

Evaluation of Various Antibiotic Treatments in Calves with Infectious Bovine Keratoconjunctivitis

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Abstract: The purpose of this study was to determine whether subconjunctival administration of enrofloxacin could ameliorate a herd outbreak of infectious bovine keratoconjunctivitis (IBK) and to compare the efficacy of this regimen with the efficacy of subconjunctival administration of a combination of penicillin+streptomycin.

The calves were assigned to 1 of 3 groups at the beginning of the study, and were examined 3 times weekly for 4 weeks. Calves in group 1 (n = 12) were treated with the subconjunctival administration of a combination of penicillin+streptomycin. This treatment consisted of 3 subconjunctival injections of penicillin+streptomycin every 48 h. Calves in group 2 (n = 13) were treated with subconjunctival administration of enrofloxacin, which consisted of 3 subconjunctival injections of enrofloxacin (30 mg) every 48 h. Calves in group 3 (n = 13) were not treated and were used as controls.

Mean time for healing of corneal ulcers and amelioration of clinical signs was significantly less for calves that received enrofloxacin or penicillin+streptomycin than for the untreated controls.

In conclusion, subconjunctival administration of enrofloxacin appears to be an effective method of reducing the severity of a herd outbreak of IBK and may be superior to treatment with penicillin+streptomycin.

Key Words: Keratoconjunctivitis, enrofloxacin, calf

İnfeksiyöz Bovine Keratokonjunktivitisli Buzağılarda Farklı Antibiyotik Tedavilerinin Değerlendirilmesi

Özet: Bu çalışmada, İnfeksiyöz Bovine Keratokonjunktivitis görülen bir sürüde subkonjunktival uygulanan enrofloksasin'in iyileşmedeki etkinliğinin belirlenmesi ve bunun subkonjunktival uygulanan penisilin + streptomisin kombinasyonu etkinliği ile karşılaştırılması amaçlandı.

Çalışma başlangıcında danalar 3 gruba ayrıldı ve haftada 3 defa olmak üzere 4 hafta boyunca muayene edildi. Grup 1'deki danalar (n = 12) subkonjunktival penisilin + streptomisin kombinasyonu uygulamasıyla sağaltıldı. Bu tedavi penisilin + streptomisin kombinasyonu 48 saat arayla 3 defa subkonjunktival uygulanarak gerçekleştirildi. Grup 2'deki danalar (n = 13) subkonjunktival enrofloksasin uygulanarak tedavi edildi. Subkonjunktival uygulama 48 saat arayla 3 defa yapıldı. Grup 3'deki danalar (n = 13) ise tedavi edilmedi ve kontrol grubu olarak kullanıldı.

Korneal ülserlerin ortalama iyileşme zamanı ve klinik bulguların düzelmesi, enrofloksasin ve penisilin + streptomisin kombinasyonu uygulanan danalarda kontrol grubundakilere göre önemli derecede daha kısa bulundu.

Sonuç olarak, enrofloksasinin subkonjunktival uygulamasının IBK' de hastalığın şiddetini azaltmada etkili bir metod olduğu ve hasta hayvanların tedavisinde penisilin streptomisin kombinasyonundan daha etkili olduğu görüldü.

Anahtar Sözcükler: Keratokonjunktivitis, enrofloksasin, buzağı

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Introduction

Infectious bovine keratoconjunctivitis (IBK, pinkeye) is an infectious and contagious ocular disease of cattle characterized by conjunctivitis and ulcerative keratitis (1-8). *Moraxella bovis* causes IBK, an important ocular disease of cattle, which occurs worldwide. The disease causes economic losses arising from decreased weight gain in beef breeds, loss of milk production, short-term disruption of breeding programs, and treatment costs (3-6,9-11). Several other infectious agents (i.e. Adenovirus, *Mycoplasma*, *Branhamella* (*Neisseria*), and *Listeria*) have been recovered from the eyes of cattle showing clinical signs similar to those seen in *Moraxella*-induced IBK (1,11-13).

The clinical signs of IBK include excessive lacrimation, blepharospasm, photophobia, corneal ulceration, opacity, and occasionally perforation. Circumlimbal corneal vascularization begins to invade the cornea 4 to 7 days after ulceration is first seen (3-5,7,10,11).

Pathogenic strains of *M. bovis* are piliated strains that initially bind through their pili to receptors on the surfaces of corneal epithelial cells (1,14-17). *M. bovis* causes the most severe disease in young cattle. The disease is transmitted by direct contact, aerosols, and fomites. Flies may serve as mechanical vectors of the bacteria (7,18).

Treatment of IBK is based on antibiotics effective against moraxella (19,20). Antimicrobial therapy should be administered subconjunctivally or topically early in the disease course (3,10,21,22). The practical problem of treating several individuals within a herd 2 or 3 times daily has inspired several studies in search of alternate, more cost-effective therapies, for treating both ulcerative keratitis and *M. bovis* in carrier animals (1,19,23,24).

Enrofloxacin, a derivative of quinolone carboxylic acid, has greater in vitro activity against *M. bovis* than norfloxacin. Enrofloxacin has high lipid solubility and low ionic partitioning, suggesting that it may be extensively distributed to ocular tissues and may, therefore, be beneficial in the treatment of IBK. Controlled studies of the efficacy of subconjunctival administration of enrofloxacin for treatment of IBK have not, to the best of our knowledge, been previously reported. Studies have shown the efficacy of parenterally administered penicillin for susceptibility of *M. bovis* (25-30).

The purpose of this study was to determine whether subconjunctival administration of enrofloxacin could ameliorate a herd outbreak of IBK and to compare the efficacy of this regimen with the efficacy of subconjunctival administration of a combination of penicillin+streptomycin.

Materials and Methods

Calves were undergoing a natural epizootic of IBK when studied. The study included 38 Holstein calves during the autumn of 2003. The 18 male and 20 female calves were between 3 and 5 months of age and weighed between 56 and 102 kg. On the first day of the study, each calf was examined for clinical signs of IBK. The eyes of each calf were examined using a portable light while the calf was restrained in a squeeze chute. All eyes were numerically scored, ranging from 1 to 6. Scores were assigned according to the following criteria: (1) normal eye; (2) 1 or more signs of IBK, without corneal ulceration; (3) corneal ulcer < 5 mm in diameter; (4) corneal ulcer \geq 5 mm in diameter; (5) corneal perforation; (6) loss of vitreous. In calves that had photophobia, blepharospasm, or epiphora, the affected eyes were stained with fluorescein dye (Fluoreszein SE Thilo, Liba Laboratuarları A.Ş.) and irrigated to detect corneal ulcers on days 0, 7, 14, and 21. On these same 4 days, Schirmer tear test strips (Schirmer Tränentest, Vet. Eickemeyer) were used to assess the amount of tear production in affected eyes. In the Schirmer's tear test I, the rate of basal and reflex tear production were measured as the animal forms tears in response to the sensation of the strip contacting the eye. Fly control was not used on these calves during the study. The research began on September 10, 2003; all calves were weaned the week prior to the study.

The calves were prospectively and randomly assigned to 1 of 3 groups at the beginning of the study, and were examined 3 times weekly for 4 weeks. Affected calves in group 1 (n = 12) were treated with subconjunctival administration of penicillin+ streptomycin (120,000 U + 1.95 g). This treatment consisted of 3 subconjunctival injections of penicillin+streptomycin every 48 h. Calves in group 2 (n = 13) with corneal ulcers were treated with subconjunctival administration of enrofloxacin. Treatment consisted of 3 subconjunctival injections of enrofloxacin (30 mg) every 48 h. Topical local anesthetic (proparacaine hydrochloride, Alcaine 0.5%, Alcon

Pharmaceuticals Ltd.) was applied to the eye, and the antibiotic was injected beneath the bulbar conjunctiva using separate syringes (0.45 x 10 mm, 26 Gx 9.5 mm). Calves in group 3 (n = 13) were not treated and were used as controls. Thereafter, calves were examined 3 times per week for a total of 12 times between September 10 and November 2, when the IBK epizootic was considered to be over and most of the eye lesions had healed. Plastic aprons, obstetric sleeves, and latex examination gloves were worn when calves were examined and treated. After examination of each calf, gloves, sleeves, aprons, and other equipment that was in contact with ocular secretions were rinsed with 1% Benzalkonium chloride solution (Zefiran sol., İltaş Ltd.) and dried, using clean paper towels.

To determine whether calves were infected with *M. bovis*, ocular secretions were collected from affected eyes of calves prior to treatment and once a week thereafter (days 0, 7, 14, and 21). Ocular secretion specimens were collected by inserting a separate sterile swab into the inferior conjunctival fornix, and then directly inoculating the secretions onto sheep blood agar plates. Inoculated plates were subsequently streaked for isolation and were incubated aerobically for 24 h at 37 °C and then examined for bacterial colonies morphologically characteristic of *M. bovis*. Colonies typical of *M. bovis* were subcultured and identified, using previously described morphologic and biochemical criteria (10,11,16). Minimum inhibitory concentrations of enrofloxacin were then determined using the agar dilution method.

A combined healing time for ulcers on calf eyes was calculated from the day an ulcer was first observed on either eye to the second consecutive day the calf did not have corneal ulcers. Clinical scores were reported as the mean for eyes of each calf on each observation day. Mean healing times, clinical scores, and Schirmer's test scores were analyzed for each time interval by use of the Kruskal-Wallis test (nonparametric ANOVA). Repeated measure of mean clinical scores and Schirmer's test scores were analyzed for each time interval by use of the Friedman test (nonparametric repeated measures ANOVA). When overall differences were found by the Kruskal-Wallis test (KW) and Friedman test (Fr), differences between treatment groups were compared by use of Dunn's test for multiple comparisons. Samples of ocular secretions from which *M. bovis* were recovered were compared for each weekly interval, as mentioned above, by use of the chi-square test (χ^2). For all tests, a value of $P < 0.05$ was considered significant.

Results

On the first day of the study, all calves had one or more clinical signs of IBK. On day 0, corneal ulcers were observed in at least one eye of all calves. Corneal ulcers were detected on the left eye and right eye in 21 (58.3%) and 15 (41.6%) calves, respectively.

Mean healing time of groups 1 and 2 were not significantly different, and mean healing time of both treatment groups was significantly less than that of the controls (Table 1).

Table 1. Analysis of healing time data.

Groups*	Healing times $\bar{X} \pm SD$ Median (Min-Max)	KW test	P
Group 1	20.08 ± 6.36 ^a 17 (14-30)	13.250	P > 0.05
Group 2	20.16 ± 4.28 ^a 19 (17-30)	14.833	P < 0.05
Group 3	29.14 ± 1.74 ^b 30 (25-30)	28.857	P < 0.05

^{a,b} Difference is statistically significant in groups having different letters in the same column (P < 0.05).

* Group 1: penicillin+streptomycine combination; group 2: enrofloxacin; group 3: control.

Mean clinical scores of all calves were not significantly different on day 0 (Table 2). From day 14 of the study and continuing until the end of the study, mean clinical scores of groups 1 and 2 were significantly less than those of the controls. Significant differences in weekly clinical scores were not found between groups 1 and 2 at any of the weekly intervals.

Mean clinical scores of groups 1 and 2 were not significantly different between day 0 and day 7 (Table 3). From day 14 and continuing until the end of the study, mean clinical scores were significantly less than on day 0.

Mean Schirmer's test scores of all calves were not significantly different on day 0 (Table 4). On days 7 and 14, mean Schirmer's test score for group 1 was significantly less than that of the controls. Significant differences were not found in weekly Schirmer's test

scores between groups 1 and 2 at any of the weekly intervals.

Mean Schirmer's test scores of all calves were not significantly different at any of the weekly intervals (Table 5).

On day 0, *M. bovis* was isolated from the ocular secretions of 10, 9, and 10 calves in group 1, group 2, and group 3, respectively (Table 6). On day 7, *M. bovis* was isolated from 3 calves in group 1, 2 calves in group 2, and 10 calves in group 3. On day 14, *M. bovis* was isolated from 3 calves in group 1, 1 calf in group 2, and 9 calves in group 3. On day 21, *M. bovis* was isolated from 2 calves in group 1, 0 in group 2, and 8 calves in group 3. Frequency of *M. bovis* isolation was significantly lower in calves from groups 1 and 2 compared to the control group on all observation days after day 0.

Table 2. Analysis of clinical score data.

Groups	Day 0 Med (Min-Max)	Day 7 Med (Min-Max)	Day 14 Med (Min-Max)	Day 21 Med (Min-Max)
Group 1	3.0 (3-5)	2.5 (1-4)	1.5 (1-3) ^a	1.0 (1-2) ^a
Group 2	3.0 (2-6)	2.5 (1-5)	1.5 (1-5) ^a	1.0 (1-5) ^a
Group 3	3.0 (3-5)	3.0 (3-5)	3.0 (1-5) ^b	3.0 (1-4) ^b
KW test	0.467	5.723	13.231	16.535
P	P > 0.05	P > 0.05	P < 0.05	P < 0.05

^{a,b} Difference is statistically significant in groups having different letters in the same column (P < 0.05).

Table 3. Analysis of repeated measures of clinical score data for each group.

Groups	Day 0 Med (Min-Max)	Day 7 Med (Min-Max)	Day 14 Med (Min-Max)	Day 21 Med (Min-Max)	Fr test	P
Group 1	3.0 (3-5) ^a	2.5 (1-4) ^{ab}	1.5 (1-3) ^b	1.0 (1-2) ^b	29.969	P < 0.05
Group 2	3.0 (2-6) ^a	2.5 (1-5) ^{ab}	1.5 (1-5) ^b	1.0 (1-5) ^b	29.292	P < 0.05
Group 3	3.0 (3-5)	3.0 (3-5)	3.0 (1-5)	3.0 (1-4)	4.385	P > 0.05

^{a,b} Difference is statistically significant in groups having different letters in the same horizontal line (P < 0.05).

Table 4. Analysis of Schirmer's test score data.

Groups	Day 0	Day 7	Day 14	Day 21
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)
Group 1	26.75 ± 5.83	27.58 ± 5.33 ^a	26.41 ± 5.74 ^a	27.91 ± 3.42
	25.5 (20-35)	27.5 (17-35)	26.5 (18-35)	28.5 (22-34)
Group 2	29.92 ± 5.38	30.00 ± 4.55 ^{ab}	27.75 ± 5.19 ^{ab}	29.16 ± 3.85
	31.0 (21-35)	30.5 (20-35)	27.5 (20-35)	28.5 (23-34)
Group 3	31.58 ± 2.75	32.50 ± 1.78 ^b	31.58 ± 2.11 ^b	30.08 ± 1.31
	31.5 (27-35)	32.0 (30-35)	31.0 (29-35)	30.0 (27-32)
KW Test	4.228	6.362	7.561	3.817
P	P > 0.05	P < 0.05	P < 0.05	P > 0.05

^{ab} : Difference is statistically significant in groups having different letters in the same column (P < 0.05).

Table 5. Analysis of repeated measures of Schirmer's test score data for each group.

Groups	Day 0	Day 7	Day 14	Day 21	Fr test	P
	Median	Median	Median	Median		
	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)		
Group 1	25.5	27.5	26.5	28.5	0.868	P > 0.05
	(20-35)	(17-35)	(18-35)	(22-34)		
Group 2	31.0	30.5	27.5	28.5	4.205	P > 0.05
	(21-35)	(20-35)	(20-35)	(22-34)		
Group 3	31.5	32.0	31.0	31.0	4.330	P > 0.05
	(27-35)	(30-35)	(29-35)	(29-35)		

Table 6. Isolation of *Moraxella bovis* from ocular secretions.

Groups	Day 0		Day 7		Day 14		Day 21	
	n	(%)	n	(%)	n	(%)	n	(%)
	Group 1	10	(83.3)	3 *	(25.0)	3*	(25.5)	2*
Group 2	9	(75.0)	2 *	(16.7)	1*	(8.3)	0*	(0)
Group 3	10	(83.3)	10	(83.3)	9	(75.0)	8	(66.7)

* Significantly different from control group (P < 0.05).

Discussion

In this study, enrofloxacin and a combination of penicillin+streptomycin were both found to be effective in the treatment of naturally induced IBK, as healing times of corneal ulcers were significantly shorter in the treatment groups compared to the control group. Subconjunctival administration of enrofloxacin and penicillin+streptomycin also resulted in significant reductions in clinical score, Schirmer's tear test score, and the rate of *M. bovis* isolation from ocular secretions.

Clinical signs of infection and corneal lesions observed in the study calves were similar to those of clinical cases (4,5,7,13,29). Variability in the severity of ocular lesions may have resulted from immunologic and genetic factors.

A previous study of calves with IBK that were treated with procaine penicillin G suggested that corneal epithelium may regenerate at a constant rate following clearance of an *M. bovis* infection (28,30), and, therefore, elimination of *M. bovis* infection is considered important for achieving resolution of IBK. Enrofloxacin and procaine penicillin G have both been shown to eliminate *M. bovis* (14,29); however, the comparative efficacy of these 2 antibiotics remains unknown.

Enrofloxacin may be an effective therapeutic alternative to penicillin+streptomycin combination for the treatment of IBK in the event that *M. bovis* develops penicillin resistance.

In the present study, significant differences in healing times, clinical scores, and Schirmer's Test scores were probably attributable to the effectiveness of the antibiotic treatment to eliminate *M. bovis* infection. The healing rate of corneal ulcers is directly and linearly correlated to maximal ulcer size, providing the bacterial infection has been eliminated (22,25). Although healing time was similar for calves treated with enrofloxacin and penicillin+streptomycin, calves treated with enrofloxacin had a lower prevalence of IBK compared to the calves treated with the penicillin+streptomycin combination. Initial treatment of calves with enrofloxacin was effective in eliminating most ocular infections, as evidenced by the lower frequency of *M. bovis* isolation in this group.

In conclusion, subconjunctival administration of enrofloxacin appears to be an effective method of reducing the severity of a herd outbreak of IBK and may be superior to treatment of affected animals with penicillin+streptomycin.

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