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Comparison of emergency eye-wash products in burned porcine eyes

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Abstract *Background:* The long-term prognosis of patients with chemical eye burns depends on immediately rinsing the eye after the trauma. The chemical properties and tolerance of currently used rinsing solutions were examined. *Methods:* NaCl 0.9%, Ringer lactate, balanced salt solution (Aqsia), phosphate buffer, tap water, and Previn were analyzed. The buffer capacities were determined by titration with HCl and NaOH. The osmolarity of the solutions and the osmolarity of 100 healthy and 100 alkali burned porcine corneas were determined by means of freezing point depression. 56 enucleated porcine eyes were burned and rinsed with NaCl solutions of different osmolarities (0–1200 mosmol/l), Previn, NaCl 0.9% or phosphate buffer, respectively. The different swelling behaviors were determined by pachymetric measurements, and the resulting corneal osmolarity after irrigation was assessed. The effect of Previn as a hyperosmolar solution in comparison with isoosmolar phosphate buffer was examined on 10 healthy human eyes. *Results:* Only phosphate buffer and Previn show high buffer capacities. The osmolarity of the healthy/burned porcine corneas was 329±61/1203±289 mosmol/kg. Except for Previn (862±3 mosmol/l), all solutions are hypo- or almost isoosmolar in comparison with the healthy cornea. Rinsing of the burned corneas causes swelling in all groups in inverse proportion to the osmolarity of the solution. Thus, the lower the solution's osmolarity, the stronger the swelling reaction of the cornea. The resulting corneal osmolarity following rinsing behaves proportionally to the osmolarity of the rinsing solution. Therefore, a high osmolarity of the rinsing solution correlates with a high corneal osmolarity. No long-term effects in healthy eyes were observed after rinsing with Previn or phosphate buffer. *Conclusion:* Corneal thickness and osmolarity are significantly correlated to the osmolarity of the rinsing solution. Corneal edema dilutes the agent in the stroma. Therefore, we recommend solutions with low osmolarity (tap water) or high buffer capacity (Previn) for the initial post-trauma irrigation.

Introduction

Severe chemical eye burns cause up to 26.5% of all traumatic ocular injuries [5, 10,15]. Up to 23% of these cases result in permanent bilateral visual impairment. The population at greatest risk is young males [12]. Most of the accidents occur at work and in domestic situations. A smaller number of burns result from personal assault [6]. Alkali burns occur more frequently than eye burns caused by acid substances. The treatment of alkali burns often requires long periods of hospitalization and extended therapy [17]. Depending on the remaining visual acuity, job retraining or retirement is often inevitable [7]. This study intends to improve the immediate post-trauma treatment, which is the critical factor in determining long-term prognosis.

The corneal epithelium and endothelium act like membranes localized between the stroma and the anterior chamber or the medium located on the corneal surface (e.g., tear fluid, eye drops, contact lenses), respectively. If a burning agent comes into contact with the cornea, the epithelium is destroyed first, and the agent is able to invade the stroma. Due to the concentration gradient, water flows into the cornea from tear fluid and later from aqueous humor, which causes stromal edema [14]. If the agent is a highly concentrated alkaline, the pH inside the anterior chamber rises rapidly within 1–2 min and irreversible damage of intraocular structures may occur once the intracameral pH exceeds 11 [2,11]. The immediate rinsing of the burned eye prevents further damage to the eye in two ways. First, the invading agent is diluted and removed. Second, and more desirable, the agent is neutralized. All the irrigation solutions that are currently used fulfill the cleansing requirements. However, the buffer capacity and osmolarity of the different rinsing solutions vary. The properties of common rinsing solutions were examined in several studies with regard to their buffer capacity, osmolarity, and their influence on corneal thickness. As differences in osmolarity between cornea and rinsing solution can cause epithelial damage and discomfort, healthy human eyes were irrigated with Previn in comparison with phosphate buffer solution in order to determine the effect of high tonicity.

Material and methods

Study 1: Buffer capacity

Buffer capacity is defined as the ability of a solution to absorb additional alkali or acid while maintaining its pH. As cornea and aqueous humor alone have low buffer capacities [3], it is imperative to rinse initially with a solution of high buffer capacity in order to ensure swift binding of the harmful agent. The importance of phosphate buffer capacity for the initial treatment of burns was described by Laux in 1975 [9].

In the first study, the buffer capacity of commonly used rinsing solutions was evaluated. The buffer range between pH 5 and pH 8 was chosen as being medically relevant, since the eye tolerates pH changes within this range without resulting in great damage [18]. The buffer capacity of the following solutions was examined: (1) tap water, (2) NaCl 0.9%, (3) Ringer lactate, (4) balanced salt solution (BSS; Aqsia), (5) phosphate buffer, and (6) Previn (Prevor, France). Previn contains diphoterine, a high-molecular amphoteric molecule which buffers both H^+ and OH^- ions. The buffer capacities were determined by measuring the pH with a microelectrode (MI-413, Microelectrodes, USA) after titration with 0.1 N HCl and 0.1 N NaOH in steps of 100 µl.

Study 2: Osmolarity

The osmolarity is defined as the concentration of osmotically active particles expressed in terms of milliosmoles of solute per liter of solution (mosmol/l) or per cornea mass (mosmol/kg). This influences the swelling and de-swelling capacities of the healthy cornea.

Osmolarity of the above-mentioned solutions was determined by means of freezing point depression with an Osmomat 030, Gonotec. Ten specimens (100 µl) of each solution were measured. In a second experiment, 100 healthy porcine corneas and 100 porcine corneas burned with 4 N NaOH for 60 s were carefully excised to determine the corneal osmolarity. Following fixation with liquid nitrogen, the corneal wet weight was determined. After lyophilization of the corneas over 48 h, their dry weight was defined (Lyovac GT 2 E, Finn-Aqua). The corneas were ground and rehydrated by adding their water content (water content = wet weight – dry weight). The suspensions' osmolarity was also measured with the Osmomat 030.

Study 3: Correlation between corneal swelling and osmolarity

The concentration gradient is defined as a regular concentration change over a distance in a particular direction. Concentration gradients between solutions separated by a membrane, e.g., tear film and corneal epithelium/stroma, cause a diffusion of elements down the gradient. If a membrane is not permeable for these elements, a diffusion of water from the side of lower element concentration to the side of higher concentration results (osmosis). Since the results of the first study showed that common rinsing solutions differ distinctly concerning their osmolarity, a second study set out to illustrate the different swelling behaviors of 32 burned porcine corneas due to osmotic stress schematically. Sodium chloride solutions of different osmolarities (400 mosmol/l, 800 mosmol/l, and 1200 mosmol/l) were produced by varying the amount of NaCl. By application of a ring (17 mm in diameter) onto enucleated porcine globes, 4 N NaOH was used to burn the corneas for 60 s. Four groups of eight eyes each were rinsed with 0.5 l tap water (0 mosmol/l) or with NaCl solution of 400 mosmol/l, 800 mosmol/l, or 1200 mosmol/l for 5 min. The occurrence of corneal edema immediately after burning and during irrigation was measured by ultrasound pachymetry (Pachypen, Mentor). After 5 min the corneas were excised and the resulting corneal osmolarity was then determined as described for study 2. Then three groups of eight corneas each were burned and rinsed with phosphate buffer, Previn and NaCl 0.9% in the same manner.

Study 4: Tolerance

The application of a hyperosmolar solution causes pain in the healthy eye [13]. Therefore, we examined the effect of Previn in comparison with isoosmolar phosphate buffer on healthy eyes.

This experiment was approved by the ethics commission of the RWTH Aachen and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion to the study. Ten healthy subjects (age 27±5 years) underwent rinsing of one eye with 0.5 l of Previn or phosphate buffer solution, preserved with benzalkonium chloride, respectively. Two weeks later the second eye was rinsed with the other solution. The study was performed double-masked. Before, immediately after, and 3 days after rinsing, every patient underwent a sight test, slit-lamp examination, pachymetric measurements, and confocal microscopy (Microphthal; Hund, Wetzlar). The participants were asked about their subjective sensations on rinsing with the solution.

Results

Study 1

The buffer capacities of the different rinsing solutions are shown in Fig. 1. Both phosphate buffer and Previn are distinguished by having a very high buffer capacity for both acidity and alkalinity (Fig. 1). Tap water, BSS, Ringer lactate, and NaCl 0.9% have only low or no buffer capacity. Therefore, phosphate buffer and Previn are suitable for use in first-aid treatment in terms of buffer capacity.

Study 2

The corneal osmolarity of the 100 healthy porcine corneas was 329±61 mosmol/kg. One hundred corneas burned with 4 N NaOH showed an osmolarity of 1203±289 mosmol/kg. The osmolarity of the tested solutions differed distinctly, as shown in Fig. 2. Except for Previn (862±3 mosmol/l), all of the tested rinsing solutions are hypoosmolar or almost isoosmolar in comparison with the healthy porcine cornea (Fig. 2). Previn is hyperosmolar in comparison with healthy corneas, but is hypoosmolar relative to burned corneas. The Turkey-Kramer multiple comparisons test showed that the *P* values among all groups were less than 0.001, i.e., the differences were highly significant.

Study 3

Rinsing of the burned cornea causes an increase of corneal thickness in all groups, as shown in Fig. 3. This swelling is in inverse proportion to the osmolarity of the solution. Thus, the lower the solution's osmolarity, the stronger the swelling reaction of the cornea. Statistical analysis showed no significant difference in this respect between the corneas rinsed with NaCl solutions of 800 and 1200 mosmol/l. The *P* values of the differences among all other solutions were less than 0.001, i.e., highly significant (Turkey-Kramer multiple comparisons test).

The corneal osmolarity following burning and rinsing is in proportion to the osmolarity of the rinsing solution (Fig. 4). Therefore, a high osmolarity of the rinsing solution correlates with a high corneal osmolarity. Statistical analysis reveals a high correlation coefficient of r=0.9854.

Figure 5 shows the correlation between the corneal thickness and the resulting corneal osmolarity after rinsing with NaCl solutions of four different osmolarities, NaCl 0.9% and Previn. The corneal swelling is in inverse proportion to the resulting osmolarity.

These findings suggest that irrigation with hypoosmolar solutions causes corneal swelling of the burned cor-

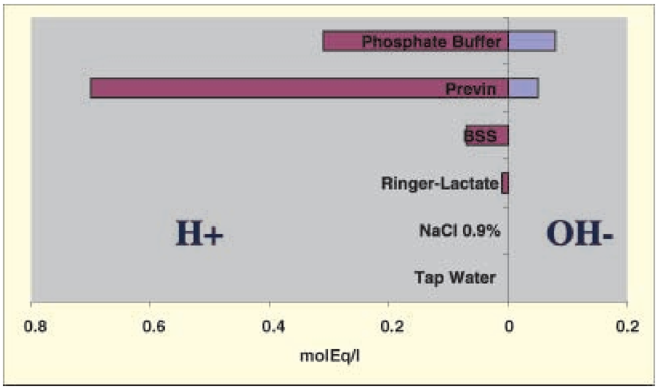

Fig. 1 Buffer capacity of different rinsing solutions, defined as the ability to absorb additional acid (*red*) or alkali (*blue*) while maintaining the solution's pH between 5 and 8

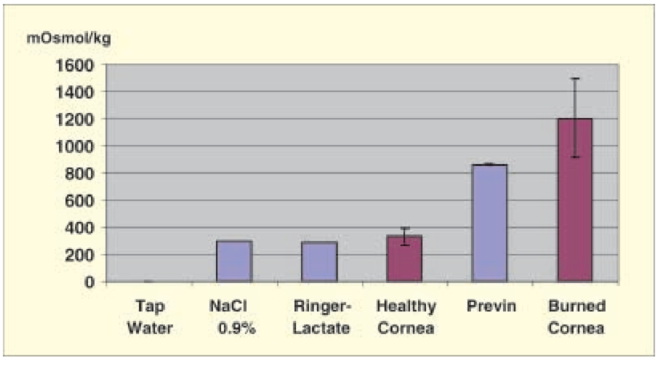

Fig. 2 Mean and standard deviation of the osmolarity of common rinsing solutions (n=40) in comparison with 100 healthy porcine corneas and 100 corneas burned with 4 N NaOH. Highly significant differences among all solutions (P<0.001; Turkey–Kramer multiple comparisons test)

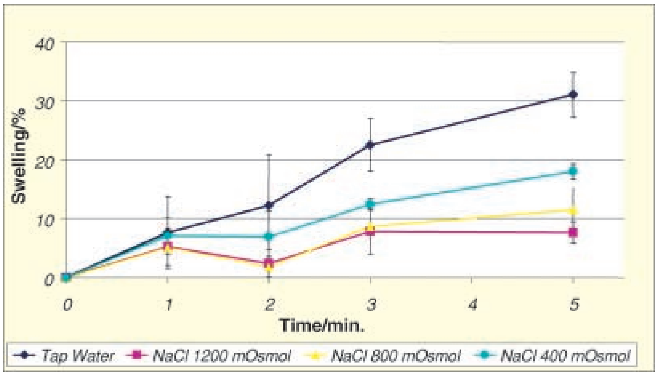

Fig. 3 Swelling of the burned porcine cornea throughout rinsing with NaCl solutions of four different osmolarities (n=32) to determine the osmotic effect schematically

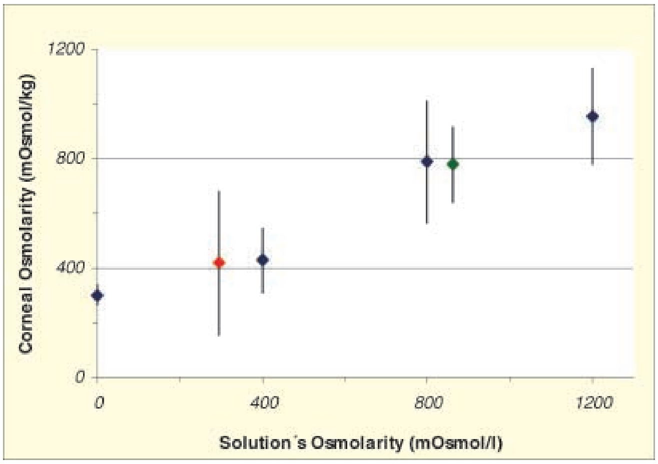

Fig. 4 High correlation between the osmolarities of the rinsing solutions and the corneal osmolarity after burning and irrigation (*n*=48); *r*=0.9854

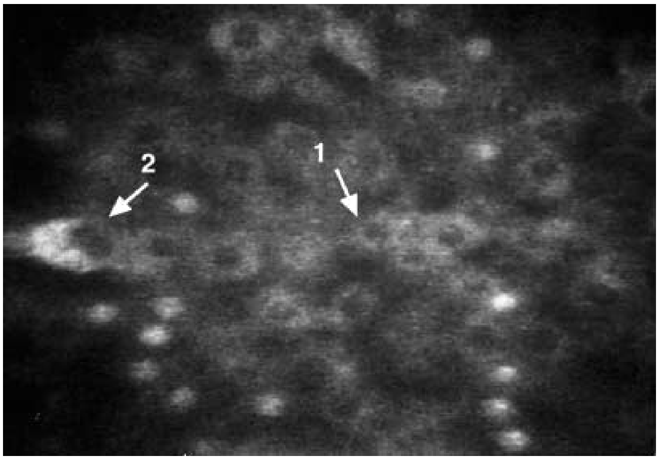

Fig. 6 Confocal microscopy: Occurrence of superficial cells(*1*) and wing cells (*2*) as indication for mechanical damage after irrigation

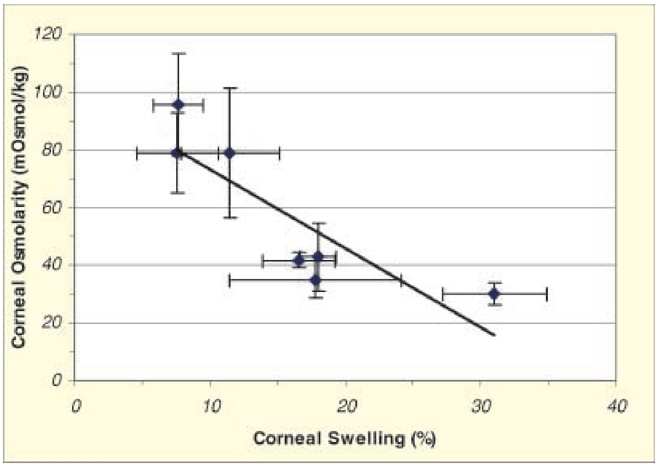

Fig. 5 Correlation between corneal edema after irrigation and resulting corneal osmolarity (*n*=56)

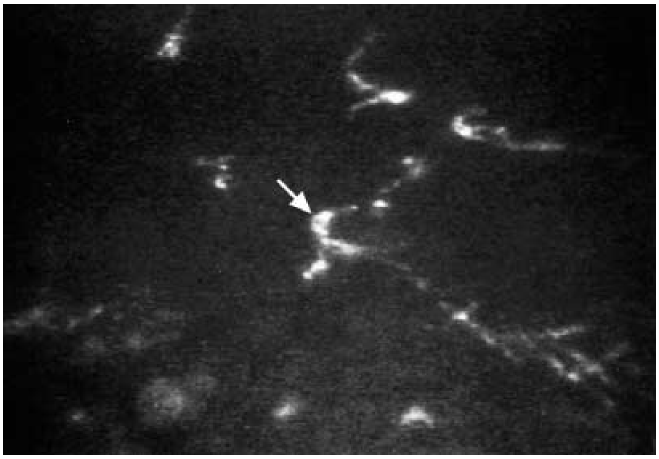

Fig. 7 Confocal microscopy of the tear film

nea due to osmosis, allowing the rinsing solution to penetrate quickly and dilute the burning agent. Hyperosmolar solutions cause less edema, suggesting that the agent remains more concentrated inside the stroma than after irrigation with lower osmolarities. These findings are in contrast to the hypothesis of Kuckelkorn et al. that hyperosmolar solutions mobilize the causative agent out of the stroma down the concentration gradient [8].

Study 4

The results and statistical analysis of study 4 are shown in Table 1. Immediately after rinsing with Previn, irritation with stipples occurred in one single case. Hyperemia and stipples occurred in seven eyes rinsed with phosphate buffer solution. The preservative of the solution, benzalkonium chloride, can be assumed to be the cause of these changes. After 3 days, complete restoration to the status before rinsing with Previn was observed. Throughout the in vivo confocal microscopic examination after rinsing, wing cells and superficial cells were visible in seven cases of both groups (Fig. 6), as well as an increase in reflecting images caused by a larger amount of tear film in five cases of the Previn group and four cases of the phosphate buffer group (Fig. 7). These are indications of epithelial edema and dissolution of cell adhesions resulting from mechanical stress. Since there is no significant difference between the two groups with regard to these findings, it is assumed that the rinsing

Table 1 Clinical findings and confocal microscopy immediately after rinsing with Previn and phosphate buffer solution containing benzalkonium chloride

Findings	Previn *n*=10	Phosphate buffer *n*=10	Significance (Fisher's exact test)
Slit lamp: hyperemia	1	7	+
Slit lamp: stipples	1	7	+
Confocal microscopy: increase of tear film	5	4	–
Confocal microscopy: wing and superficial cells	7	7	–
Subjective statement: burning throughout rinsing	2	8	+

process itself may have instigated this mechanical damage. In particular, solutions preserved by benzalkonium chloride are known to show those effects in confocal microscopy [4]. In contrast to the hypothesis, burning throughout the rinsing process was described in only two cases of the Previn group but in eight cases of the phosphate buffer group; this can also be explained as an effect of the preservative. Neither stroma nor endothelium showed any changes after rinsing. Pachymetric measurements showed no significant changes in corneal thickness after rinsing. No long-term effect could be observed on any of the healthy eyes.

Discussion

The varying effects on the thickness of healthy corneas after application of hypo- and hyperosmolar substances have already been described in several previous studies. Corneas with intact epithelium show an increased corneal thickness after application of hypoosmolar solutions and a decreased corneal thickness after rinsing with hyperosmolar solutions [1, 21]. Tear fluid has an osmolarity of 304–334 mosmol/l. Osmolarities between 290 and 350 mosmol/l are known to be well tolerated by the epithelium [19, 20]. After severe alkali burns, the epithelium is destroyed and no longer fulfills its function as a membrane. To our knowledge, the reaction of the burned cornea to different osmolarities has never been described. These studies show that, even without the epithelium, a correlation between the corneal swelling and the osmolarity of the rinsing solution can be observed. Solutions with low osmolarities neutralize the burning agent inside the cornea due to dilution, whereas solutions with high osmolarities penetrate much less and may therefore only neutralize the agent chemically by virtue of high buffer capacities. Thus, we suggest the use of tap water as a low-osmolarity solution (0 mosmol/l) without buffer capacity, and Previn as a solution with high buffer capacity and high osmolarity for the immediate rinsing after eye burns. Despite its hyperosmolarity, Previn used in healthy eyes is well tolerated with no long-term effects. When used on burned eyes, it shows a relief of corneal irritation. A clinical study is in progress at present. Long-term application of Previn leads to irritation and calcification. This effect has also been observed after irrigation with phosphate buffer. In particular, after repeated rinsing with phosphate buffer, macroscopic visible calcifications can be observed in the animal model after 4 days [16]. Figure 8 shows a patient who had suffered an alkali burn. Her eye was treated regularly with phosphate buffer included in eye drops (Isogutt) for 2 weeks. The picture shows a huge solid calcification. Therefore, eye drops containing phosphate buffer should not be used for prolonged application after corneal burns or other diseases involving epithelial damage.

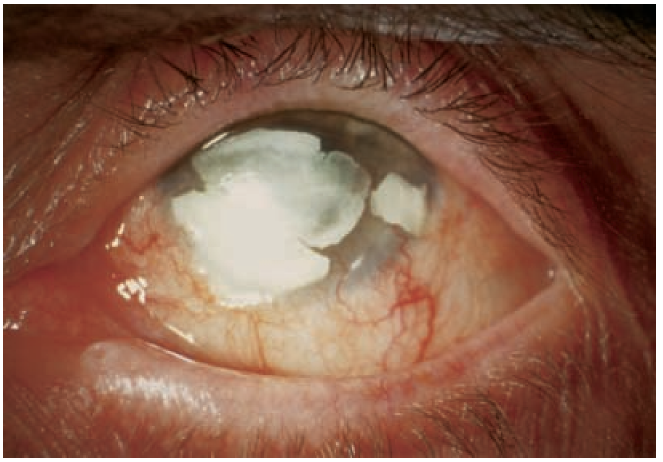

Fig. 8 Patient with alkali burn. Calcification after treatment with eye drops containing phosphate buffer (Isogutt)

The emergency treatment within the first few hours after the eye burn should consist of rinsing with a solution of high buffer capacity and with a high osmolar difference in comparison with the cornea. For subsequent treatment we recommend sterile, non-preserved solutions such as NaCl 0.9% or Ringer lactate.

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