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The effect of tear substitute and silicone oil on re-epithelisation of the cornea

D.D. GATON, H. STIEBEL-KALISH, N. LOYA, D. WEINBERGER, Y. KASHTAN, A. SOLOMON

Abstract

Purpose **An animal model study was conducted to compare the effects of recurrent applications of an artificial cellulosic tear substitute and silicone oil on corneal re-epithelisation.**

Methods **A controlled wound was inflicted to the corneas of two groups of rabbits; one group was treated with tear substitute (5 eyes), while the other group received silicone oil (5 eyes). The left eye served as the control in both groups (10 eyes). The rate of re-epithelisation was measured at intervals of 6 h until complete wound closure was observed. After complete wound closure, the rabbits were killed and histological examinations were performed.**

Results **The wounds of eyes treated with tear substitute closed at a statistically significant faster rate (at 24, 44, 80 h; $p<0.05$) than those treated with silicone oil or the untreated eyes. At 48 h after re-epithelisation, the eyes treated with tear substitute presented a normal epithelium while the untreated and silicone-treated eyes presented an abnormally structured epithelium.**

Conclusion **This study demonstrates a favourable effect of tear substitute on corneal re-epithelisation in an animal model, in terms of both rate of re-epithelisation and histological aspects of the new epithelium.**

Keywords Cellulosic tear substitute, Corneal re-epithelisation, Silicone oil, Benzalkonium chloride

Surface abnormalities of the cornea, such as exposure defects, non-healing defects, abrasions and recurrent erosions, are commonly treated by eye closure with an eye patch and antibiotic ointment application. The need for eye patching has recently been questioned,[1-4] and may actually have adverse effects. Occlusion of the eye may induce an afferent pupillary defect,[4,5] and it may also cause stromal swelling of the cornea in a normal eye when a therapeutic contact lens is used.[6] Finally, eye patching has been shown to cause patient discomfort and induce temporary corneal irregularities, with decreased visual acuity in normal eyes.[1] When applied topically tear substitute and silicone oil act as lubricants and may decrease friction between the eyelid and the corneal surface, thus reducing local trauma to the regenerating epithelium. Given the current uncertainty concerning the need for eye patching, we designed an animal model to investigate the alternative treatment of recurrent topical applications of tear substitute or silicone oil for corneal re-epithelisation without eye patching.

Materials and methods

Ten male New Zealand albino rabbits, 3–4 months of age, were anaesthetised with an intramuscular injection of 1 ml xylazine (1%) and 1 ml ketamine (10 mg/ml). A corneal wound was inflicted in the right eye of all rabbits using a specially designed instrument (similar to a trephine knife) with rotating disc 10 mm in diameter, causing an identical epithelial defect 10 mm in diameter and 40 μm deep in all rabbits. The depth of the wound was controlled by an adjustment knob on the rotating disc so that the epithelial basement membrane remained intact, in a method similar to corneal trephination.

Two lubricants were examined:

1. Lyteers (Barnes Hind, USA), composed of cellulose derivatives 0.25%, NaEDTA 0.05%, benzalkonium chloride 0.01%, KCl 0.15% and NaCl 0.65%;
2. Silicone oil, 1000 cS (Dow-Corning, USA).

Immediately after wound infliction the rabbits were randomly divided into two groups using a random number system. Group 1 was treated with a drop of Lyteers (5 right eyes) and group 2 with one drop of topical silicone oil (5 right eyes). Further applications were equally administered at 6, 12, 18, 24, 30, 36, 44, 53, 61, 70 and 80 h after wound infliction. Timing of treatment was planned so that at the acute phase of healing medication was administered four times daily, and twice daily at the end of the process, as is common in everyday practice.

D.D. Gaton ✉
H. Stiebel-Kalish
N. Loya
D. Weinberger
Department of Ophthalmology
Rabin Medical Centre
Beilinson Campus
Petah Tiqva 49 100
Israel
Tel: 972-3-937-6101
Fax: 972-3-921-9084

D.D. Gaton
H. Stiebel-Kalish
N. Loya
D. Weinberg
Sackler School of Medicine
Tel Aviv University
Tel Aviv
Israel

Y. Kashtan
A. Solomon
Goldschleger Eye Research Institute
Sheba Medical Centre
Tel Hashomer
Israel

In all 10 rabbits the left eye was wounded using the same method and served as the control, i.e. remained untreated after corneal injury (group 3).

At each application of either Lyteers or silicone oil, rabbit eyes were examined by slit lamp microscopy and colour photographs were taken. Before each examination, the rabbits were anaesthetised and their corneas stained with a 2% fluorescein solution. The colour photographs were projected onto a millimetric grid scale from a fixed distance, and the epithelial defect was measured in square millimetres. The photographs and the projection were taken at the same magnification throughout the study. The examination of the wound was performed in a masked fashion, i.e. by an examiner unaware of the treatment modality, while the treatment was administered by another study participant.

After complete re-epithelisation, the rabbits were killed: 2 from each group at 24 h after complete wound closure and 3 at 48 h. The eyes were fixed and stained wih haematoxylin–eosin for microscopic examination.

Statistical analysis of the results was performed with analysis of variance with repeated measures. Probability values less than 0.05 were considered significant.

Results

Histological

Group 1

Histological examination of the eyes treated with tear substitute showed a regular, single-layered epithelium 24 h after wound closure, and a normal, multilayered

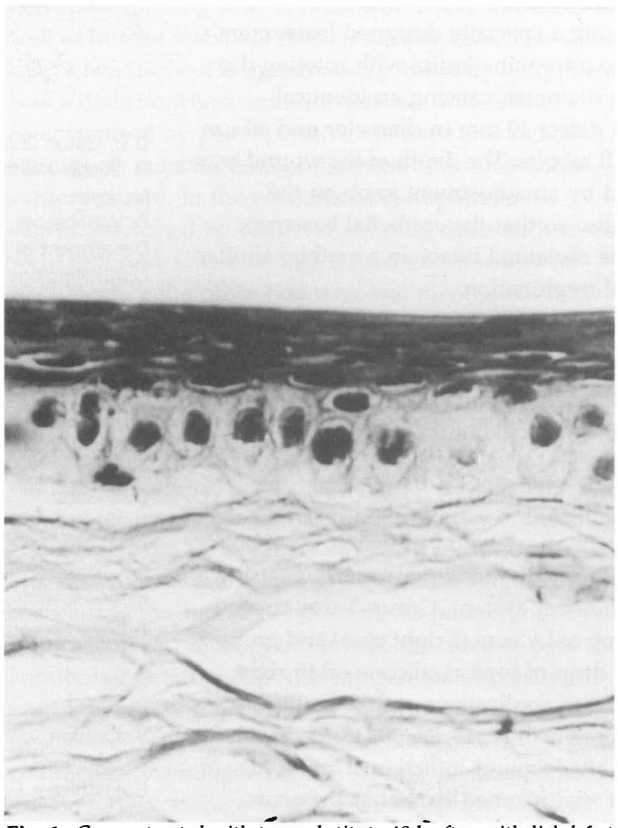

Fig. 1. *Cornea treated with tear substitute 48 h after epithelial defect healing. Note the normal multilayered epithelial structure. Haematoxylin–eosin, ×100.*

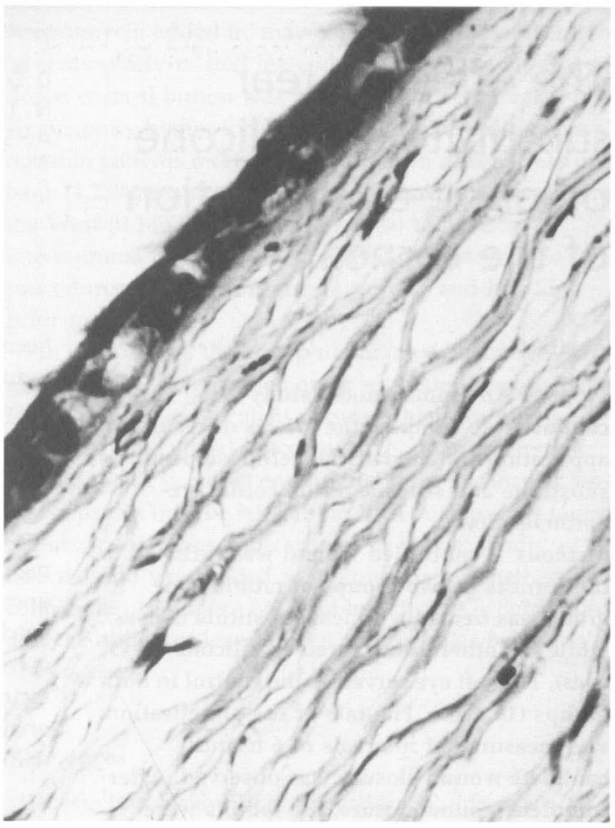

Fig. 2. *Untreated (control group) cornea, 48 h after epithelial defect healing. Note the ragged, single-layered epithelium. Haematoxylin–eosin, ×100.*

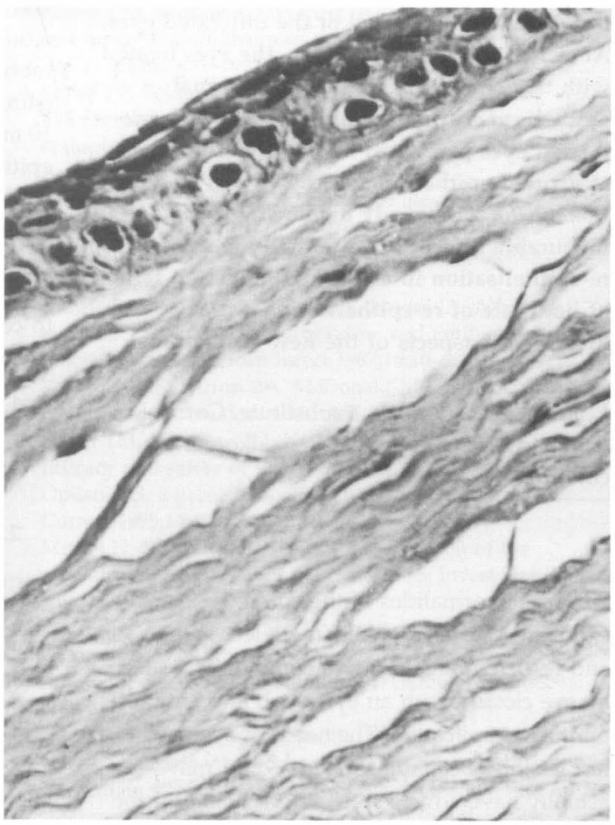

Fig. 3. *Corneal treated with silicone oil, 48 h after epithelial defect healing. A multilayered epithelium developed, but note the irregularity of the superficial epithelial layers, and the relative flattening of the cuboidal cells. Haematoxylin–eosin, ×100.*

Table 1. *Average (and SD) wound area in rabbit corneas treated with silicone oil and Lyteers (right eye) versus untreated (control) corneas (left eye).*

	Wound area (mm^2)		
Time (h)	Silicone oil-treated corneas	Lyteers-treated corneas	Untreated corneas (controls)
0	78.5 (±0)	78.5 (±0)	78.5 (±0)
6	78.5 (±0.3)	78.5 (±0.7)	78.5 (±0.5)
12	68.7 (±3.0)	68.1 (±6.4)	68.8 (±2.8)
18	59.2 (±4.7)	59.7 (±5.2)	59.2 (±5.3)
24	52.1 (±2.5)	47.7 (±5.0)	49.5 (±5.0)
30	45.4 (±3.2)	40.9 (±3.3)	44.8 (±6.7)
44	35.3 (±4.2)	29.2 (±2.4)	32.3 (±4.0)
61	24.8 (±1.7)	12.2 (±1.0)	16.4 (±2.5)
70	17.4 (±2.8)	9.4 (±2.1)	10.8 (±1.6)
80	9.6 (±3.4)	0.6 (±0.4)	3.1 (±2.2)

epithelium after 48 h of complete re-epithelisation (Fig. 1). In contrast, the control eyes showed a ragged, single-layered epithelium 48 h after clinical healing (Fig. 2).

Group 2

In the eyes treated with silicone oil, as well as in the control eyes, an irregular, multilayered epithelium was observed after 48 h of wound closure (Fig. 3).

Statistical

Group 1

Comparison of the epithelial defects, in square millimetres, between the right (treated) and the left (untreated) eye is shown in Table 1 and Fig. 4. The epithelial wounds of eyes treated with Lyteers closed at a significantly faster rate than the contralateral untreated controls. At 24 h the treated eyes had an average epithelial defect of 47.7 mm^2 as opposed to 49.5 mm^2 for the control eyes ($p>0.05$). At 44 h, the Lyteers-treated eyes had corneal wounds of 29.2 mm^2, while the wounds in the untreated eyes measured 32.3 mm^2 ($p<0.05$). After 80 h, corneas treated with Lyteers showed an average

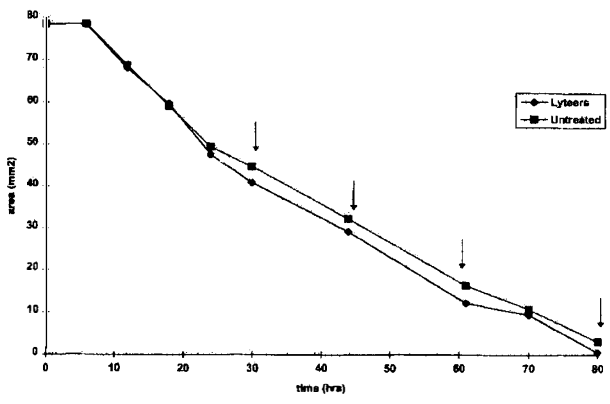

Fig. 4. *Rate of wound closure in rabbit corneas treated with Lyteers and untreated (control) corneas. The arrows indicate time points where there was a statistically significant difference (p<0.05) between the two groups.*

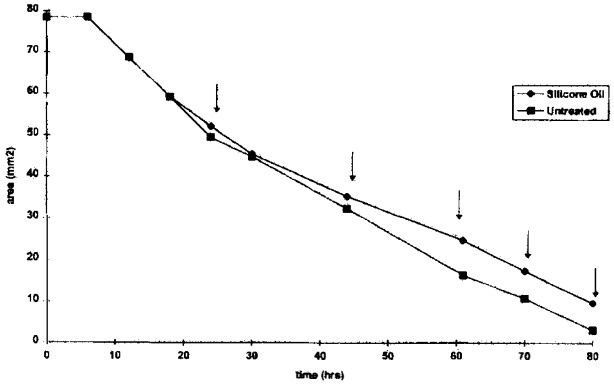

Fig. 5. *Rate of wound closure in rabbit corneas treated with silicone oil and untreated (control) corneas. The arrows indicate time points where there was a statistically significant difference (p<0.05) between the two groups.*

epithelial defect of 0.6 mm^2, while the wound of the untreated corneas measured 3.1 mm^2 at this time ($p<0.05$).

Group 2

The size of the epithelial defect and closure rate of the silicone oil and control group are also shown in Table 1 and Fig. 5, respectively. The eyes treated with silicone oil showed a significantly slower re-epithelialisation rate than the contralateral untreated eyes. At 24 h the mean epithelial defect measured 52.1 mm^2 in the treated eyes compared with 49.5 mm^2 in the untreated eyes ($p<0.05$). After 2 and 3 days this difference persisted; the defect measured 35.3 mm^2 at 44 h and 17.4 mm^2 at 70 h in the treated eyes and 32.35 mm^2 and 10.8 mm^2, respectively, in the untreated eyes ($p<0.05$).

Discussion

Artificial tear substitutes are in common ophthalmological use for 'dry eye' conditions. The commercial eye drops solution used in this study (Lyteers) contains cellulose derivatives, affording it lubricant action, and also benzalkonium chloride (0.01%) as a preservative. Lyteers proved to be effective in hastening the rate of corneal re-epithelisation, even though benzalkonium chloride is known to interfere with epithelial healing of the cornea.[7,8] It will be interesting, in the future, to study the effect of preservative-free artificial tears on corneal re-epithelisation.

Silicone oil is used for vitreoretinal surgery. Its advantages include transparency, a strong ability to dissolve oxygen,[9] and heat stability, allowing simple sterilisation.[9–12] Several studies have reported the use of silicone oil for exposure keratitis and diminished blinking conditions owing to its ability to dissolve oxygen 7 times better than saline.[11,12] In one study,[11] silicone was topically applied to rabbit eyes, resulting in only a minor effect, while in a second study[12] silicone application caused corneal oedema in rabbits. Our results

are in agreement with the latter work, although a study of a larger sample may be required to confirm these results.

The present study demonstrates a favourable effect of recurrent topical applications of tear substitute and a deleterious effect of silicone oil on corneal re-epithelisation in an animal model.

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