

The Bhaktapur eye study: ocular trauma and antibiotic prophylaxis for the prevention of corneal ulceration in Nepal

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Abstract

Aims—To determine the incidence of ocular trauma and corneal ulceration in the district of Bhaktapur in Kathmandu Valley, and to determine whether or not topical antibiotic prophylaxis can prevent the development of ulceration after corneal abrasion.

Methods—A defined population of 34 902 individuals was closely followed prospectively for 2 years by 81 primary eye care workers who referred all cases of ocular trauma and/or infection to one of the three local secondary eye study centres in Bhaktapur for examination, treatment, and follow up by an ophthalmologist. All cases of ocular trauma were documented and treated at the centres. Individuals with corneal abrasion confirmed by clinical examination who presented within 48 hours of the injury without signs of corneal infection were enrolled in the study and treated with 1% chloramphenicol ophthalmic ointment to the injured eye three times a day for 3 days.

Results—Over the 2 year period there were 1248 cases of ocular trauma reported in the population of 34 902 (1788/100 000 annual incidence) and 551 cases of corneal abrasion (789/100 000 annual incidence). The number of clinically documented corneal ulcers was 558 (799/100 000 annual incidence). Of the 442 eligible patients with corneal abrasion enrolled in the prophylaxis study, 424 (96%) healed without infection, and none of the 284 patients who were started on treatment within 18 hours after the injury developed ulcers. Four of the 109 patients (3.7%) who presented 18–24 hours after injury developed infections, and 14 (28.6%) of the 49 patients who presented 24–48 hours subsequently developed corneal ulceration.

Conclusions—Ocular trauma and corneal ulceration are serious public health problems that are occurring in epidemic proportions in Nepal. This study conclusively shows that post-traumatic corneal ulceration can be prevented by topical application of 1% chloramphenicol ophthalmic ointment in a timely fashion to

the eyes of individuals who have suffered a corneal abrasion in a rural setting. Maximum benefit is obtained if prophylaxis is started within 18 hours after injury.

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Corneal opacity is second only to cataract as the most important cause of blindness worldwide.^{1–5} Traditionally, the main diseases considered responsible for the high prevalence of corneal scars in developing countries have included trachoma, neonatal ophthalmia, xerophthalmia, and onchocerciasis (in Africa), as well as harmful eye practices by patients, village healers, and poorly trained medical personnel.^{2–7} Recent evidence suggests, however, that primary corneal ulceration is a much more common event than was previously recognised and that it is a major cause of corneal scarring and visual loss in developing countries.⁸

Valid estimates of the annual incidence of infective ulceration are difficult to obtain in most countries. Available data indicate that, while in the United States there are 11 corneal ulcers per 100 000 population annually,⁹ in south India the number is 10 times higher with 113 per 100 000 population per year.¹⁰ By conservative estimates corneal ulcers blind at least 1.5 million eyes every year in the world, and the true number may be several times greater.⁸ Since blindness from microbial keratitis is usually unilateral, millions of cases are not reported. These individuals are partially sighted, visually handicapped, poor and medically underserved, and are the victims of the “silent epidemic” of global blindness caused by corneal ulceration.⁸

Treatment of microbial keratitis is difficult for a variety of reasons. When the presentation to the physician is delayed, extensive corneal stromal damage is common. Difficulties in obtaining suitable antibiotics and antifungal medications in many developing countries often lead to inadequate treatment. The result may be severe corneal scarring at best and corneal perforation with endophthalmitis, panophthalmitis, and loss of the eye as the worst outcome. Even with moderate corneal scarring, blindness is often the final result because

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of the lack of suitable donor material for a corneal graft. The poor visual outcome that invariably occurs with even successful treatment makes the management of microbial keratitis an unrewarding experience for most physicians in developing countries. In addition, the cost of prolonged treatment is financially prohibitive for most poor patients, many of whom are living a subsistence existence well below the poverty line. For these individuals the treatment for a corneal ulcer is simply not cost effective when the visual outcome is functional blindness whether they are treated or not.

Most cases of microbial keratitis are reported to follow minor ocular trauma sustained during agricultural work or in domestic activities.^{11 12} These injuries are usually trivial superficial corneal epithelial abrasions. There is evidence that several hours to sometimes several days are required before these abrasions become infected and develop into true corneal ulcers. During that time there may be a "window of opportunity" to prevent the ulcer from developing. This study was designed to test the hypothesis that the application of antibiotic in an eye that has suffered a traumatic corneal abrasion prevents the subsequent development of suppurative ulceration in the treated cornea. The study was also designed to determine the optimum period of time during which antibiotic prophylaxis is effective. This investigation is part of a larger ongoing study to develop strategies for prevention of corneal ulceration in rural communities in countries in the developing world.

Methods

The district of Bhaktapur was chosen for this prospective population based intervention study for several reasons. Bhaktapur is an ancient, well established, rural community in the Katmandu valley located 20 km east of Kathmandu, the capital of Nepal. Its proximity to Tribhuvan University Teaching Hospital allowed for close supervision and daily monitoring of the study by the university faculty and staff. It is also representative of other districts in Nepal with regard to terrain, occupation of the population, ethnicity, and socioeconomic conditions. A previous study in the area delineating the epidemiological profile of corneal trauma also documented the frequent occurrence of corneal ulceration in this defined population of 34 902 individuals living in the southern half of Bhaktapur District.¹³ The population is administratively divided into nine village development committees (VDCs) consisting of around 4000 inhabitants each. Each VDC is further subdivided into nine wards, each with a population of approximately 400 individuals living in 60–150 households.

Eighty one primary eye care workers were recruited from the community and trained. Each worker was given primary responsibility for keeping track of every one of the 400 individuals in his or her ward. Eye care workers were trained to recognise corneal abrasions using fluorescein stain and a blue torch. A manual for primary eye care workers was

developed and distributed, and workers were provided with supplies including a blue torch, fluorescein dye, chloramphenicol ointment Applicaps, and registration and referral forms. A health education publicity campaign was initiated to make certain that the entire community was aware of the study, and surveys were periodically taken to test for public awareness of the services available. Primary eye care workers were given specific guidelines for referring any questionable problems to one of the three secondary eye centres serving the nine VDCs 24 hours a day. All the secondary eye centres were staffed by ophthalmic assistants around the clock and by attending ophthalmologists and residents in ophthalmology during the day. Secondary eye centres were equipped with Haag-Streit 900 slit lamps and other necessary equipment and supplies for managing ocular trauma and corneal ulcers.

PATIENTS

Inclusion criteria

- (1) All individuals with a history of corneal abrasion confirmed by clinical examination and positive fluorescein staining.
- (2) Resident of the study area (South Bhaktapur District) at time of injury.
- (3) All injuries sustained within 48 hours before presentation.

Exclusion criteria

- (1) Presence of clinical signs of corneal infection.
- (2) All penetrating corneal injuries, including lamellar lacerations.
- (3) All cases of bilateral ocular trauma.
- (4) Pre-existing visual loss in the non-traumatised eye.
- (5) All cases in which the diagnosis of corneal abrasion was not confirmed by the attending ophthalmologist.
- (6) All persons receiving topical or systemic antibiotics prior to presentation.

TREATMENT

Individuals meeting the eligibility criteria were treated with 1% chloramphenicol ophthalmic ointment three times a day for 3 days. They were seen at the secondary eye centre daily for 3 days and instructed to bring the used Applicap containers with them to confirm that the antibiotic had been used. At each visit the patients were examined at the slit lamp for evidence of epithelial healing and for signs of infection. The presence of ointment in the eye at each examination was noted and used as an index of treatment compliance. Those individuals not returning to the secondary centre for follow up were visited at their homes by ophthalmic assistants and examined with fluorescein and a blue torch to rule out the development of corneal ulceration. The patients were then asked to return to the secondary eye centre the following day for examination by the ophthalmologist.

FINAL OUTCOME

All patients in the study were treated with 1% chloramphenicol ointment. The end point of prophylactic therapy was either complete

Table 1 Findings in persons reporting ocular trauma in Bhaktapur (population 34 902) from January 1992 to December 1993

Clinical findings	No of cases	Annual incidence per 100 000
Corneal abrasion	551	789
Corneal ulcer	253	362
Conjunctival injury	114	163
Lid injury	28	40
Miscellaneous	33	47
No clinical findings	189	271
Reported only	80	115
Total	1248	1788

epithelialisation of the cornea without evidence of infection or, alternatively, the development of a corneal ulcer at the site of the abrasion.

Results

During the 2 year study period from January 1992 to December 1993, 1248 individuals reported to the network of services with a history of injury to the eye (Table 1). Of this total number 551 individuals were found to have corneal abrasions, and of these patients 109 were eliminated from the study because of the exclusion criteria. The remaining 442 cases of corneal abrasion were included in the prophylaxis study. Analysis of the age and sex distribution of the 442 cases revealed that most of the injuries occurred in the second and third decades of life with twice as many males as females sustaining corneal abrasions (Fig 1). Of the 442 patients with corneal abrasion treated with 1% chloramphenicol ophthalmic ointment three times a day, 424 (96%) healed without sequelae and 18 (4%) developed corneal ulcers (Table 2). A closer analysis of the 424 patients who healed without sequelae revealed that 362 (82%) healed without any evidence of corneal scarring while 62 (14%) healed with a faint "ghost" scar in Bowman's membrane that was discernible by slit lamp but did not cause any visual impairment (Table 2).

The time interval that elapsed before initiation of prophylactic treatment appeared to have a direct correlation with the development of corneal ulceration (Table 3). None of the 284 (64.2%) patients who presented to the clinic within 18 hours after ocular injury and were started on prophylactic antibiotic ointment three times a day for 3 days developed a

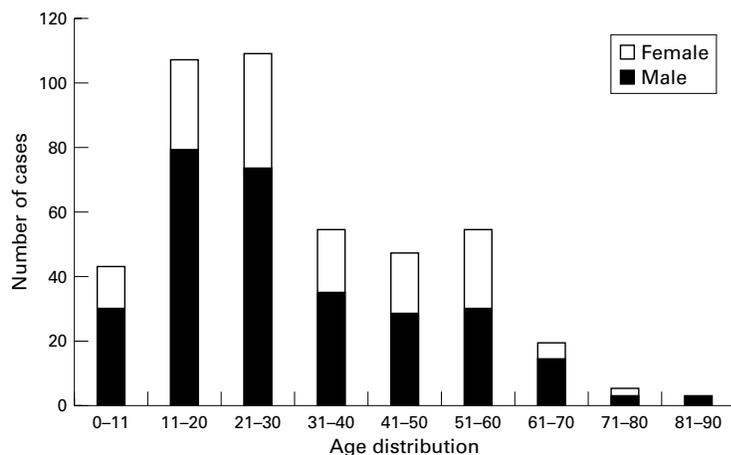


Figure 1 Age and sex distribution of 442 treated corneal abrasion cases.

Table 2 Outcome of corneal abrasion prophylactic treatment in 442 cases

Clinical findings	No of cases	%
Healed without scar	362	82
Healed with mild scarring without visual loss	62	14
Developed ulcer	18	4
Total	442	100

Table 3 Time interval between corneal abrasion and initiation of antibiotic prophylactic treatment in 442 patients

Hours elapsed	No (%) of patients with abrasion	No of patients developing an ulcer
0-6	150 (33.9%)	0
7-12	23 (5.2%)	0
13-18	111 (25.1%)	0
19-24	109 (24.7%)	4
24-48	49 (11.1%)	14
Total no of patients	442	18

Table 4 Location of corneal ulcers and visual outcome in 18 patients

Location of ulcer	No of patients	Pretreatment visual acuity	Post treatment visual acuity
Peripheral	11	6/6	6/6
Paracentral	4	6/9	6/9
	1	6/9	6/12
Central	2	<6/36	<6/36

corneal ulcer. Of the 109 patients who presented 19-24 hours after the injury, four (3.7%) developed an ulcer, and of the 49 patients who presented 24-48 hours after injury 14 (28.6%) developed a corneal ulcer. Fortunately, 393 (88.9%) of all patients presented to the clinic within 24 hours after injury, reinforcing the importance of readily available medical coverage at the primary level. It is also of interest that none of the corneal ulcers that developed while on treatment was culture positive for fungi. Cultures were positive only for bacteria.

Of the 18 cases of corneal ulceration that developed on prophylactic treatment, 11 were in the periphery, five were paracentral, and two were located centrally (Table 4). The best corrected visual acuity of the treated patients was 6/6 pre- and post-treatment in 11 of the cases, 6/9 pre- and post-treatment in four patients, decrease from 6/9 to 6/12 in one patient, and diminished to <6/36 in the two patients with central ulcers. Even though all the ulcers were successfully treated, the two patients with central ulcers were functionally blind in the treated eye because of dense scarring in the visual axis.

Discussion

In this study a population of 34 902 individuals living in South Bhaktapur District was kept under daily surveillance for a period of 2 years from January 1992 to December 1993. The study design provided a true population based data set for the period of observation. The individuals who were studied had very limited access to other healthcare facilities, and a large scale publicity and health education campaign was undertaken to assure that all cases of ocular trauma reported to the study group. The effectiveness of the campaign was periodically verified by surveys of the population to test for

awareness and utilisation of the services available.

One of the main outcomes of the study was the determination of the true incidence of ocular trauma in this defined population. Even though the importance of ocular trauma as a major cause of blindness worldwide has recently been documented,^{14, 15} reliable population based data are difficult to obtain, especially in developing countries. Over the 2 year period of this study there were 1248 cases of reported ocular trauma, 979 (78%) of which were confirmed by clinical examination. This total number can be expressed as an annual incidence of 1788 cases of ocular trauma per 100 000 population, or 1.8% of the inhabitants of Bhaktapur sustaining some degree of ocular trauma every year. The most common ocular injury documented was corneal abrasion. There were 551 cases during the 2 year period, or an annual incidence of 789 abrasions per 100 000 population. In straightforward terms almost 1% of the population of Bhaktapur sustained a clinically proved corneal abrasion every year.

During the 2 years of this study 253 corneal ulcer patients, all with a history of a traumatic corneal abrasion, were seen at a secondary eye care centre for diagnosis and treatment. In addition there were 18 ulcers that were prophylactic treatment failures, giving a total of 271 traumatic ulcers. Even though the focus of this study was primarily on the prevention of microbial keratitis in patients with evidence of corneal abrasion, all other corneal ulcers in the study area were also documented during the 2 year period including those without a history of a corneal abrasion and those with a risk factor other than corneal trauma. There were 287 of these non-traumatic ulcers, giving a total of 558 corneal ulcers seen over the 2 year period in the Bhaktapur study population of 34 902. Therefore, on an annual basis the incidence of microbial keratitis in Bhaktapur, calculated from the total number of ulcers clinically documented, was 799 per 100 000 population. This incidence of ulceration is seven times greater than that reported recently from south India¹⁰ and 70 times the incidence reported in the USA.⁹ Even though the incidence of microbial keratitis in Bhaktapur is many times greater than that reported in any previous study, we are inclined to believe that this may still be an underestimate. The individuals in the study area had easy access to the study healthcare facilities, but it is very probable that some of them did not report to these facilities or for that matter to any healthcare provider for treatment of their ulcer. Likewise, a small number may have chosen to consult other physicians outside the study area. This surprisingly large number of ulcers emphasises the enormity of the current public health problem that is posed by the epidemic of corneal ulceration in Nepal. It may also be an indication that similar epidemics are occurring in developing countries around the world at the present time without our knowledge.

The primary outcome of this study was to determine whether or not antibiotic prophylaxis can prevent corneal ulceration. Chloramphenicol ointment was selected for the study because it is the most readily available, inexpensive, broad spectrum topical ophthalmic antibiotic medication currently available in most developing countries, and it is widely used in spite of the controversial question regarding its association with systemic side effects. In this context, it was impressive that microbial keratitis did not develop in 424 (96%) of the 442 patients who were prophylactically treated with 1% chloramphenicol ophthalmic ointment three times a day for 3 days following corneal abrasion. Even more impressive was the fact that none of the 284 patients who presented for treatment within 18 hours of ocular injury developed a corneal ulcer. It is true that patients with large abrasions may have been more motivated to continue to seek treatment after 18 hours because of the persistence of their symptoms compared with patients who had small abrasions that healed quickly without complications. As a group, patients with large abrasions may also have been at greater risk for developing microbial keratitis because of the extent of their injuries. However, the fact remains that, as the time to initiation of prophylactic treatment increased, the occurrence of ulceration also increased dramatically by the hour. Of the 109 patients presenting for treatment 19–24 hours after injury four (3.7%) later developed ulcers, and of the 49 patients presenting 24–48 hours after the event, 14 (28.6%) subsequently developed corneal ulceration. Significantly, of the 18 patients who developed “breakthrough” corneal ulcers after prophylactic treatment, none had the severity of corneal scarring usually seen with healed ulcers in this population, and only two had a final visual acuity of less than 6/36.

It is impossible to estimate how many of the 442 corneal abrasions seen during the 2 years of the study would have become infected had they not been treated prophylactically. To determine this number would have required a placebo controlled study comparing antibiotic ointment with an ointment base. This approach was considered ethically unacceptable. We do know, however, that 14 (28.6%) of the 49 patients with corneal abrasions who presented 24–48 hours after the injury subsequently developed ulceration in spite of receiving prophylaxis. This was a surprisingly high rate of infection after corneal abrasion, possibly the result of a number of epidemiological factors yet to be elucidated, but it is likely that the rate would have been even higher had antibiotic prophylaxis not been administered.

During the course of this study an event occurred in the community over which we had no control but which provided us with more information about the natural course of untreated corneal abrasions. We documented 253 cases of corneal ulceration following known abrasions. In a sense, these patients provided a natural control group because, by their own choice, they did not report to the

study centre until 48 hours or later after their injuries. Even under these unique circumstances, however, this group of patients still did not provide us with a truly accurate determination of the risk of corneal ulceration after corneal abrasion. It likely that the rate is higher than 28% but, because we are constrained from following a control group of corneal abrasion patients prospectively without treating them, the basic question of ulceration risk remains unanswered. This is an important issue, nevertheless, and the evidence both from a clinical and public health perspective remains clearly in favour of the efficacy of prophylaxis for the prevention of ulceration after corneal abrasion.

This study provides highly supportive evidence that corneal ulceration can be prevented by application of 1% chloramphenicol ophthalmic ointment in a timely fashion to the eyes of individuals who have suffered a corneal abrasion in a rural setting. Maximum benefit is obtained if prophylaxis is begun within 18 hours after injury. Because the treatment of microbial keratitis is expensive and often unsuccessful, we believe that the development of a "grass roots" corneal ulcer prevention programme is a cost effective way of preventing blindness from infective ulceration in rural communities in the developing world. To initiate a large scale prevention programme by modifying the existing healthcare infrastructure requires a surprisingly modest input of time and energy in most developing countries where resources are limited. In response to the findings of this study, a nationwide corneal

ulcer prevention programme is at present being developed in rural areas of Nepal. The experience gained from this national intervention programme should prove to be of great importance for other developing countries with high rates of corneal ulceration.

- 1 Chirambo MC, Tielsch JM, West KP, et al. Blindness and visual impairment in southern Malawi. *Bull World Health Organ* 1986;64:567-72.
- 2 Rapoza PA, West SK, Katala SJ, et al. Prevalence and causes of vision loss in central Tanzania. *Int Ophthalmol* 1991;15:123-9.
- 3 Brilliant LB, Pokhrel RP, Grasset NC, et al. Epidemiology of blindness in Nepal. *Bull World Health Organ* 1985;63:375-86.
- 4 Gilbert CE, Wood M, Waddell K, et al. Causes of childhood blindness in East Africa: results in 491 pupils attending 17 schools for the blind in Malawi, Kenya, and Uganda. *Ophthalmol Epidemiol* 1995;2:77-84.
- 5 Waddell K. Childhood blindness and low vision in Uganda. *Eye* 1998;12:184-92.
- 6 Smith GT, Taylor HR. Epidemiology of corneal blindness in developing countries. *Refract Corneal Surg* 1991;7:436-9.
- 7 Yorston D, Foster A. Traditional eye medicines and corneal ulceration in Tanzania. *J Trop Med Hyg* 1994;97:211-4.
- 8 Whitcher JP, Srinivasan M. Corneal ulceration in the developing world: a silent epidemic. *Br J Ophthalmol* 1997;81:622-3.
- 9 Eric JC, Nevitt MP, Hodge DO, et al. Incidence of ulcerative keratitis in a defined population from 1950-1988. *Arch Ophthalmol* 1993;111:1665-71.
- 10 Gonzales CA, Srinivasan M, Whitcher JP, et al. Incidence of corneal ulceration in Madurai District, South India. *Ophthalmol Epidemiol* 1996;3:159-66.
- 11 Upadhyay MD, Karmacharya PC, Koirala S, et al. Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal. *Am J Ophthalmol* 1991;111:92-9.
- 12 Srinivasan M, Gonzales CA, George C, et al. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, South India. *Br J Ophthalmol* 1997;81:965-71.
- 13 Upadhyay MP, Bajracharya HB, Shrestha JK, et al. *Bhaktapur Eye Survey 1991*. Department of Ophthalmology, Tribhuvan University, Kathmandu, Nepal, 1992.
- 14 Thylefors B. Epidemiological patterns of ocular trauma. *Aust NZ J Ophthalmol* 1992;20:95-8.
- 15 Negrel AD, Thylefors B. The global impact of eye injuries. *Ophthalmol Epidemiol* 1998;5:143-69.