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Comparison of Vancomycin and Cefazolin Therapeutic Effect with Povidone Iodine on Corneal Ulcer in Rabbits

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ABSTRACT

Background: Corneal ulcer is a common cause of blindness in developing countries, as itleads to corneal perforation and blindness if not properly treated.
Objectives: This study aimed to determine the effects of intraocular 5 % and 10 % topical povidone iodine in the treatment of bacterial corneal ulcer in a rabbit model, comparing the effectiveness of vancomycin and cefazolin eye drops.
Materials and Methods: Total of 40 eyes ofrom 20 wild rabbits were randomly assigned to four equal groups, five in each (n = 5), they included; group 1. 5 % povidone iodine and vancomycin; group 2.5 % povidone iodine and cefazolin; group 3.10 % povidone iodine and vancomycin; group 4.10 % povidone iodine and cefazolin (one drop every two hours for seven days and nights). The animals were first anesthetized with ketamine hydrochloride and xylazine chloride. Then, a 27-gauge needle attached to a 1-ml syringe was tunneled through the clear cornea to approximately midstromal depth, stopping at the edge of the 2-mm optical zone. Finally, 0.02 ml of *Staphylococcus* contaminated media containing about 100 organisms was injected, forming a central intra-stromal infiltrate.
Results: There was no statistically significant difference in the density of infiltration, size of infiltration, hypopyon, or fibrin formation between the four groups. However, epithelial defect, stromal edema, conjunctival injection, and chemosis were significantly higher in the 5 % and 10 % povidone iodine groups when compared to the cefazolin and vancomycin groups. Thinning was more common in the cefazolin group. There was one sealed corneal perforation in the cefazolin group at the beginning, and at day 6, one perforation in the cefazolin group and one perforation in the 10 % povidone iodine group also developed.
Conclusions: Cefazolin and vancomycin had a superior clinical effect on the staphylococcal corneal ulcers in this study. 5 % and 10 % povidone iodine was toxic to the corneal epithelium. Thinning and perforation was more common with cefazolin.

Implication for health policy/practice/research/medical education:
Lower effect of povidone iodine may be the result of the lack of deep penetration of this drug into the corneal stroma, but other factors may be involved.

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1. Background

Corneal ulcer is an infectious condition, and follows the destructive influence of bacteria, viruses and fungi (1). This disease is a common cause of blindness and financial loss in developing countries, and leads to corneal perforation and blindness if not treated properly (2). *Staphylococcus* species, particularly *Staphylococcus au-*

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reus and *Staphylococcus epidermis* are the most common bacterial causes of corneal ulcer in the world (3). The current approved therapies in gram-positive corneal ulcers include drugs such as cefazolin and vancomycin (4). The disadvantages of fortified antibiotics include symptom difficulties such as; burning, redness and eye irritation, being it is relatively expensive and there is a lack or limit of commercial samples.

Povidone iodine is a topical antiseptic that effects bacteria, fungi and viruses by the gradual liberalization of iodine (5). Nowadays, preparations of eye medications with povidone iodine that have a broad-spectrum antibiotic effect at the start of thsurgery are used to prevent post surgical bacterial corneal ulcers (6).

2. Objectives

This study aimed to determine the clinical effects of 5 % and 10 % topical povidone iodine in the treatment of bacterial corneal ulcers in a rabbit model, as well as to compare the results with fortified vancomycin and cefazolin eye drops.

3. Materials and Methods

3.1. Animals

Total of 40 eyesfrom 20 wild rabbits (Laboratory Animals Care and Breeding Center of Ahvaz Jundishapur University of Medical Sciences, Ahwaz, Iran), were randomly assigned to 4 equal groups, five in each (n = 5) they included; group 1.5 % povidone iodine (Aida Chemical Co. Iran) eye drops in one eye and fortified vancomycin in the other eye every 2 hours; group 2.5 % povidone iodine eye drops in one eye and fortified cefazolin (Jabber Ibn Hayan Co., Iran) in the other eye every 2 hours; group 3.10 % povidone iodine eye drops in one eye and fortified vancomycin (Jabber Ibn Hayan Co., Iran) in the other eye every 2 hours; group 4.10 % povidone iodine eye drops in one eye and fortified cefazolin in the other eye every 2 hours. Ten variables for all of the rabbits were checked on a daily basis and the results were recorded on the first day - 48 hours after inoculation and before drug therapy - which was considered as the baseline and then the same examinations were applied for seven days, but this time with the instillation of the different drops. All procedures were approved by international guidelines of the Institute Research Ethics and Animal Care and Use Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS). Every effort was made to minimize the number of animals used and their suffering.

3.2. Surgery and Corneal Ulcer Measurement

The animals were anesthetized with 35mg/kg of ketamine hydrochloride and 5mg/kg xylazine chloride. Each rabbit was given a local anesthetic with tetracaine chloride (Sina Darou, Iran) eye drops. A 27-gauge needle attached to a 1-ml syringe was then tunneled through the clear cornea to approximately midstromal depth, stopping at the edge of the 2-mm optical zone. Then 0.02 ml of *Staphylococcus* contaminated media containing approximately 100 organisms (ATCC29213) was injected, forming a central intrastromal infiltrate. After 48 hours, the corneas were checked for infection**.** Rabbits were excluded from the study in cass the absence of the development of a corneal ulcer after five days. Specimens were then collected from the infected corneal ulcers with a swab and samples were sent for culture to ensure that the ulcer had been created by *Staphylococcus aureus*.

Treatment was started and continued for a week, changes to the dimensions, characteristics and features of the corneal ulcer that were examined by a *Topcon* SP-78 Specular *Microscope* (*Topcon***,** Tokyo, *Japan*). The dimensions of the epithelial defect were measured using *fluorescent* viability *staining* and then measured with *a* Moria caliper (Moria S.A., France). 10 variables were checked every day during the therapy. At the conclusion of the study, all variables were given a rating from 0 to +4, a score for each eye per day was given to a total of ten variables, therefore the scores ranged between zero and 40. Thus, each eye was compared between all four groups during the study.

3.3. Statistical Analysis

Data were tabulated for descriptive and statistical analysis using the analysis of variance (ANOVA) and Kruskal-Wallis test it was deemed appropriate. SPSS 16.0 software was used.

4. Results

All eyes that were evaluated in terms of clinical infections were also confirmed by culture. Two eyes that showed no infection were in the 5 % povidone iodine group; therefore, this group included only 8 eyes.

The defect size (in mm^2) at baseline between each of the 4 groups had no significant difference (*p* value for cefazolin-betadine 5 % $P = 0.992$, for cefazolin-betadine 10 % $P = 1$, for vancomycin-betadine5 % $P = 0.989$, for vancomycin-betadine10 % $P = 1$), however, after starting the second day of drug treatment a significant difference was found, as the group receiving povidone iodine 5 % and 10 % showed significantly higher values than the cefazolin and vancomycin groups. This significant difference continued until the eighth day. (*p* value for cefazolin-betadine 5 % and for cefazolin-betadine 10 % from the second day to the eighth day was 0. p value for vancomycin betadine 5 % from the second day to the eighth day was 0.001,0,0,0,0,0,0. p value for vancomycin-betadine 10 % from the second day to eighth day was 0.009, 0.001 ,0,0,0,0,0)

There was no statistically significant difference in the density of infiltration (0 to 4+ grading scale), size of infiltration (in mm^2), hypopyon (in mm) and fibrin formation (0 to 4+ grading scale) between the four groups (*Table 1*).

However, epithelial defect (in mm^2), stromal edema (0 to 4+ grading scale), conjunctival injection (0 to 4+ grading

Table 1. Comparing the Various Variables of Interest in Different Study Times Between Four Study Groups

	P values							
	Baseline	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Density of infiltration								
Cefazolin betadine5 %	0.833	0.436	0.873	0.974	0.982	1	1	0.962
Cefazolin-batadine10 %	0.993	0.647	0.650	0.688	0.493	0.237	0.339	0.127
Vanco-betadine5 %	0.889	0.945	0.873	0.876	0.998	0.968	0.839	0.889
Vanco-betadine10 %	0.978	0.735	0.971	0.999	0.828	0.523	0.861	0.755
Size of infiltration								
Cefazolin-betadine5 %	1	0.996	0.977	0.996	0.998	0.978	0.954	0.970
Cefazolin-batadine10 %	0.997	1	0.947	0.988	0.979	0.988	0.999	0.990
Vanco-betadine5 %	0.926	0.989	0.969	0.968	0.998	0.985	1	0.994
Vanco-betadine10 %	0.973	0.923	0.983	0.979	0.979	0.981	0.867	0.725
Hypopyon								
Cefazolin-betadine5 %	0.615	0.730	0.725	0.421	0.770	0.455	0.958	0.971
Cefazolin-batadine10 %	0.944	0.831	0.900	0.983	0.986	0.999	0.508	0.508
Vanco-betadine5 %	1	0.687	0.798	0.576	0.644	1	1	1
Vanco-betadine10 %	0.915	0.792	0.945	1	0.999	0.335	0.234	0.261
Fibrin formation								
Cefazolin-betadine5 %	0.962	0.999	0.469	0.842	0.244	0.601	0.495	0.474
Cefazolin-batadine10 %	0.986	0.986	0.629	0.779	0.826	0.998	0.998	0.980
Vanco-betadine5 %	0.851	0.195	0.893	0.998	0.974	0.786	0.950	0.983
Vanco-betadine10 %	0.735	0.343	0.979	0.999	0.890	0.998	0.874	0.866

scale), and chemosis (0 to 4+ grading scale) were significantly higher in the 5 % and 10 % povidone iodine groups when compared to the cefazolin and vancomycin groups (*Table 2*). Thinning was more common in the cefazolin group. There was one sealed corneal perforation in the cefazolin group at the beginning, and on day six; one perforation occurred in the cefazolin group and one perforation in the 10 % povidone iodine group (*Table 3*). At the end of the study, all ten variables; rat from 0 to +4; were summed together and a score was given for each eye per day, which produced a number in a range between zero and 40. Thus the eye was compared between all four groups during the study. The

Table 2. Comparing the Various Variables of Interest in Different Study Times Between Four Study Groups

	P values							
	Baseline	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Epithelial defect								
Cefazolin-betadine5 %	0.992	0	0	0	0	0	0	0
Cefazolin-batadine10 %	1	0	0	0	0	0	0	0
Vanco-betadine5 %	0.989	0.001	0	0	0	0	0	0
Vanco-betadine10 %	1	0.009	0.001	0	0	0	0.021	0
Stromal edema								
Cefazolin-betadine5 %	0.016	0.524	0.038	0.058	0.055	0.017	0.007	0.007
Cefazolin-batadine10 %	1	0.626	0.026	0.012	0.001	0	0	0
Vanco-betadine5 %	0.395	0.406	0.201	0.412	0.469	0.142	0.022	0.031
Vanco-betadine10 %	0.303	0.495	0.166	0.159	0.041	0.008	0	0
Conjunctival injection								
Cefazolin-betadine5 %	0.117	0.999	0.848	0.662	0.375	0.846	0.03	0.06
Cefazolin-batadine10 %	1	1	0.886	0.127	0.011	0.001	0	0
Vanco-betadine5 %	0.057	0.485	0.606	0.041	0.043	0.117	0.007	0.06
Vanco-betadine10 %	0.983	0.342	0.031	0.002	0	0	0	0
Chemosis								
Cefazolin-betadine5 %	0.331	0.002	0	0	0	0	0	0
Cefazolin-batadine10 %	0.850	0.027	0	0	0	0	0	0.009
Vanco-betadine5 %	0.897	0.002	0	0.008	0.003	0	0	0
Vanco-betadine10 %	0.993	0.027	0.061	0.002	0.001	0	0	0.009

Table 3. Comparing the Various Variables of Interest in Different Study Times Between Four Study Groups

		Study Time Course (Mean ± SD)						
	Base line	**2 nd day**	**3 nd day**	**4 th day**	**5 th day**	**6 th day**	**7 th day**	**8 th day**
Defect								
Cefazoline	17.35 ± 23.68	5.62 ± 6.29	11.77 ± 19.77	7.82 ± 17.28	19.97 ± 40.28	14.3 ± 31.09	3.27 ± 5.31	2.42 ± 4.93
Betadine 10 %	17.85 ± 20.53	87.3 ± 42	96.75 ± 35.43	96.9 ± 33.56	105.7 ± 19.3	106.7 ± 18.04	108.8 ± 17.78	108.8 ± 17.78
Vancomycine	17.1 ± 11.39	35.17 ± 34.38	35.07 ± 30.87	30.32 ± 25.19	29.1 ± 27.06	29 ± 27.05	34.65 ± 34.74	31.5 ± 31.8
Betadine 5 %	19.68 ± 8.14	106 ± 43.6	112 ± 45.97	111.62 ± 43.88	113 ± 43.99	123 ± 19.68	121.19 ± 23.33	119.38 ± 26.1
Infiltration density								
Cefazoline	2.4 ± 1.28	1.7 ± 0.94	1.85 ± 0.94	1.9 ± 0.87	1.8 ± 0.91	1.6 ± 0.87	1.3 ± 0.94	1.1 ± 0.77
Betadine 10 %	2.5 ± 0.52	2.1 ± 0.73	2.25 ± 0.71	2.3 ± 0.82	2.3 ± 0.82	2.3 ± 0.82	1.95 ± 0.92	1.9 ± 0.84
Vancomycine	2.35 ± 0.74	2.45 ± 0.64	2.4 ± 0.65	2.35 ± 0.74	2 ± 0.62	1.8 ± 0.58	1.65 ± 0.57	1.55 ± 0.59
Betadine 5 %	2.06 ± 0.49	2.25 ± 0.65	2.12 ± 0.69	2.06 ± 0.77	1.93 ± 0.72	1.62 ± 0.95	1.31 ± 0.92	1.28 ± 0.93
Infiltration size								
Cefazoline	7.27 ± 7.06	7 ± 7.54	5.9 ± 4.95	6.47 ± 5.97	6.47 ± 5.97	6.55 ± 5.86	6.42 ± 5.97	6 ± 6.22
Betadine 10 %	7.95 ± 6.75	6.82 ± 5.56	7.7 ± 6.43	7.57 ± 6.03	7.57 ± 6.03	7.45 ± 6.43	6.77 ± 5.92	6.76 ± 5.94
Vancomycine	9.42 ± 8.5	9.02 ± 7.91	8.9 ± 8.13	8.9 ± 8.13	6.47 ± 5.86	6.4 ± 5.92	4.77 ± 5.04	4.12 ± 4.23
Betadine 5 %	7.18 ± 8.34	7.84 ± 10.26	7.31 ± 9.74	7.28 ± 9.76	5.91 ± 7.07	5.38 ± 6.49	5 ± 6.28	4.81 ± 6
Hypopyon								
Cefazoline	1.2 ± 1.15	1.4 ± 1.57	1.3 ± 1.6	0.9 ± 1.07	0.45 ± 0.68	0.37 ± 0.56	0.11 ± 0.31	0.1 ± 0.31
Betadine 10 %	0.9 ± 1.66	0.85 ± 1.37	0.8 ± 1.75	0.7 ± 1.63	0.6 ± 1.34	0.4 ± 0.84	0.4 ± 0.84	0.4 ± 0.87
Vancomycine	0.55 ± 0.83	1.45 ± 1.6	1.2 ± 1.63	0.75 ± 1.35	0.55 ± 1.16	0	0	0
Betadine 5 %	0.5 ± 0.92	0.68 ± 1.13	0.5 ± 1.41	0	0	0	0	0
Corneal edema								
Cefazoline	1.95 ± 1.3	1.17 ± 0.92	0.6 ± 0.8	0.55 ± 0.98	0.45 ± 1.01	0.4 ± 0.87	0.3 ± 0.63	0.25 ± 0.54
Betadine 10 %	2 ± 1.05	1.6 ± 0.69	1.65 ± 0.74	1.85 ± 0.74	2.05 ± 0.68	1.95 ± 0.76	2.1 ± 0.7	1.9 ± 0.93
Vancomycine	1.2 ± 0.91	1.1 ± 0.77	0.9 ± 0.73	1 ± 0.81	0.95 ± 0.79	0.75 ± 0.63	0.45 ± 0.43	0.45 ± 0.28
Betadine 5 %	0.43 ± 0.49	1.68 ± 0.7	1.65 ± 0.87	1.65 ± 0.99	1.56 ± 1.01	1.56 ± 0.82	1.43 ± 0.94	1.43 ± 0.94
Fibrin in AC								
Cefazoline	0.1 ± 0.31	0.1 ± 0.31	0.8 ± 1.13	0.9 ± 1.19	0.8 ± 1.13	0.4 ± 0.84	0.4 ± 0.73	0.4 ± 0.84
Betadine 10 %	0.2 ± 0.42	0.2 ± 0.42	0.74 ± 0.23	0.5 ± 0.84	0.5 ± 0.81	0.35 ± 0.74	0.35 ± 0.74	0.3 ± 0.67
Vancomycine	0.5 ± 1.08	0.7 ± 1.15	0.5 ± 0.81	0.45 ± 0.76	0.25 ± 0.54	0.3 ± 0.67	0.15 ± 0.47	0.1 ± 0.31
Betadine 5 %	0.25 ± 0.46	0.06 ± 0.17	0.21 ± 0.41	0.53 ± 0.89	0.09 ± 0.26	0	0	00
Thinning								
Cefazoline	0.1 ± 0.31	0.5 ± 0.52	0.7 ± 0.48	0.9 ± 0.87	1.2 ± 1.31	1.7 ± 1.63	1.9 ± 1.72	2.1 ± 1.72
Betadine 10 %	0.1 ± 0.31	0.1 ± 0.31	0.1 ± 0.31	0.4 ± 0.51	0.4 ± 0.51	0.7 ± 1.25	0.6 ± 1.26	0.6 ± 1.26
Vancomycine	0	0	0	0	0	0	0	0.35 ± 0.57
Betadine 5 %	0	0	0	0	0	0	0	0.18 ± 0.53
Injection								
Cefazoline	1.8 ± 0.78	1.8 ± 0.91	1.8 ± 0.91	1.4 ± 0.96	0.8 ± 1.13	0.6 ± 1.07	0.1 ± 0.31	0.1 ± 0.31
Betadine 10 %	1.8 ± 0.42	1.8 ± 0.42	2 ± 0.47	2 ± 0.36	1.9 ± 0.56	1.9 ± 0.56	1.7 ± 0.48	1.6 ± 0.51
Vancomycine	1.9 ± 0.73	1.3 ± 0.48	1.2 ± 0.42	0.9 ± 0.56	0.4 ± 0.51	0.1 ± 0.31	0	0.1 ± 0.31
Betadine 5 %	1.12 ± 0.35	1.75 ± 0.7	1.56 ± 0.49	1.75 ± 0.46	1.37 ± 0.51	0.87 ± 0.64	0.62 ± 0.51	0.62 ± 0.51
Chemosis								
Cefazoline	0.8 ± 1.13	0.2 ± 0.42	0	0	0	0.1 ± 0.31	0	0
Betadine 10 %	0.5 ± 0.84	0.95 ± 0.68	1 ± 0.47	1 ± 0.15	1.15 ± 0.47	1.3 ± 0.48	1.1 ± 0.56	0.6 ± 0.51
Vancomycine	0.4 ± 0.7	0.2 ± 0.42	0.5 ± 0.52	0.4 ± 0.51	0.4 ± 0.51	0.1 ± 0.31	0	0
Betadine 5 %	0.12 ± 0.35	1.25 ± 0.7	1.43 ± 0.49	1 ± 0.53	1.12 ± 0.35	1.12 ± 0.35	1 ± 0.53	0.87 ± 0.64

course of the drug treatment when the various conditions are carefully compared, revealed the differences between povidone iodine and the other two drugs, and these can be seen in the graph (*Figure*). Cefazolin and vancomycin exhibited a constant downward slope, but this was not the case of povidone iodine. On the other hand, a similar downward slope was seen on the sixth day for povidone iodine 10 % and on the fourth day in the case of povidone iodine 5 %, which may reveal the need to review the use of Betadine at much lower concentrations.

5. Discussion

Using an anti-microbial agent, that is readily available, inexpensive, easy to use, effective against a wide range of

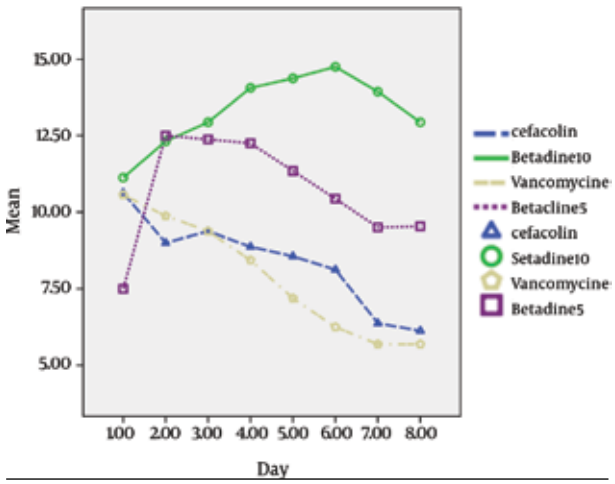

Figure. Course of Drug Treatment Compared for All Study Groups

microbes, and which has the least number of complications, has always been the ideal. Despite the large numbers of therapies that have been developed for the treatment of corneal ulcer, many of these useful drugs arenot commercially available yet.

Povidone iodine has traditionally been used to prepare the tissues around the eyes and the eye itself, before applyi ophthalmologic surgery (7). Povidone iodine has been reported to be effective as a topical antibiotic in treating conjunctivitis and keratoconjunctivitis, as well as being effective in the decontamination of donor corneas (8-11). Although this solution has been reported to be an effective method against various microorganisms in vitro (8, 11), with only a small spectrum of side effects its clinical effect on infections has not been proven and there is a need forfurther research.

Studies on the effect of povidone iodine in the treatment of ocular infections, including a study that was conducted by Sharma *et al.* (12) to compare the effect of topical povidone iodine 0.1 %, and gentamicin in the treatment of primary corneal ulcer created by coagulase-positive staphylococcus, have been reported previously. They concluded that povidone iodine is a very effective solution and that it reduces the morbidity period in staphylococcus infection, which was in contrast with the present study. This may be due to the different concentrations of povidone iodine used in these studies (12).

In agreement with the present study Gregori *et al.* compared the effect of 5 % povidone iodine with placebo drops (one drop of each,10 minutes before antibiotic treatment) in the treatment of corneal ulcer, and they concluded that the effect povidone iodine has no effect in reducing the number of bacteria on the cornea (13). In agreement with the present study Melki *et al.* compared the effect of 0.5 % and 10 % povidone iodine with ofloxacin 0.3 % on 21 rabbit eyes for a period of eight hours, and revealed that although 0.5 % povidone iodine has a greater bactericidal effect compare to the untreated cases, but however, its effect is less than ofloxacin (14). Michalova *et al.* studied the effect of 5 % povidone iodine on *Pseudomonas* infectious keratitis in rabbits for 24 hours, and claimed that povidone iodine is not effective against *Pseudomonas*, which was similar to the present study; although it was another infectious organism (15).

Xu-wang Shiun *et al.* have reported that 2 % povidone iodine is effective in the treatment of dog's infectious conjunctivitis (15). The present study was performed focusing on a larger number of variables compared to similar studies and continued the treatment for 7 days. Epithelial defects clearly increased after only 24 hours in the 5 % and 10 % povidone iodine groups during the 7 days of treatment, and involved almost the entire surface of the cornea in most of the eyes of these two groups, which may indicate the high toxicity of povidone iodine on the epithelium. The lowest toxicity for the epithelium belonged to the cefazolin group.

In the case of the 5 % and 10 % povidone iodine groups, corneal edema was present during the treatment and remained relatively stable, while in the cefazolin and vancomycin groups, corneal edema decreased gradually during the study and was significantly less than in the povidone iodine groups. Considering the results of the present study, it can be said that at least in *Staphylococcus keratitis*, 5 % and 10 % povidone iodine solutions cannot be used as a good alternative to standard therapies such as cefazolin and vancomycin.

Our study also had other deficiencies, for example despite attempts to inject a similar number of organisms into all of the corneas, different ulcer sizes were observed and that revealed that the number of organisms was probably not quite the same. This may have been due to human error in the injection or reflux of organisms from the injection tunnel within the stroma. In addition, the duration of treatment was short and we should perhaps have assessed longer treatment, although according to the course of change variables it does not seem that we would have obtained a different result with longer treatment. In this study, 5 % and 10 % povidone iodine were toxic to the corneal epithelium. Thinning and perforation were more common than with cefazolin. The ower effect of povidone iodine may have been the result of a lack of deep penetration of this drug into the corneal stroma, but other factors may also be involved.

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