Effect of topical 10% ascorbate solution on established corneal ulcers after severe alkali burns

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When established corneal ulcers induced by alkali burning were treated with 10% ascorbate drops, no perforations occurred, in contrast to a 25% incidence in the control group. If perforations and descemetoceles were grouped together, these differences became insignificant (i.e., 14.2% ascorbate-treated vs. 25% control). Prolongation of descemetocele presence without perforation in the ascorbate-treated group indicated some therapeutic effect. We conclude that topical ascorbate does not substantially alter the outcome of established corneal ulcers. (INVEST OPHTHALMOL VIS SCI 22:382-385, 1982.)

Key words: vitamin C, corneal ulcers, corneal alkali burns, rabbits

The high concentration of ascorbic acid in the aqueous humor is achieved by its selective transport from plasma perfusing the ciliary body.[1] In an alkali burn of the eye the ciliary body is injured, the ascorbic acid concentration in the aqueous humor falls to one third of normal levels, and corneal ulcerations and perforations develop.[2] When ascorbate injections raise the level of ascorbic acid in the aqueous humor to near normal levels, the incidence of corneal ulcerations and perforations is significantly reduced.[2, 3]

The efficacy of ascorbate treatment of alkali-burned eyes is dependent on the severity of the burn and the route of administration. Burns of lesser severity (20 sec, 12 mm, 1N NaOH) have decreased ulcerations and perforations when ascorbate is administered topically or by subcutaneous injection.[2-4] More severe burns (35 sec, 12 mm, 1N NaOH) respond to topical applications alone; the parenteral approach is ineffective by reason of inadequate intraocular penetration of ascorbate.[5]

In previous experiments with rabbits, ascorbate therapy was initiated immediately after the burn and continued to the termination of the study.[2-5] Clinically, it is important to know whether corneal ulcers, once established, respond favorably to topical ascorbate treatment. The present double-masked study reports the changes occurring in established corneal ulcers in response to topical ascorbate or placebo treatment.

Materials and methods

General considerations. Thirty-seven New Zealand Dutch strain albino rabbits of both sexes weighing 2.7 to 4.0 kg were used in this study. Anesthesia was achieved with 9 mg/kg xylazine and 9 mg/kg ketamine HCl administered intramuscularly. Each eye received topical tetracaine and was proptosed for alkali burning. A

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Table I. Results for treatment of established corneal ulcers with Adsorbotears (controls)

Identification	*Initial ulcer stage*	*Final ulcer stage*	*Aqueous ascorbic acid (mg%)*
C-1 OD	Anterior 3rd	Totally vascularized	13.43
C-2 OD	Anterior 3rd	Totally vascularized	11.24
C-3 OS	Anterior 3rd	Posterior 3rd	4.62
C-4 OD	Anterior 3rd	Totally vascularized	14.68
C-5 OS	Anterior 3rd	Totally vascularized	10.97
C-6 OS	Anterior 3rd	Totally vascularized	10.33
C-7 OS	Middle 3rd	Totally vascularized	15.03
C-8 OS	Middle 3rd	Perforated	8.59
C-9 OD	Middle 3rd	Superficial	2.25
C-10 OS	Middle 3rd	Perforated	11.74
C-11 OS	Middle 3rd	Totally vascularized	10.27
C-12 OD	Middle 3rd	Totally vascularized	10.69
C-13 OD	Middle 3rd	No ulcer	3.05
C-14 OS	Middle 3rd	Perforated	3.01
C-15 OS	Middle 3rd	Totally vascularized	6.78
C-16 OD	Middle 3rd	Totally vascularized	12.85
C-17 OD	Posterior 3rd	Totally vascularized	7.75
C-18 OS	Posterior 3rd	Perforated	12.50
C-19 OS	Posterior 3rd	Perforated	—
C-20 OS	Posterior 3rd	No ulcer	6.10
			$\overline{9.26 \pm 0.92}$ (S.E.M.)

OD = right eye; OS = left eye.

sharply defined 12 mm corneal burn was produced by pipetting 0.4 ml of 1N sodium hydroxide into a 12 mm plastic well held firmly against the cornea for 35 sec.[1] The interior of the well and the surface of the eye were then thoroughly irrigated with saline. Erythromycin ointment (0.5%) was immediately applied to each eye and three times daily thereafter. All eyes were examined daily by penlight. Examination of each eye for presence and depth of ulceration or perforation began on day 7 after injury. When ulceration was suspected, each eye was examined under a slit-lamp and binocular Nikon dissecting microscope to determine qualification for the study.

Criteria for entry into the study. To qualify for entry into the study, ulcers found in the anterior one third of the cornea needed to be present for a minimum of four successive daily observations (72 hr). Ulcers to the depth of the middle one third of the corneal stroma, posterior one third of the stroma, or descemetocele were admitted into the study on the day observed. These criteria ensured that the corneal ulcers entered into the study were active and not equivocal or transient. Corneal ulcers at each level were entered alternately into the experimental or control groups. If the second eye of a study animal ulcerated, it was entered into the same group as the first eye. In this manner 21 ulcers in 15 rabbits were entered into the experimental group and 20 ulcers in 14 rabbits entered into the control group.

Treatment and observation. Ulcerated eyes of the 15 experimental rabbits were treated topically with 10% sodium ascorbate in Adsorbotear (pH 7.2), and the control corneal ulcers from 14 rabbits were treated with Adsorbotear drops alone. The dropping regimen consisted of 2 drops of the appropriate solution applied to each eye at hourly intervals from 8:00 A.M. to 9:00 P.M. Each study eye was examined three times per week by a double-masked design.

Animals were terminated from the study before 66 days if the study eye progressed to perforation or the cornea totally vascularized; the earliest day of termination was 38 days. On the day of termination, eye drops begun at 8:00 A.M. were continued in the usual fashion to 1:00 P.M. Aqueous humor samples were obtained 15 to 45 min after the last drops. Ascorbic acid[6, 7] determinations were made on all samples. Data were evaluated statistically with the paired t test for significance of difference in proportions and test for outlying observations.[8]

Results

In this investigation 53 of 74 eyes ulcerated (71.6%), 41 of which qualified for entry into the study. The results of this experiment are summarized in Tables I and II. The only significant difference between groups was the five perforations occurring in 20 eyes of the

Table II. Results for treatment of established corneal ulcers with 10% ascorbate in Adsorbotear

Identification	*Initial ulcer stage*	*Final ulcer stage*	*Ascorbic acid (mg%)*
E-1 OS	Anterior 3rd	Totally vascularized	10.25
E-2 OD	Anterior 3rd	No ulcer	—
E-3 OS	Anterior 3rd	Totally vascularized	17.82
E-4 OD	Anterior 3rd	No ulcer	23.29
E-5 OS	Anterior 3rd	Totally vascularized	15.01
E-6 OS	Anterior 3rd	Posterior 3rd	17.68
E-7 OD	Middle 3rd	No ulcer	15.78
E-8 OD	Middle 3rd	Totally vascularized	24.07
E-9 OS	Middle 3rd	Totally vascularized	24.68
E-10 OD	Middle 3rd	No ulcer	28.39
E-11 OS	Middle 3rd	Totally vascularized	24.77
E-12 OD	Middle 3rd	Totally vascularized	3.95
E-13 OS	Middle 3rd	Totally vascularized	4.93
E-14 OD	Middle 3rd	Descemetocele	24.68
E-15 OS	Middle 3rd	Descemetocele	26.53
E-16 OS	Middle 3rd	No ulcer	—
E-17 OS	Middle 3rd	Totally vascularized	24.11
E-18 OD	Posterior 3rd	Totally vascularized	13.35
E-19 OS	Posterior 3rd	Anterior 3rd	18.91
E-20 OD	Posterior 3rd	Anterior 3rd	28.16
E-21 OD	Descemetocele	Descemetocele	31.85
			19.91 ± 1.80 (S.E.M.)

OD = right eye; OS = left eye.

Table III. Analysis of clinical observations for established corneal ulcers at end of experiment

	Experimentals (n = 21)	*Controls (n = 20)*	*Significance*
Total vascularizations	10	11	None
Nonulcerated corneas (excluding total vascularizations)	5	2	None
Anterior stromal ulcers	2	1	None
Posterior stromal ulcers	1	1	None
Descemetoceles	3	0	None
Perforations	0	5	$p < 0.02$
Perforations plus descemetoceles	3	5	None

control group (25%); none of the 21 eyes in the ascorbate-treated group perforated. However, if perforations and descemetoceles are considered together in each study group, the incidence in the ascorbate-treated group (14.2%) is not significantly different from the incidence in the control group (25%).

Descemetoceles in the ascorbate-treated group showed marked stability and, in some cases, evidence of healing (Table II). One ascorbate-treated eye with a descemetocele healed to a posterior stromal ulcer after 26 days. The three ascorbate-treated descemetoceles remaining at the end of this experiment remained stable for 28, 44, and 46 days without perforating. In contrast, five descemetoceles in the control group progressed to perforation in an average of 14.2 days, the longest period before perforation being 28 days (Table I). One additional descemetocele in this group progressed to total vascularization. The rest of the clinical data for the two groups did not differ significantly at the end of the experiment. Clinical data are summarized in Table III.

The mean aqueous humor ascorbate level of the control group was 9.2 mg% (n = 19), compared with 19.91% (n = 19) in the ascorbate-treated group. This difference is very significant ($p < 0.001$).

Discussion

Previous studies have demonstrated that when topical ascorbate treatment is instituted immediately after 20 or 35 sec alkali

burns (12 mm, 1N NaOH hydroxide) to the rabbit cornea, the subsequent incidence of ulceration and perforation is significantly reduced.[4, 5] The present study, designed to examine the effect of topical ascorbate therapy on established corneal ulcers, shows relatively few statistically significant differences between the ascorbate-treated and control groups. The incidence of perforations in the control group (25%) compared with that in the ascorbate-treated group (0%) suggests a stabilizing influence of topical ascorbate on descemetoceles, which is not readily understood. The difference cannot easily by discounted when one considers the rapidity of perforation in the five control corneas (mean 14.2 days from descemetocele to perforation) compared with the longevity of three descemetoceles without perforation in the ascorbate-treated group (28, 44, and 46 days at time of termination). Although statistically significant, clinicians may admittedly regard such differences as trivial, since large descemetoceles and perforations may be considered together as indications for surgical repair. Nevertheless, if corneal perforation, iris prolapse, and prolonged hypotony occur, they may present serious and well-known ocular complications.

Persistence of descemetoceles without perforation in the ascorbate-treated group cannot be considered specific evidence for healing. Such repair can only be suggested from two ulcers in the ascorbate-treated group that became descemetoceles but later partially healed to anterior and posterior ulcers. Such findings must not, in fact, be considered strong evidence for healing.

Changes in corneal ulcer depth, ulcer disappearance, and total vascularization in the remaining eyes did not show any significant differences or trends. One interesting observation was the statistically similar aqueous humor ascorbate levels in the eyes having totally vascularized corneas in the ascorbate-treated and control groups. As previously demonstrated, the intact epithelium over the totally vascularized cornea probably acts as a formidable barrier to corneal penetration by ascorbate.[4] The higher mean aqueous humor ascorbate level in eyes with epithelial defects but lacking total corneal vascularization supports this contention.

The results of this experiment suggest that for topical ascorbate treatment to be effective in alkali-burned animal eyes, it is necessary for it to be administered prior to the development of corneal ulcers. The effect of any delay in treatment prior to ulceration is unknown.

In summary, we conclude that topical ascorbate might provide some protection from perforation, even in the presence of descemetocele formation. There appears to be some trend for healing of some descemetocele in the ascorbate-treated group, but this is not statistically significant. Changes in ulcer presence, size, depth, or total vascularization in the remaining eyes of the ascorbate-treated and control series show no notable differences.

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