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Corneal calcification after chemical eye burns caused by eye drops containing phosphate buffer

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Abstract

Purpose: Chemical burns with calcium containing corrosives as well as irrigation with phosphate buffer solutions after eye burns bear the risk of corneal calcification. The aim of this study was to evaluate the correlation between the occurrence of corneal calcification after chemical injuries and the usage of phosphate buffer containing local therapeutics.

Methods: We reviewed the data of 179 patients who have been treated in the University Eye Clinic Aachen, Germany, between 1941 and 2000. Only when the corrosive did not contain calcium and when the initial irrigating solution did not contain phosphate buffer, respectively, were patients included in the study. The cases were analyse, if the patient was treated with phosphate buffer containing eye drops/ointment during the first 7 days of hospitalization or as an out-patient, and if corneal calcification was visible by slit-lamp examination during the follow-up. Statistical analysis was performed using Fischer's exact test.

Results: 152 eyes were included. From 63 eyes treated with phosphate buffer containing eye drops, 31 eyes (49%) developed corneal calcification. From 89 eyes treated without phosphate buffer containing eye drops, only 23 eyes (26%) developed corneal calcification. The two-sided p-value of Fischer's exact test is 0.0036.

Conclusion: During follow-up after chemical eye burns, eye drops containing phosphate buffer double the risk of corneal calcification. We recommend avoiding these agents in order to prevent the burned cornea from additional opacity. Substances containing phosphate buffer are listed in this article.

Keywords: Eye burn; Calcification; Cornea; Calcium; Phosphate; Irrigation; Phosphate buffer

1. Introduction

Severe chemical eye burns cause up to 27% of traumatic ocular injuries [1–3]. Up to 23% of these cases result in permanent visual impairment [4]. Since eye burns, depending on their severity, present a chronic inflammatory disease, follow-up treatment of these eyes often requires long periods of hospitalization and extended therapy [5,6]. The relation between corneal calcifications and eye burns with calcium containing corrosives (lime, cement) has been studied in detail and has been reported in the past. The risk of developing calcification with visual impairment is significantly higher when the corrosive contains calcium.

It has been described that initial irrigation with solutions containing phosphate buffer induce corneal calcification, thus the benefit of an initial irrigation with tap water or sodium chloride solution, respectively, has become widely accepted [7]. Irrigating solutions containing chelating agent (e.g. Previn®/Diphotérine®, Prevor, France) with enhanced buffer properties are widely discussed and may be an alternative to sodium chloride solution or tap water [8]. Because, severe eye burns are most often due to accidents or assaults, and the lack of special sterile irrigating solutions and the absence of medical knowledge of the first aiders often lead to the use of tap water, that is still the most frequent and accessible solution for the initial irrigation, in

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addition low priced, with best properties concerning intraocular pH-changes avoiding following intraocular injury [9], and decreasing the risk of ocular calcification.

The initial "professional" treatment of patients with eye burns by qualified staff, either hospitalized or as an out-patient, consists of repeated irrigation with sterile solutions, removal of the causative agent, if necessary including surgical intervention, and the frequent application of eye drops and ointment (steroids, antibiotics and moistening substances) depending on the severity of the ocular damage. Whereas, isolated severe eye burns are mostly treated in highly specialized ophthalmologic centers, patients with additional severe skin burns or organ damage are often hospitalized in intensive care units without specialized ophthalmologic personnel.

This study intends to evaluate the correlation between the occurrence of corneal calcification after chemical injuries and the usage of phosphate buffer containing eye drops and ointment, in order to improve the post trauma treatment in non-ophthalmologic units, which is one of the critical factors in determining long-term prognosis.

2. Methods

We reviewed the data of 179 patients suffering from eye burns who have been treated in the University Eye Clinic Aachen, Germany, between 1941 and 2000. Ninety-seven percent were within the last 20 years. Only when the corrosive did not contain calcium and when the initial irrigating solution did not contain phosphate buffer, respectively, were the eyes included in the study. The eyes were analysed if the patient was treated with phosphate buffer containing eye drops or ointment during the first 7 days of hospitalization or as an out-patient, and if corneal calcification, no matter the quantity, e.g. as total opacity (Fig. 1) or just as a haze (Fig. 2) was visible by slit-lamp examination during the follow-up. Statistical analysis was performed using Fischer's exact test.

Fig. 1. Corneal calcification as dense opacity after corneal eye-burn.

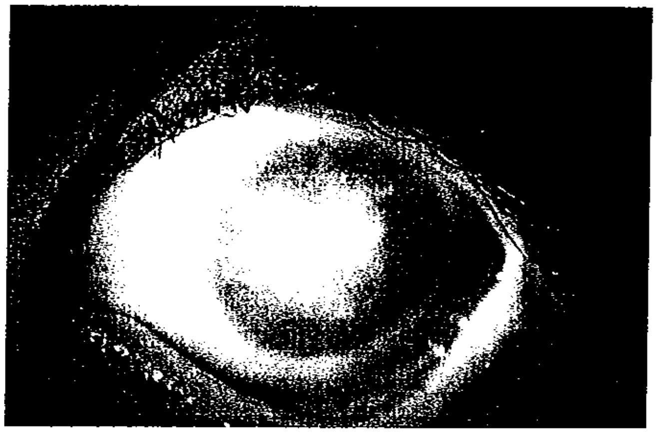

Fig. 2. Corneal calcification as haze after corneal eye-burn.

3. Results

One hundred and fifty-two eyes were be included in the analysis. In 82% the burned eyes were classified as severe eye burns, grade III or IV according to Reim with the prognosis of a defect healing (grade III) or even function loss (grade IV) [10]. This is a relatively high rate compared to other studies [11,12] and may be explained by an accumulation of these cases in our clinic specialized in the follow-up treatment of severe eye burns, but also due to the slightly worse prognosis after burns with caustic potash or sodium hydroxide solution, compared with lime-burns, an agent that contains calcium.

Twenty percent of the prescribed substances in our study contained phosphate buffer. These substances are listed in Table 1. From 63 eyes treated with phosphate buffer containing eye drops, 31 eyes (49.2%) developed corneal calcification during the follow-up. From 89 eyes treated without phosphate buffer containing eye drops, only 23 eyes (25.8%) resulted in corneal calcification, whereas, 66 corneas remained clear (Table 2). The two-sided p-value of Fischer's exact test is 0.0036, considered very significant. The row/column association is statistically significant.

4. Discussion

Although phosphate buffer is known for its neutralization of alkaline and acid corrosives and has proven to have a positive influence on intraocular pH levels after eye burns [13–17], several authors have recommended the avoidance of phosphate buffer containing irrigating solutions for emergency treatment due to the high incidence of corneal calcification [7,8,18]. Already in 1982, based on animal experiments and clinical observations, Reim and Schmidt-Martens stated that initial irrigation with phosphate buffer solution has been proven of value in the treatment of eye-burns, but may lead to indissoluble precipitation of calcium phosphate in the cornea [10]. Consecutive animal experiments have shown that, after repeated irrigation with

Table 1
Substances/eye drops containing phosphate buffer used in our study

Drug	Company
Adsorbonac 5%	Alcon
Alcon BSS PLUS	Alcon
Alerg	I A Pharma
Aquapred-N	Winzer
Arrutimol uno 0.25%/0.5%	Chauvin ankerpharm
Artelac-/EDO	Mann
Arteoptic 1%/–2%	Novartis Ophthalmics
Aruclonin 1/16%	Chauvin ankerpharm
Arufil/-uno	Chauvin ankerpharm
Arutimol 0.25%/–0.5%	Chauvin ankerpharm
Berberil Dry Eye/-EDO	Mann
Berberil N/EDO	Mann
Betam-Ophtal	Winzer
Biolon/-Prime	Pharma Stulln
Blephamide N Liquifilm	Pharm-Allergan
Carbamann 1%/–2%/–3%	Mann
Chibro-Timoptol 0.1%/–0.25%/–0.5%	Chibret
Clonid-Ophtal 1/16%/18%/–1/8% sine	Winzer
Corneregel Fluid	Mann
Cromohexal + U D	Hexal
DexaEDO	Mann
Dexamytrex	Mann
Dexa-sine	Alcon
Dexa-sine SE	Alcon
Dispacromil/-sine	Novartis Ophthalmics
Dispasan/-plus	CIBA Vision
Dispatim 0.25%/0.5% sine	Norvatis Ophthalmics
Dispatim 0.25%/–0.5%	Norvatis Ophthalmics
DNCG STADA	STADA
DNCG Trom	Trommsdorff
Duo Visc	Alcon
Efflumidex	Pharm-Allergan
Efflumycin Liquifilm	Pharm-Allergan
Enuclen	Alcon
Fluoreszein SE Thilo	Alcon
Fluoro-Ophthal	Winzer
Fluoropos	Ursapharm
Gentamytrex (Ophthiole)	Mann
Gent-Ophtal	Mann
Healon/-GV/-5	Pharmacia
Hylo-COMOD	Ursapharm
Iridil N sine	Winzer
Isoglaucon 1/–16%/–1/8%/–1/4%	Alcon
Isogutt/ATlösung	Winzer
Isopto-Dex	Alcon
Isopto-Flucon	Alcon
Kombi Stulln N	Pharma Stulln
Lacri-Stulln U D	Pharma Stulln
Levophta	Novartis Ophathalmics.Winzer
Liquifilm N	Pharm-Allergan
Mydrum	Chauvin ankerpharm
Neo-Mydrial 10%	Winzer
Ophtagram	Chauvin ankerpharm
Ophtalmin N	Winzer
Ophtalmin N sine	Winzer
Pan-Ophtal	Winzer
Posilent	Ursapharm
ProVisc	Alcon
Refobacin	Merck
Remydrial	Winzer
Siccaprotect	Ursapharm
Sic-Ophtal N	Winzer
Sic-Ophtal sine	Winzer
Terracortril N	Mann
Terramycin N	Mann
Timo-Comod 0.1%/–0.25%/–0.5%	Ursapharm
TimoEDO 0.25%/–0.5%	Mann
Timohexal 0.1%/–0.25%/–0.5%	Hexal
Timolol CV 0.1%/–0.25%/–0.5%	Norvatis Ophthalmics
Timolol-POS 0.1%/–0.25%/–0.5%	Ursapharm
Timolol-ratiopharm 0.25%/–0.5%	Ratiopharm
Timomann 0.1%/–0.25%/–0.5%	Mann
Tim-Ophtal 0.1%/–0.25%/–0.5%	Winzer
Tim-Ophtal 0.1%/–0.25%/–0.5% sine	Winzer
Timosine mite 0.25%/–0.5%	Chibret
Timo-Stulln 0.25% U D/0.5 U D	Pharma Stulln
Timpilo/-forte	Chibret
Totocortin	Winzer
Vasopos N	Ursapharm
Vidisept	Mann
Visiol	TRB Chemedica
Vislube	TRB Chemedica
Vismed	TRB Chemedica
Vistagan Liquifilm 0.1%/–0.25%/–0.5%	Pharm-Allergan
Vistagan Liquifim 0.5% OK	Pharm-Allergan
Xalacom	Pharmacia
Xalatan	Pharmacia

phosphate buffer, macroscopic visible calcifications occurred after 4 days [18]. These findings have also been published in human case reports [7].

The biochemical mechanism of corneal calcification is not yet completely understood. In the past, authors have discussed a complex formation of the phosphate and uncombined calcium, either from the decomposing tissue, the corrosive itself, status of inflammation or the calcium-ions in the tear-film. In previous animal experiments, we rinsed burned rabbit corneas with phosphate buffer solution. The mineral content of the cornea was determined in different stromal layers using energy-dispersive X-ray analysis (EDXA) in the scanning electron microscope. EDXA revealed a higher content of calcium and phosphate in the anterior stroma compared with the posterior stroma, indicating an inflow of phosphate ions from the irrigating solution [18]. When the solubility product of free calcium and phosphate ions is exceeded, calcium phosphate precipitations may result. These precipitations are promoted by the loss of non-ionic calcium-stabilizing proteins such as

Table 2
Contingency table for Fischer's exact test, comparing corneal calcification and phosphate buffer content of eye drops

	Corneal calcification		Total
	Yes	No	
Eye drops containing phosphate buffer	31 (20%)	32 (21%)	63 (41%)
Eye drops without phosphate buffer	23 (16%)	66 (43%)	89 (59%)
Total	54 (36%)	98 (64%)	152 (100%)

p-Value = 0.0036, considered very significant.

fetuin or hyaluronic acid [19]. After the denaturation of these proteins caused by the eye-burn, they lose their calcium-binding properties and release ionized calcium, which in combination with the phosphate ions from the irrigating solution, leads to corneal calcification.

Taravella et al. reviewed cases of calcific band keratopathy associated with the use of topical steroid-phosphate preparations and assumed a combination of several factors like epithelial defects, topical application of eye drops, inflammation, penetrating keratoplasty, HSV-infection and dry eyes as causatives for corneal calcifications. He recommends withdrawal of steroid-phosphate preparations in patients who develop band keratopathy [20]. These results indicate that corneal calcification is not only a problem in severe eye burns, but also in other diseases with stromal disturbance. Based on Travella's results, Pavan-Langston concludes that the concentration of calcium and phosphate ions in the tear film comes close to saturation. Additional topical phosphate may cause imbalance between the substances and consecutive corneal calcification, aggravated by dry eye and/or corneal ulceration [21]. Most of the authors have concluded that eye drops containing phosphate buffer should not be used for prolonged application not only after corneal burns, but also for other diseases with epithelial damages e.g. Steven's Johnson Syndrome [20,22]. Nevertheless, according to our knowledge, the reaction of the burned cornea to eye drops containing phosphate buffer during long-term treatment, which is often inevitable, has not been proven until now. The analysis of these data is subject to eye clinics with high volumes of severely burned patients or to controlled animal experiments in order to obtain reliable data.

The result of our study, that 25.8% of the patients, although they were not treated with phosphate buffer containing eye drops or ointment, developed corneal calcification supports the hypothesis that corneal calcification is a complex event with numerous causes that needs further experiments to find a biochemical explanation.

Although this is not a controlled study and therefore conclusions are limited, the statistically significant results suggest that after chemical eye burns, the usage of eye drops or ointment containing phosphate buffer correlates with corneal calcification. It may therefore increase the risk of corneal opacity. Thus, we recommend the avoidance of drugs containing phosphate buffer not only for the initial irrigation, but also during the follow-up treatment, when opacity of the cornea is undesirable in order to prevent the burned cornea from additional complications.

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