Corneal ulceration in south-east Asia III: prevention of fungal keratitis at the village level in south India using topical antibiotics

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Aim: To determine whether topical antifungal prophylaxis distributed by paid village health workers (VHWs) in south India is necessary after corneal abrasion to prevent fungal keratitis in a population where half of the ulcers are fungal.

Methods: Two panchayaths (village administrative units in Madurai district with a combined population of 48,039) were followed prospectively for 18 months by 15 VHWs who were trained to identify post-traumatic corneal abrasions. Patients fulfilling the eligibility criteria were randomised into two groups and treated with either 1% chloramphenicol and 1% clotrimazole ointment or 1% chloramphenicol and a placebo ointment three times a day for 3 days. Patients, doctors and VHWs were blinded to treatment.

Results: During the 18-month period, 1,365 people reported to VHWs with ocular injuries, of whom 374 with corneal abrasions were eligible for treatment. Of these, 368 (98.5%) abrasions healed without complications. Two patients had mild localised allergic reactions to the ointment, two dropped out and two patients in the placebo group developed microscopic culture-negative corneal stromal infiltrates that healed in 1 week with natamycin drops.

Conclusions: Both fungal and bacterial ulcers that occur after traumatic corneal abrasions seem to be effectively prevented in a village setting using only antibiotic prophylaxis.

Abbreviation: VHWs, village health workers
were residents of the study area; had pre-existing blindness (had corneal abrasion after ocular injury; confirmed by reported within 48 h of the injury; Age and sex distribution of 374 patients treated for corneal had bilateral ocular trauma; had incomplete lid closure; had penetrating corneal injury or stromal laceration; had dacryosystitis had trichiasis; were unwilling to participate. were patients aged were not residents of the study area;

Patients
Inclusion criteria
Participants were included in the study if they

- were residents of the study area;
- had corneal abrasion after ocular injury; confirmed by clinical examination with fluorescein stain and a blue torch;
- reported within 48 h of the injury;
- were patients aged > 5 years of age.

Exclusion criteria
Patients were excluded from the study if they

- were not residents of the study area;
- had clinically evident corneal infection;
- had penetrating corneal injury or stromal laceration;
- had bilateral ocular trauma;
- had pre-existing blindness (< 6/60) in the non-traumatized eye;
- had initiation of topical or systemic antibiotic treatment before examination by study personnel;
- had incomplete lid closure;
- had diabetes;
- had other injuries requiring hospitalisation;
- had trichiasis;
- had dacryosystitis
- were unwilling to participate.

Treatment
The VHWs accompanied all eligible patients to one of the two referral centres, where the diagnosis of a corneal abrasion was confirmed by an ophthalmologist. After obtaining written consent, patients were randomised by computer-generated numbers into two treatment groups, and each patient was given two tubes of ointment that were labelled A or B. Ophthalmologists, VHWs and patients were blinded to the contents of the tubes. Eligible patients were treated immediately with an application of one ointment, and instructed to apply both ointments two more times the first day and three times daily for the next 2 days, making a total of nine applications. House visits were made during the 3-day period by the VHWs to check for compliance. On the third day, the participants were brought to the referral centre by the VHWs to be examined by an ophthalmologist at the slit lamp. Those participants not returning to the referral centre were visited at their homes by the VHWs and examined with a fluorescein strip and a blue torch. The primary outcome was complete epithelialisation of the cornea without evidence of infection, or alternatively, the development of a corneal infiltrate or ulcer at the site of the abrasion. All study drugs (1% chloramphenicol ointment, 1% clotrimazole ointment and placebo ointment) were prepared by the pharmaceutical division at the Aravind Eye Hospital and seemed to be identical in both groups. The biostatistics department at Aravind Eye Hospital was custodian of the treatment code. The study was approved by the institutional review board of the Aravind Eye Care system and the WHO South East Asia Regional Office in Delhi.

RESULTS
During the 18-month period (October 2002–March 2004), 1365 ocular injuries were reported and identified by the VHWs. Of these, 409 (30%) patients had corneal abrasions, 334 (24.5%) had conjunctival lacerations, 91 (6.7%) had corneal injuries other than abrasions and 8 (0.59%) presented with corneal ulcers (table 1). Thirty five patients with corneal abrasion were excluded from the study because of the exclusion criteria, and of the remaining 374, 123 (32.9%) reported in the first 12 h, 89 (23.8%) from 13 to 18 h, 94 (25.1%) from 19 to 24 h and 68 (18.2%) from 25 to 48 h (table 2). Most abrasions occurred in the 21–40-year-old group (51.9%), and more male patients (66.3%) than female patients (33.7%) were diagnosed with abrasions (fig 1).

The 374 eligible patients with abrasions were enrolled and 205 (54.8%) were randomised to treatment A and 169 (45.2%) to treatment B. Four of the patients had adverse events, two dropped out of the study for unspecified personal reasons and 368 (98.5%) healed without complications. When the codes for treatment A (1% chloramphenicol ointment and placebo ointment) and treatment B (1% chloramphenicol ointment and 1% clotrimazole ointment) were unblinded, the four patients with adverse reactions were all in the treatment A (placebo) group. Two of the patients had mild chemosis and irritation secondary to the antibiotic and placebo ointments that were applied, and two of the patients developed small single corneal infiltrates at the site of the abrasion measuring < 0.5 mm in diameter at the slit lamp and located in the anterior stoma just beneath Bowman’s membrane. Both infiltrates, when cultured, were negative for fungi, but were treated empirically with 5% natamycin drops every 2 h for 1 week and resolved completely without complications.

Figure 1: Age and sex distribution of 374 patients treated for corneal abrasions.
DISCUSSION

This study is the third of a multicentre project carried out in three countries in South East Asia (Bhutan, Burma and India) in collaboration with WHO in New Delhi and the Aravind Eye Hospital in Madurai. In this population-based, placebo-controlled, prospective, double-blinded clinical treatment trial, a population of 48 039 living in the Sholavandan and Melur panchayaths of Madurai district was kept under daily surveillance for a period of 18 months from September 2002 to March 2004. All people with corneal abrasions who met the eligibility criteria were randomised and treated with topical chloramphenicol and clotrimazole, or topical chloramphenicol and a placebo ointment, to determine whether or not antifungal prophylaxis is necessary for the prevention of corneal ulcers in this population in which 50% of all ulcers are positive for fungi. The surprising primary outcome of the study was that an antifungal prophylaxis is apparently not necessary to prevent fungal keratitis. This becomes even more interesting when we consider that 47% of all the fungal ulcers in south India are caused by *Fusarium* spp., arguably one of the most destructive and invasive of all corneal pathogens.

These results are difficult to explain. There are examples of some antibiotics having antifungal activity. *Fusarium oxysporum* keratitis has been reported to respond to treatment with tobramycin, and in vitro studies have shown antibiotic inhibition ofpectolytic and cellulolytic enzyme activity in *F. oxysporum* by amoxycillin, and to a lesser extent by chloramphenicol, erythromycin and rifacilin. In the outbreak of *Fusarium* keratitis associated with contact lens wear that was recently reported from Singapore, 11 (16.2%) of the 68 eyes treated with topical antibiotics alone (gentamicin and cefalzolin) resolved “without the need for specific antifungal therapy”. *Fusarium* spp was isolated from all 11 eyes. A more pedestrian explanation, however, for why we did not see fungal ulcers in our study, even in the placebo group, is that our long-held belief that fungal organisms are inoculated into the corneal stoma at the time of the corneal abrasion is incorrect. This is reinforced by data from India, showing that abrasions caused by organic materials are just as likely to develop bacterial as fungal ulcers. Fungal pathogens may only be opportunists, waiting in the environment for a slow-healing epithelial abrasion to provide access to the corneal stroma. Perhaps rapid epithelialisation combined with a modest antifungal effect from the antibiotic, or from the ointment base itself, is enough to discourage corneal infection. The fact remains that at an incidence of 113 per 100 000, we expected 80 corneal ulcers, half of them fungal, to occur in our study population of 48 039 over 18 months. Instead, only eight “non-abrasion associated” corneal ulcers were seen (11/100 000), and 368 (98.5%) of the 374 abrasions receiving prophylactic treatment healed without complications. In the placebo treatment group, where we expected to see 20 breakthrough fungal ulcers, we found only two patients with culture-negative microscopic stromal infiltrates that we presumed were fungal. By contrast, a large nearby “control” village of 3094 people had five ulcers in 1 year, an incidence of 161 per 100 000.

Secondary outcomes of the study included a determination of the incidence of ocular trauma in the population (table 1), which was comparable to the data reported from Nepal. Unlike the studies in Nepal, Bhutan and Burma, patients with corneal abrasions in south India reported for treatment over a longer period (table 2), but this did not seem to affect the efficacy of the ulcer prevention regimen. In addition, paid non-governmental VHWs hired locally in India were found to be as effective in implementing and sustaining a corneal ulcer prevention programme as were volunteer VHWs in Bhutan and governmental VHWs in Burma. As in those countries, the compliance of the Indian population was directly related to the local involvement of the VHWs.

These findings raise an important question. We have shown previously that microbial keratitis after corneal abrasion can be prevented at the village level by simple public health strategies using antibiotic and antifungal prophylaxis tailored to the prevalence of pathogens causing corneal ulcers in the population. This study, however, raises the key question of which therapeutic regimen is actually most cost-effective in achieving this goal. At present, another trial with a larger population is being conducted in south India to determine whether antibiotics alone can indeed prevent both fungal and bacterial keratitis after corneal abrasion. Hopefully the question will be definitely answered.

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REFERENCES


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