DOI 10.1007/s00417-004-1089-2

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Relationship of eye burns with calcifications of the cornea?

Received: 26 September 2004
Accepted: 27 October 2004
Published online: 9 March 2005

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Abstract *Introduction:* The clinical pattern of corneal calcification has been considered to be a part of chronic eye diseases, such as uveitis, severe glaucoma, keratitis and eye burns. Since, in some cases of eye burns, we have found corneal calcifications to be related to the initial calciferous caustic agents and to the use of phosphate-buffer-containing fluids, we have reviewed our files of clinical eye burns for the incidence and appearance of corneal calcification. *Methods:* A total of 176 burnt eyes of 98 patients suffering from severe eye burns were retrospectively reviewed. The following data set was acquired: the type of caustic agent, the time of the burns, the delay and type of immediate treatment and the time and type of first aid, the subsequent medication, the clinical grading and the later results. *Results:* Calciferous burning agents and corneal calcification are correlated ($P<0.01$). Initial single rinsing with phosphate does not produce corneal calcification ($P=0.134$). There is evidence that corneal calcifications are correlated with chronically administered phosphate-buffered eye drops ($P<0.005$). *Discussion:* Eye burns followed by calcifications follow two different major patterns: the corrosive substance contained calcium or the continued therapy was applied with phosphate-buffered eye drops. We present case reports of three different types of eye burns and later therapy resulting in corneal calcification. Corneal calcifications are presumably related to longer-lasting phosphate application. One suspicious mechanism is the low content of calcium ion stabilizing proteins such as hyaluronate or fetuin in treatments for severe eye burns. The exceeding of the solubility product of Ca^{2+} and PO_4^- results in the precipitation of calcium phosphates. In cases of chronic corneal disturbance, we recommend the elimination of phosphate-buffered medications to prevent corneal calcification.

Keywords Cornea · Calcification · Eye drops · Eye burns · Chronic inflammation

Introduction

Timolol-containing drugs in chronic glaucoma therapy have been implicated, in case reports, as a causative factor in corneal calcifications [4, 5]. Newer publications on corneal excimer surgery report similar corneal calcifications [2, 8]. If we focus on topically applied medications on such eyes, we find that these eye drops contain combinations of dexamethasone- or prednisolone-phosphate in phosphate-buffered aqueous drops. This has been argued by Taravella et al. to be the fundamental mechanism of band keratopathy [14]. A surplus supply of phosphate may exceed the physiological levels of phosphorous in the corneal stroma [7, 11].

Since we have found corneal calcifications after lime burns [10, 12], we have tried to identify the origin of this common clinical pattern. This was the starting point for animal experiments in which eye burns produced by sodium hydroxide were treated with a variety of rinsing solutions. We used saline solution, phosphate buffer at pH 7.4 and diphoterine in single applications of 500 ml and did not observe any calcifications of the corneas. If rinsing was increased to a 160-ml application of phosphate buffer, three times daily, for longer than 3 days, a 100% corneal calcification appeared compared with no calcifications in the saline treated group [13]. The appearance of calcium seems also to be related to degenerative processes such as scars [1].

Clinically, we have tried to verify our hypothesis that after, eye burns, an excessive supply with phosphate buffer increases the incidence of corneal calcification. This question has to be answered with respect to the corrosive agent and the galenics of topically applied therapeutics. To find parallels in clinical treatments and to verify our hypothesis, we have reviewed 496 records of patients with eye burns treated in Aachen within the last 20 years. As there exists no prospective studies on clinical eye burns, we have reviewed clinical retrospective data to identify similar clinical patterns on the current background of strong experimental animal data.

Methods

Retrospective study

In a retrospective study of the records of our patients treated in Aachen because of eye burns, we evaluated 176 eyes being completely documented concerning the corrosive substance, the burning accident itself, the initial rinsing fluids, the circumstances of emergency help and the continued therapy. We identified the type of eye burns and the corrosive substance and tried to evaluate whether this contained any calcium. Furthermore, we reviewed treatment data of initial and continued topical medications on the basis of whether the applied therapeutics contained phosphate buffer.

Statistics were performed on single eye data assuming independence of the right and left eye. This assumption results from observations in animal experiments [15] and on a patient being treated initially with phosphate buffer in one eye and with saline in the other eye. This patient showed a calcification in the phosphate-treated eye and none in the saline-treated eye. We used the exact test of Fisher. Post-testing was carried out with the Tukey–Kramer Test. All statistical tests were performed by Instat software (Graph Pad). Eyes with lime or concrete eye burns were excluded from further statistical testing of the influence of medications because the independence of local factors could not be assumed.

Results

We included 98 patients with 176 burnt eyes. The mean age of these patients was 36±13.5 at the date of the eye burn. There was no difference in age between women and men. The gender distribution was 90 male and 8 female. We included three children aged less than 10 years. We found no statistical difference in patients age or gender compared between the group of persons with calcified corneas or non-calcified corneas (Table 1).

The type of burning agent was distinguished in calciferous and non-calciferous corrosives. There was a strong correlation (Fisher's exact test $P<0.001$) between the clinical sign of corneal calcification and whether the corrosive contained calcium (Table 2).

First case report

This was a case of eye burns without calcium but continuously treated with phosphate buffer. The 35-year-old nurse was preparing a disinfectant solution (Spitacid). Large splashes of the concentrated fluid projected into her right eye. Spitacid contains in 100 g: 46 g ethanol (96%), 27 g isopropanol and 1 g benzyl alcohol with no calcium ions or phosphate buffer. After initial irrigation with phosphate buffer, the patient was treated with continued eye rinsing with phosphate buffer for 3 days, three times daily. The patient presented with total corneal erosion that did not resolve during treatment. The patient herself remarked an early clouding of the cornea and a severe decrease of vision during the first 3 days of treatment. Three weeks later, she presented at our department (Fig. 1). We found intense corneal calcification of the right cornea.

Second case report

This case concerned eye burns with lime, treated with phosphate buffer initially. The young man of 18 years suffered from lime burns as a projection of dry lime powder into both eyes. Rinsing was delayed for less than 30 s. Initial rinsing was performed with water and some minutes later continued for 3 days with Isogutt. The patient

Table 1 Demographic data

Age in years	Women	Men	Total	Sample
0–10	2	3	5	–
11–20	1	15	16	–
21–30	6	38	44	–
31–40	4	43	47	176
41–50	4	30	34	–
51–60	3	22	25	–
61–70	0	5	5	–

Table 2 Clinical result with respect to burning agent. The alkaline corrosive contained calcium in 56 cases and no calcium in 100 cases. Fisher's test $P<0.001$ indicates a significant correlation between the burning agent and corneal calcification

Calcium within the corrosive substance?	Non-calcified corneas	Calcified corneas
Yes	25	31
No	77	23
Total	102	54

presented at our department with the beginning of corneal calcifications on day 4 after the eye burn accident (Fig. 2).

Third case report

This case involved eye burns with lime, treated without phosphate-buffer-containing eye drops and rinsing solutions. The 32-year-old male patient was hit by a projection of calcium oxide powder from a bursting tube. His eyes were rinsed within 3 min with saline solution. Rinsing and local therapy was continued without phosphate-containing eye drops. Figures 3 and 4 show an initially opaque but not clearly calcified cornea. There is a distinct development of corneal calcification.

Type of initial rinsing fluid

The type of initially used fluid was noted as to whether it was phosphate-containing or non-phosphate containing. This was not statistically correlated with corneal calcifications (Table 3; $P=0.134$). Furthermore, we tried to evaluate

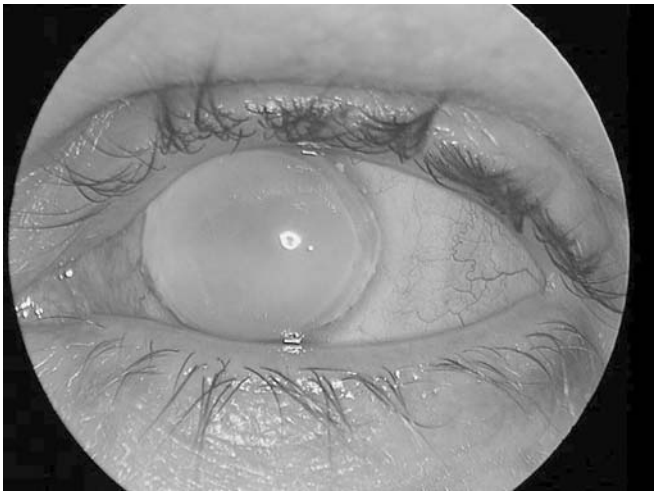

Fig. 1 Corneal calcification of a burnt eye. This eye was burnt with Spittacid disinfectant. The therapy consisted of intensive rinsing with phosphate buffer for 3 days. The image shows the case 4 weeks after eye burns

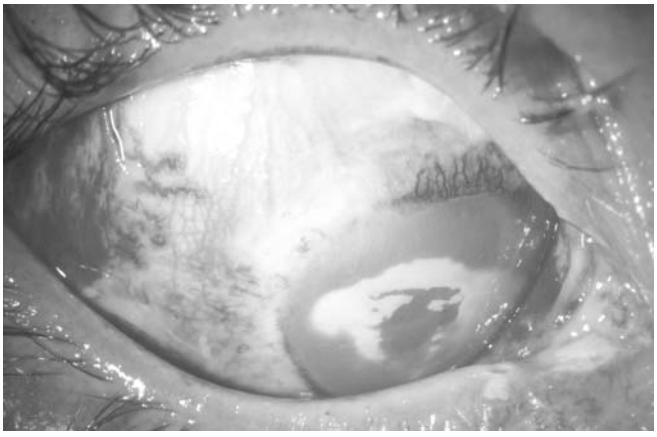

Fig. 2 Corneal calcification after severe eye burns with lime. Conjunctival necrosis and ischemia are visible. The initial rinsing with Isogutt was discontinued after 3 days and Reim's scheme of ascorbate-steroid and "Aachener Cocktail" was applied. The first image was taken 5 days after burning of the eye.

cases with continued phosphate-buffer rinsing, which we rarely found documented in our records, other than the two cases presented as case reports. We assume that this rinsing has taken place more often but is not documented in the patient files. Although there is evidence that continued rinsing can cause corneal calcification, as seen in the patient shown in Fig. 1, we do not enough cases definitively to prove that the origin of calcification is continued eye rinsing with phosphate buffer.

It was an interesting finding that the rinsing agent changed with the team involved in the treatment. First-aid kits at the work-place are equipped with specified first-aid rinsing solutions, such as Tim-Ohthal, Isogutt or similar products, whereas ophthalmologists and hospitals tend to use saline or other preparations, such as balanced salt solutions or Ringer lactate.

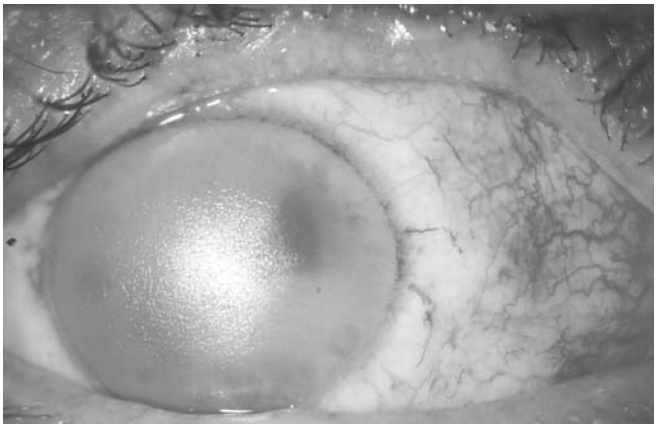

Fig. 3 Eye burnt with lime; grey opaque but not calcified cornea. Conjunctival ischemia is still present

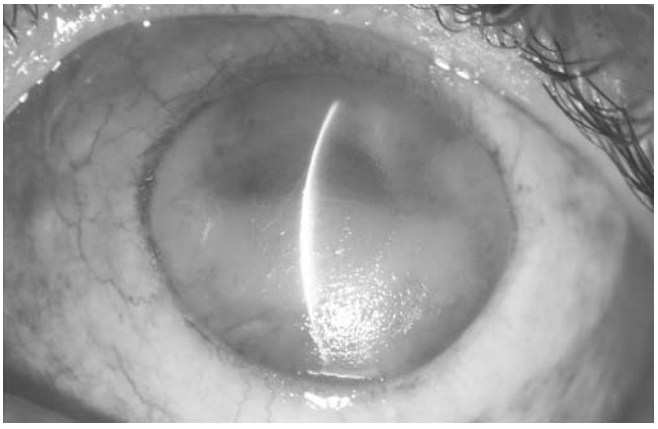

Fig. 4 The eye shown in Fig. 3 but two months later, having been treated with phosphate-free eye drops for 6 months. Small intrastromal hazy calcification is visible

Continued medication

We found that corneal calcification correlates positively with administered phosphate-containing eye drops in long term treatment (Table 4; Fisher's exact test $P<0.005$). Therapy with phosphate-containing eye drops is common because at least two thirds of the topical eye drops available on the German market contain phosphate buffer as a typical galenic component.

Discussion

Animal experiments show that calcification is a result of continued application of phosphate after eye burns [13]. Clinical cases represent similar patterns [14]. Single rinsing procedures seem to be harmless with respect to this phenomenon in experimental groups. The normal constituents of the corneal stroma [7] have been detected and the initial therapy of eye burns changes the corneal constituents in animals significantly [15], i.e. we have evidence that the cornea is susceptible to electrolyte conditioning after eye burns. This susceptibility is increased when the natural protective mechanisms are removed by the burns themselves. Calcium-binding proteins such as fetuine and hyaluronate are therefore necessary in these cases. Our measurements of sulphur in the burnt cornea indicate a loss of sulphurinated acid glycosaminoglycans caused by corneal burning and the subsequent rinsing therapy [7, 14]. Further, the burning agent remains within the cornea and the conjunctiva [9–11, 13]. Our present study in the clinical situation confirms these experimental results. The calciferous agent burning the cornea results in a significantly elevated rate of calcifications within the patients corneas (cases 2 and 3). The continued therapy with phosphate-containing eye drops and rinsing fluids acts in the same way.

The mechanism of the calciferous precipitation may involve the exceeded solubility product of free calcium and phosphate ions leading to calcium phosphate precipitations. These precipitations are promoted by the loss of non-ionic calcium-stabilising proteins such as fetuin [6] or hyaluronic acid. If these proteins are denatured by eye burns, they lose their calcium-binding properties and release ionized calcium. Thus, the concentration of free ionized calcium increases and ionized phosphate is added as a treatment. Furthermore, collagen fibres denuded of their glycosaminic envelope proteins are known to act as nucleic crystallisation inductors, as occurs during bone matrix formation. Therefore, calcium phosphate probably precipitates onto the collagen fibres. Calcification should be inhibited not by using phosphate-buffered solutions in emergency care. There are alternatives, such as borate buffers, acetate buffer, Ringers-Lactate and Previn. These alternatives should not promote complications. Our group uses non-phosphate-containing eye drops in eye burns therapy as long as corneal erosion is present.

Table 3 Clinical severity and status of corneal calcification after eye burns in relation to initial rinsing fluid. Initial treatment: 32 eyes with and 96 eyes without phosphate buffer. The Fisher test gives a P value of 0.24 resulting in a not significant correlation between initial rinsing and severity of eye burns and a P value of 0.14 showing that there is no evidence for corneal calcification correlating with initial therapy (56 eyes burnt by calciferous corrosives were removed from these data analysis, see Table 2, row 1)

Severity of eye burns and outcome	Type of initial rinsing therapy		Missing data
	With phosphate buffer	Without phosphate buffer	
Grade I/II	5	26	–
Grade III/IV	27	70	–
Total	32	96	48
Clinical result			–
Cornea calcified	15	31	–
Cornea not calcified	17	65	–

Table 4 Clinical result with respect to continued eye drops and rinsing therapy differentiated into phosphate-containing and not-phosphate-containing.The Fisher test gives a P-value <0.005 meaning that there is a significant correlation between columns and rows interpreted as a correlation between calcifications and phosphate containing eye drop treatment

Severity of eye burns and outcome	Treatment in continued eye care		Total
	With phosphate buffer	Without phosphate buffer	
Severity of eye burns, n (eyes)=152			
Grade I/II	12	22	34
Grade III/IV	51	67	118
Total	63	89	152
Clinical outcome			
Calcified	31	23	54
Non calcified	32	66	98

Nevertheless, rinsing is the best recommended first-aid measure to be taken in cases of eye burns. None of the readership should delay rinsing a burnt eye. Nearly all types of potable cold fluids, such as water, lemonade, coke or milk are applicable. All these are better than waiting for sterile solutions. The overwhelming aim during the first few seconds of therapy by rinsing is to eliminate excess corrosive substance and to minimize the amount of penetration into the tissue. Currently used rinsing hypotonic solutions without phosphate are: tap water or distilled water. Non-phosphate-containing fluids with serum osmolarity are: sterile 0.9% saline solution (e.g., Wero-medical, NaCl 0.9%, Baun Melsungen), balanced salt solution (BSS from Alcon, Opsia), Ringers solutions (from Fresenius or Braun Melsungen). The phosphate-buffer-containing rinsing fluids of serum osmolarity are Eye-saline, Isogutt, Tim-Ophthal and BSS-plus. Other hyperosmolar fluids used in eye burns rinsing are the amphoteric rinsing solutions containing a new substance called Diphoterine. All fluids are good for initial rinsing but their subsequent specific action may be less effective. We wish to point out the obvious side-effects of corneal calcification resulting from phosphate buffer application during the continued care of eye burns.

Conclusion

These findings support the hypothesis that continued therapy must be adjusted to the organ being treated. For intraocularly applied fluids, this is a well-accepted truth [15] but, for the therapy of the cornea, we need adjusted fluids to support the specific re-establishment of corneal electrolytic hemostasis. Phosphate buffer in eye drops for chronic diseases such as glaucoma and uveitis should be reviewed carefully regarding their manner of action. The previously reported cases of corneal calcification following treatment with steroids and timolol have not yet been collected in a statistically valuable database. The authors believe that, following their experience with eye burns, the type and development of complications is similar but not so obvious.

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