ORAL TETRACYCLINE IN THE TREATMENT OF RECURRENT CORNEAL EROSIONS

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SUMMARY

We report the results of a prospective, randomised controlled, 24 week trial to assess the efficacy of oral tetracycline and oral tetracycline with topical prednisolone in the treatment of recalcitrant recurrent corneal erosions, i.e. those which fail to respond to standard therapy. A total of 30 patients were randomly allocated to either standard treatment (group A), standard treatment and oral tetracycline (group B) or standard treatment, oral tetracycline and topical prednisolone (group C). Treatment groups B and C were instructed to perform daily lid hygiene. There was a significant reduction in the number of recurrent corneal erosions during the 24 week study period in group B (p = 0.04) and in group C (p = 0.0003) but not in group A (p = 0.66). There was a significant difference in the accelerated healing time of recurrent corneal microerosions between groups A and B (p = 0.001) and between groups A and C (p = 0.001). There was a significant improvement in the symptom scores during the study in treatment groups B and C (p = 0.005) but not in group A (p = 0.15). We conclude that lid hygiene and oral oxytetracycline 250 mg twice daily for 12 weeks with or without topical prednisolone for the first 7 days is beneficial in the management of recalcitrant recurrent corneal erosions.

Recurrent corneal erosion is a relatively common disorder, characterised by repeated episodes of early morning symptoms, with pain, difficulty opening the eyes, watering and photophobia.[1,2] The treatment of recurrent corneal erosions is difficult. The vast majority of patients respond to conventional therapy with topical lubricating ointment at night and patching in the acute stages.[3] There is a small group of patients, however, who fail to respond to conventional therapy. We have introduced the term 'recalcitrant recurrent corneal erosions' for that group of patients who continue to suffer recurrent corneal erosions in spite of conventional therapy. A variety of desperate therapeutic measures have been tried in this group in an effort to control the disorder, with limited success.[4]

Over a period of time we have observed extensive meibomian gland dysfunction in patients with recurrent corneal erosions. The purpose of this study was to evaluate in patients with recalcitrant recurrent corneal erosions the effect of treatment of meibomian gland dysfunction on (1) the rate of recurrent corneal erosions, (2) the symptoms in the recurrent corneal erosion syndrome and (3) the rate of healing of recurrent corneal erosions.

MATERIALS AND METHODS

The details of patient examination and clinical features are reported elsewhere.[5]

Materials

Standard treatment was defined as the following: (1) Simple eye ointment every night. (2) A macroerosion was treated with a single dose of preservative-free guttae (g) cyclopentolate 1% and g chloramphenicol, followed by patching for 24 hours and analgesia as required. (3) If the corneal epithelium was wrinkled and mobile and lying loosely over the underlying stroma, manual debridement of the corneal epithelium was performed.

Treatment with tetracycline consisted of 12 weeks of oral oxytetracycline 250 mg twice daily (b.d.). Preservative-free g prednisolone 0.5% four times daily (q.i.d.) was given for 7 days only. Lid hygiene involved the use of hot compresses for 5–10 minutes followed by lid cleaning using a moistened cotton-wool bud along the lid margins to remove debris from the lids and eyelashes.

Patient Selection and Entry

This study was approved by the Ethical Review Board at the Birmingham and Midland Eye Hospital. All patients gave written informed consent prior to study entry.

Exclusion criteria included: (1) any contraindication to oral tetracycline therapy, (2) previous treatment with oral

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Table I. Regime and duration of treatment in each group

	Group A	Group B	Group C
Standard therapy	24w	24w	24w
Lid hygiene	No	24w	24w
Oral oxytetracycline	No	12w	12w
Topical prednisolone 0.5%	No	No	1w

w, weeks.

tetracycline, (3) any concurrent ocular medication other than the study drugs.

Study Design

This was a single-centre randomised controlled study. At the initial study visit patients were randomised to one of three groups, using random number tables. All patients received standard therapy as detailed above for the entire 24 week study period. Group A was the control group. Group B was allocated to receive oral oxytetracycline 250 mg b.d. for the first 12 weeks of the study. Group C received preservative-free g prednisolone q.i.d. for 7 days at the commencement of the study and oral oxytetracycline 250 mg b.d. for the first 12 weeks of the study. Groups B and C were also instructed to perform daily lid hygiene (Table I).

At the initial study visit each patient was instructed in the use of a visual analogue scale. There were three symptom indices: pain, light sensitivity and watering. The visual analogue scale was an uncalibrated 10 cm line, which patients were instructed to cross to indicate the severity of symptoms for the preceding week. The right-hand side of the line represented the most severe symptoms and the left-hand side the least severe symptoms. A symptom score sheet was given for each week and patients were instructed to complete the symptom sheet on a weekly basis. They were also instructed to record the number of recurrent corneal erosions for that week and the duration of each recurrent corneal erosion.

Study visits thereafter were performed at 4, 12 and 24 weeks following study entry. At each review visit the number, type and duration of recurrent corneal erosions for the preceding time interval was documented. The symptom score sheets were collected. At each study visit the patients were given an appropriate number of score sheets to complete prior to the next visit.

Statistical Methods

For each group, repeated measures analysis of variance investigated the changes in the number of erosions over the 24 week study period by comparing the number of erosions at each week and adjusting for the correlation between data from different weeks. Changes in the symptom scores over this period were analysed in an identical fashion. The Mann–Whitney test was used to compare any improvements in the healing time of recurrent corneal erosions between groups A, B and C.

Table II. Demographic characteristics of patients with recurrent corneal erosions

	Group A: control (n = 10)	Group B: tetracycline (n = 10)	Group C: tetracycline and prednisolone (n = 10)
Males	2	6	5
Females	8	4	5
Mean age (years)	47.6	44.8	43.4
Age range (years)	27–69	33–56	30–77

RESULTS

The results of this study demonstrating the effect of treatment of recurrent corneal erosions are shown in Tables II–IV and Figs. 1 and 2.

Thirty patients were entered in the study. In group B, 1 patient discontinued oral tetracycline after 6 weeks of treatment, but he continued to attend for assessment and was analysed on an intention-to-treat basis. Twenty-nine patients completed the study per protocol and 30 patients are included in the analysis.

The demographics of the 30 patients analysed are shown in Table II. There were no statistically significant differences observed between the groups with regard to age, gender and recurrent corneal erosion history. The mean duration of symptoms was 5.3 years (range 0.4–47 years).

Recurrent Corneal Erosions

The number of recurrent corneal erosions, both microerosions and macroerosions, for each week of the 24 week study period was evaluated for each group. Using repeated measures analysis of variance, there was found to be a significant reduction in the number of erosions during the 24 week study period in group B ($p = 0.04$) and in group C ($p = 0.0003$) but not in group A ($p = 0.66$). The results are illustrated in Fig. 1.

A similar change was seen when the number of recurrent corneal microerosions was evaluated. During the course of the study, from commencement to 24 weeks, there was a significant reduction in the number of microerosions in group B ($p = 0.04$) and in group C ($p = 0.0003$) but not in group A ($p = 0.76$) (repeated measures analysis of variance). The results are illustrated in Fig. 2.

During the 24 week study period there was a total of 11 recurrent corneal macroerosions in group A, 2 in group B and 3 in group C. The difference between the three groups did not reach statistical significance, however, due to the small numbers involved (Table III).

Table III. Total number of recurrent corneal macroerosions: the total number of macroerosions for each group during the 24 week study period at selected time intervals

Time interval (weeks)	Number of macroerosions		
	Group A	Group B	Group C
0–4	4	0	1
5–12	2	0	1
13–24	5	2	1
Total	11	2	3

Table IV. Median healing time of recurrent corneal microerosions

Group	No. of patients	Healing time prior to enrolment (minutes)	Healing time at study completion (minutes)	Difference in healing time (minutes)
A	9	60	60	0
B	9	90	5	70
C	10	30	7.5	25

This table shows the median healing time of recurrent corneal microerosions at study enrolment and study completion. There was a significant difference in the accelerated healing time between groups A and B ($p = 0.001$) and between groups A and C ($p = 0.001$) but not between groups B and C ($p = 0.07$) (Mann–Whitney test).

The healing time of recurrent corneal microerosions at the commencement of the study was compared with the healing time at the completion of the study. There was an acceleration in the healing time of microerosions in group B and in group C but not in group A. There was a significant difference in the accelerated rate of healing in group B compared with group A ($p = 0.001$) and group C compared with group A ($p = 0.001$), but not between groups B and C ($p = 0.07$) (Mann-Whitney test). The results are shown in Table IV.

The symptom scores for pain, photophobia and lacrimation were summed for each week and the decrease in scores from baseline to completion was examined. The mean symptom scores at the commencement of the study were 9.27 in group A and 10.26 in groups B and C. At the completion of the study at week 24, the mean symptom scores were 6.6 in group A and 1.8 in groups B and C. At the completion of the study at week 24, the mean symptom scores measured 6.6 in group A and 1.8 in groups B and C. Repeated measures analysis of variance showed a statistically significant decrease in symptom scores in groups B and C ($p = 0.005$) but not in group A ($p = 0.15$).

No patients required epithelial debridement during the study. Two patients complained of slight alteration of bowel habit following commencement of oral oxytetracycline and this resolved within a few days with no sequelae. No other side-effects were reported.

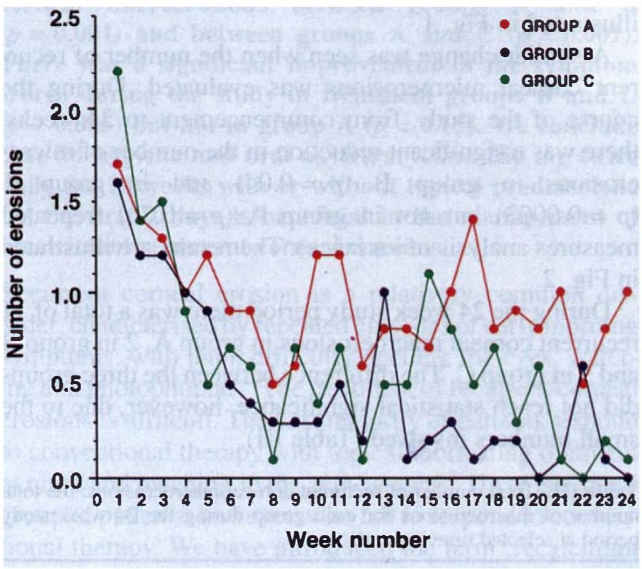

Fig. 1. *Number of recurrent corneal erosions. This shows the mean number of both microerosions and macroerosions for groups A, B and C. The mean number of recurrent corneal erosions for each week of the study from commencement to completion is illustrated. Over the 24 week study period there was a significant reduction in the number of recurrent corneal erosions in group B* (p = *0.04) and group C* (p = *0.0003) but not group A* (p = *0.66).*

DISCUSSION

The management of recurrent corneal erosions can be one of the most frustrating experiences in an ophthalmologist's practice. Delayed epithelialisation, persistent sloughing of the newly formed epithelium and recurrent episodes of epithelial loss are common problems. The ultimate cure has remained elusive. The mainstay of standard prophylactic treatment is lubricating eye ointment instilled at night, combined with epithelial debridement, if indicated.[3,6]

Various lubricating agents have been used: methylcellulose drops, 10% boric ointment, 5% hypertonic saline and liquid paraffin. The prevention of attacks is probably due to the oily film of ointment on the corneal surface which reduces contact of the corneal epithelium with the lids and tear film.

Epithelial debridement was first described in 1906 by Franke,[7] who combined mechanical debridement with chemical cautery using chlorine water. In addition to chlorine water, trichloroacetic acid, phenol and iodine have been used for chemical cauterisation.[3,8,9] Cogan *et al.*,[10] in 1964, refined the procedure and performed mechanical debridement of the corneal epithelium without the use of a chemical agent. The technique has been further modified to include a total superficial keratectomy with or without the use of contact lenses.[11] There have, however, been no

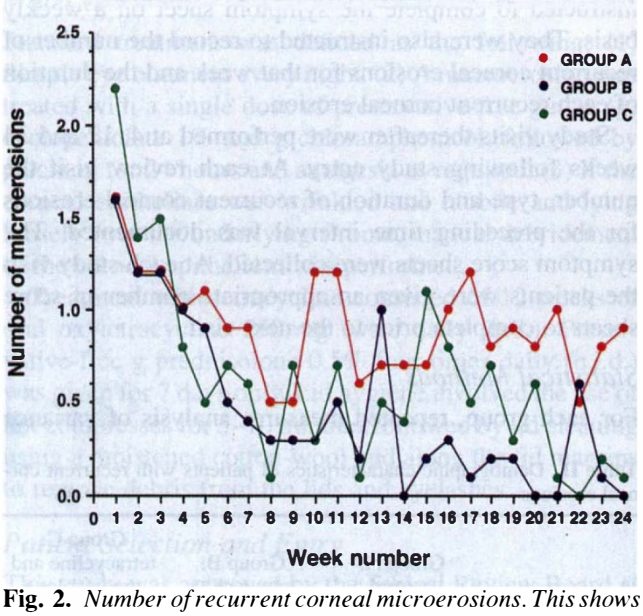

Fig. 2. *Number of recurrent corneal microerosions. This shows the mean number of microerosions for groups A, B and C. The mean number of recurrent corneal microerosions for each week of the study from commencement to completion is illustrated. Over the 24 week study period there was a significant reduction in the number of microerosions in group B* (p = *0.04) and group C* (p = *0.003) but not group A* (p = *0.76).*

controlled studies evaluating epithelial debridement in the management of recurrent corneal erosions.

We believe that corneal epithelial debridement is indicated only if the epithelium is wrinkled and freely mobile over the underlying stroma. We also believe that chemical cautery should not be performed due to the risk of scar formation. The corneal epithelium should be removed without disturbance of the underlying Bowman's layer in an effort to avoid corneal scarring.

Therapeutic contact lenses, anterior stromal puncture, topical steroids and surface diathermy and recently excimer laser have all been used with varying degrees of success in patients with recalcitrant recurrent corneal erosions.[12–15] These therapeutic manoeuvres are potentially associated with severe side-effects, including infection, corneal vascularisation and scarring, with subsequent impairment of vision. None of these approaches has cured the problem of recurrent corneal erosions.

In this study, we treated a group of patients suffering from recalcitrant recurrent corneal erosions. All had failed to respond to standard therapy. Treatment with lid hygiene and oral oxytetracycline 250 mg for 12 weeks resulted in a significant improvement in the control of recalcitrant recurrent corneal erosions. In spite of the relatively small numbers in each group, patients in the treatment groups had significantly fewer recurrent corneal erosions (group B, $p = 0.04$; group C, $p = 0.003$), the healing time of erosions was significantly accelerated (group B, $p = 0.001$; group C, $p = 0.001$) and symptoms improved (groups B and C, $p = 0.005$) compared with a control group. We were unable to find a significant difference between the group treated with topical prednisolone and tetracycline and those receiving tetracycline alone.

The pathogenesis of recurrent corneal erosions is poorly understood.[12,16] Patients frequently present following a superficial injury to the cornea. Other types of injury, such as chemical injuries, bacterial and viral corneal infections, have also been implicated. A history of trauma is not, however, invariable.[17] Recurrent corneal erosions can occur secondary to a number of corneal dystrophies.[2]

The corneal epithelium is normally firmly attached to basement membrane, which is adherent to Bowman's layer. Hemidesmosomes are anchoring fibrils which attach the epithelial basement membrane to Bowman's layer and to the underlying stroma. Following a superficial injury to the cornea, epithelial migration and multiplication occurs and the corneal epithelium forms new basement membrane and hemidesmosomes.[18] The restoration of maximum adhesion of the corneal epithelium to the underlying stroma takes 8 weeks.[19] This normal healing process is disrupted in the syndrome of recurrent corneal erosions.[20]

Histopathological examination in recurrent corneal erosions reveals abnormalities of the corneal epithelium, basement membrane and hemidesmosomes.[21,22] The corneal epithelium contains pale, swollen basal epithelial cells. Pseudocystic collections of cellular and amorphous debris are found within the epithelium and are thought to be due to entrapment of epithelium by aberrant basement membrane. The basement membrane is multilaminar, thickened and may be focally absent. Sheets of aberrant basement membrane may be found within the epithelium. Ultrastructural analysis reveals localised absence of hemidesmosomes.[23]

One theory to explain recurrent corneal erosions is that abnormal corneal epithelium results in abnormal hemidesmosome–basement membrane adhesion complexes.[1,16] There is periodic 'lift off' of the corneal epithelium which allows debris to accumulate subepithelially, providing an inadequate substrate for already defective basement membrane. The cycle is self-perpetuating. Separation of the corneal epithelium is more prone to occur at night. Tears become relatively hypotonic at night due to reduced evaporation, and superficial corneal odema may develop. It is thought that suction of the lids on opening results in tearing of the fragile epithelial attachments, which have been weakened by the associated odema.[1]

We believe that meibomian gland dysfunction is a causative factor in the pathogenesis of recurrent corneal erosions, based on a number of observations. (1) Superficial corneal injuries cause recurrent corneal erosions in some patients and no sequelae in others, so there must be some underlying ocular abnormality in those patients developing recurrent corneal erosions. (2) The commonest site of recurrent corneal erosions is not at the site of original trauma but the inferior cornea, that part of the cornea which has maximum contact with the tear film.[12] (3) We evaluated a group of patients with recalcitrant recurrent erosions and found extensive meibomian gland dysfunction in all patients as manifest by: dropout and inspissation of meibomian glands, reduced tear film break-up time in the presence of a normal aqueous component, injection of the conjunctival blood vessels and accompanying facial cutaneous changes.[5] (4) This study has shown that treatment of meibomian gland dysfunction alleviates the syndrome of recalcitrant recurrent corneal erosions.

The meibomian glands secrete the most anterior zone of the tear film, a lipid layer which enhances tear film stability and prevents evaporation of the preocular tear film.[24] Increased quantities of fatty acids have been demonstrated in the tears of patients with meibomian gland dysfunction.[25] It is possible that these fatty acids could interfere with the normal healing of corneal epithelium and the formation of hemidesmosomes which then causes the syndrome of recurrent corneal erosions.

Oral tetracycline administered in low doses is effective in the management of meibomian gland dysfunction. Our understanding of the exact mechanism by which tetracycline is effective in the treatment of meibomian gland dysfunction is limited as it has a variety of actions. Tetracycline may act by inhibition of the production of extracellular enzymes by the ocular flora or inhibition of the synthesis of lipids by meibomian glands.[26,27] Tetracycline also has an anti-inflammatory action independent of the antimicrobial effects and has been shown to bind to conjunctiva and the goblet cells.[28]

Many questions remain unanswered regarding the role of meibomian glands and tetracycline in recalcitrant recurrent corneal erosions. We do not know whether the meibomian gland dysfunction present in association with recalcitrant recurrent corneal erosions is a primary or secondary phenomenon. We do not understand the mechanism by which oral tetracycline is effective in recalcitrant recurrent corneal erosions. Further research into these aspects of the disease is necessary.

The results of our study show that treatment of recalcitrant recurrent corneal erosions can be successfully achieved by treatment of associated meibomian gland dysfunction with lid hygiene and oral tetracycline.

Key words: Macroerosion, Meibomian gland, Meibomian gland dysfunction, Microerosion, Oral tetracycline, Recurrent corneal erosion, Recalcitrant recurrent corneal erosion.

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