Grid keratotomy as a treatment for superficial nonhealing corneal ulcers in 10 horses

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Abstract

Objective To describe the clinical symptoms of 10 cases of superficial nonhealing corneal ulcers in horses and to evaluate the results of grid keratotomy in these patients.

Design Retrospective study.

Animals Ten horses with superficial nonhealing corneal ulceration in one eye.

Procedure The signalment, history and clinical symptoms are reported of 10 patients with superficial nonhealing corneal ulcers during the period from August 2003 to February 2005. Grid keratotomy was performed in all cases. In addition, the surgical procedure of grid keratotomy and response to therapy are described.

Results Horses generally responded well to grid keratotomy (eight cases healed after one grid keratotomy and one horse healed after a second grid keratotomy; one case was not available for follow-up). Only 2/10 had discomfort after treatment and only 2/9 had some degree of scarring after treatment. The healing time, which was known in seven cases, averaged 8.4 days (± SD 4).

Conclusions and clinical relevance Grid keratotomy is an appropriate option for treatment of superficial nonhealing corneal ulcers in horses. The procedure is simple to perform. It generally induces a rapid and uncomplicated healing of the cornea. Only in a limited number of cases does a small amount of scarring occur.

Key Words: grid keratotomy, horse, superficial nonhealing corneal ulcer

INTRODUCTION

In horses there is a high incidence of superficial corneal disease.[1] Most of these ulcerations heal within 24 to 72 h by mitosis and migration of the adjacent healthy epithelial cells.[2,3] In cases of a superficial indolent corneal ulcer this rapid and simple healing process does not occur. This failure to repair epithelium is attributed to a failure to generate normal basement membrane.[2] The characteristic features of superficial nonhealing corneal ulcers are a noninfected epithelial defect without stromal loss, with a positive fluorescein staining that is present for 7 to 10 days minimum, depending on its size.[4] As well as this, the defect shows mal-attached margins of necrotic epithelial cells, and overall there is no sign of corneal vascularization. Most patients suffer from minimal or no ocular discomfort.[2] Generally, no causative infectious agent can be determined.[1] Medical treatments such as antibiotics, atropine, hyperosmotics, enzymatic inhibitors, fibronectin and epithelial growth factor have been used separately and in combination, with disappointing results.[3,5–7]

Superficial nonhealing corneal ulcers have also been referred to as indolent(-like) corneal ulcers, refractory ulcers, refractory epithelial erosions, persistent corneal ulcers, recurrent corneal erosion syndrome, chronic erosions, spontaneous chronic corneal epithelial defects and Boxer ulcers (in dogs). They have been reported in cats, dogs and horses.[6,8,9] In dogs the options of therapy are debridement, grid keratotomy or punctate keratotomy, superficial keratectomy, thermal cautery of the cornea, conjunctival grafts or flaps and temporary tarsorrhaphy.[5,7,8] In a study by Stanley *et al*.[8] both grid keratotomy and superficial keratectomy were shown to be highly successful. However, in cats grid keratotomy has been reported not to have a beneficial effect. In this species the procedure may well result in the development of a corneal sequestrum.[10]

Although there are no reports of using punctate keratotomy in horses, the options of therapy for equine indolent corneal ulcers are similar to those applied in dogs.[1,4,6,7,11]

In this paper 10 horses with superficial nonhealing corneal ulcers will be described. Grid keratotomy was performed in all cases. The procedure of grid keratotomy and the results obtained in these patients will be discussed.

Table 1. Signalment and clinical history of the patients on admission

No.	Breed	Sex	Age	Eye	Duration of symptoms (days)	Treated eyes		Other ocular symptoms
						Corneal vascularization	Ocular pain	
1	Zangersheide Warmblood	Gelding	10	OS	28	Small	Yes	OD: healing corneal ulcer
2	German Warmblood	Gelding	16	OD	14	No	Yes	Yearly recurrent corneal ulcers
3	Dutch Warmblood	Mare	11	OD	60	Small	No	Treated earlier with debridement
4a	Dutch Warmblood	Gelding	3	OS	120	No	No	OD: healing corneal ulcer
4b	Dutch Warmblood	Gelding	3	OS	120	No	No	OD: healing corneal ulcer OS: not responding to first GK (4a)
5	Frisian	Mare	27	OD	42	No	Yes	
6	Frisian	Mare	4	OS	45	Small	Yes	Uveitis OS
7	Frisian	Gelding	24	OD	21	No	Yes	
8	Dutch Warmblood	Stallion	2	OS	28	No	Yes	OD: healing corneal ulcer
9	Dutch Warmblood	Gelding	13	OS	150	No	Yes	History of corticosteroids treatment
10	Dutch Warmblood	Gelding	11	OS	28	No	No	Recurrent corneal ulcers

MATERIALS AND METHODS

Case history and signalment

Between August 2003 and February 2005 indolent corneal ulcers were diagnosed in 10 horses that were referred to the Department of Equine Sciences, Utrecht University, because of corneal problems (Table 1).

Six horses were geldings, three were mares and one was a stallion. Ages ranged from 2 to 27 years; mean age was 12 years. Seven horses were Warmbloods and three were Frisians. The right eye was affected in four cases and the left eye in six.

All horses had a history of superficial corneal ulcers with a fluorescein positive defect and duration ranging from 2 weeks to 5 months (mean duration of symptoms of 53.6 ± SD 46 days). They all had been treated with varying topical drugs, such as antibiotics, mydriatics and corticosteroids, but none of the horses had responded well to the medical treatment. One horse (no. 3) had unsuccessfully been treated by means of corneal debridement.

Two horses (nos. 2 and 10) had a history of yearly recurrent corneal ulcers. Three horses (no. 1, 4 and 8) had corneal ulcers on both eyes; in each of these horses one eye showed signs of healing (ingrowth of blood vessels, formation of granulation tissue) but the other eye did not.

Clinical findings

On admission all horses were submitted to a full ophthalmic examination.

In seven cases (nos. 1, 2, 5, 6, 7, 8 and 9) only slight blepharospasm, lacrimation and conjunctival hyperemia could be observed. In all horses the most striking finding was the presence of a discrete, shallow ulceration in the cornea with a narrow zone of peripheral stromal edema. In all cases fluorescein staining (Chauvin Benelux NV, Brussels, Belgium) was positive. Fluorescein could also be detected underneath the epithelial margins, which indicated that these had become loosened from the underlying stroma. In three cases (nos. 1, 3 and 6) a slight corneal neovascularization was present, but none of the blood vessels had made connection to the corneal defect. In all cases no cause for the persistency of the ulcer could be found.

In addition to the indolent corneal ulcers, other ocular abnormalities were observed in two cases. One eye (no. 6) showed signs of chronic uveitis: slight cataract and inflammatory detritus in the vitreal body. Mydriasis was present as a consequence of atropine administration. In another horse (no. 9) a small deposit of stromal pigment was located in the cornea at the site of the ventral part of the ulcer.

In all cases the diagnosis 'superficial nonhealing corneal ulcer' was made upon history and clinical signs.

Surgical treatment

Grid keratotomy was performed in all cases. In nine horses the procedure was performed on the recumbent animal under general inhalation anesthesia (premedication with detomidin (Pfizer Animal Health, Capelle a/d IJssel, the Netherlands; 10 μg/kg IV); general anesthesia was induced with midazolam (Pharmacy Faculty of Veterinary Medicine, Utrecht University, the Netherlands; 0.06 mg/kg IV) and ketamine (Chassot AG, Belp, Switzerland; 2.2 mg/kg IV) and maintained with isoflurane-oxygen in a semiclosed circle system with assisted ventilation).

Two horses (nos. 5 and 6) were treated while standing. Horse no. 5 had been sedated with a combination of detomidin (Pfizer Animal Health; 5 μg/kg IV) and nalbuphine hydrochloride (Endo Pharmaceuticals, Chadds Ford, PA, USA; 70 μg/kg IV). Horse no. 6 had been sedated with only detomidin (Pfizer Animal Health; 10 μg/kg IV).

In all patients the conjunctival sac and cornea were rinsed,[6] after which the cornea was topically anesthesized with tetracaine (Chauvin Benelux NV) drops (5 mg).

Firstly, the loosened edges of the epithelium were removed by debridement using a small curette. Subsequently, a grid keratotomy was performed using a 23-gauge needle, making superficial horizontal and vertical scratches in the cornea that resulted in a grid pattern (Fig. 1). The scratches were made

Figure 1. Horse no. 10, a grid keratotomy is performed under general anesthesia using a 23-gauge needle. Little edema is present around the defect.

Figure 2. The same horse (no. 10) 3 days after grid keratotomy. There is no ocular discomfort and no vascularization is visible. The fluorescein staining had become negative. The grid pattern is still visible and there is still some edema around the former defect.

over the corneal defect and extended in the surrounding cornea for about 1–2 mm. The distances between the successive scratches amounted to approximately 1 mm. A small amount of pressure on the needle was needed in order to create scratches that penetrated the basement membrane of the epithelium and the superficial layer of the stroma.

In horse no. 4 a second grid keratotomy of the same eye was performed 25 days after the first surgery, because the eye had not responded to the first grid keratotomy.

Postoperative treatment and postoperative course

After the surgical procedure all eyes were treated topically with broad-spectrum antibiotics (Pfizer Animal Health; q 6–8 h). In six cases (cases 1, 2, 3, 4, 6 and 7) a mydriatic agent (Veterinary Hospital Pharmacy, Utrecht University, the Netherlands; q24 h) was also administered, and in three cases (nos. 7, 8 and 9), vitamin A ointment (Veterinary Hospital Pharmacy; q8 h). In each horse, healing of the cornea was evaluated by repeated ophthalmic examination, including fluorescein staining (every 2–3 days depending on the status of the eye). As soon as the fluorescein staining was negative we defined the cornea as healed.

In six horses (cases 1, 2, 4, 8, 9 and 10) fluorescein staining was already found to be negative during the stay at the clinic. After fluorescein staining had become negative, medical treatment was stopped and the horses were sent home.

Three horses (nos. 3, 6 and 7) left the clinic before the fluorescein staining had become completely negative. These horses showed sufficient healing tendency to be discharged. The owner was advised to continue the medical treatment for a period of 1 to 2 weeks as long as the defect was visible. Two of these patients (nos. 3 and 6) returned for follow-up after a prolonged period (45 and 35 days, respectively). Case no. 7 was unavailable for follow-up.

The owner of patient no. 5 was a client of our ambulatory clinic. Because of severe problems traveling with the horse we performed the grid keratotomy on location. The owner administered postoperative medication and our veterinarians monitored the horse.

RESULTS

Healing

Eight patients healed after the first keratotomy (Table 2; Fig. 2). In patient no. 4 the cornea still stained fluorescein positive on the 25th day postoperatively and a second grid keratotomy was performed. After that the corneal defect healed within 9 days. In one case (no. 7) further information about the postoperative course is unknown as the horse left the clinic and did not return for follow-up.

Table 2. Clinical symptoms and healing after grid keratotomy

No.	Pain	Neovascularization	Negative fluorescein staining (days)	Scarring
1	No	No	7	No
2	Yes	Yes	6	No
3	No	No	45	No
4a	No	No	–	–
4b	No	No	9	No
5	No	Yes	7	Yes
6	No	No	35	Yes
7	Yes	No	?	?
8	No	No	12	No
9	No	No	15	No
10	No	No	3	No

In six horses the grid pattern remained visible for 2 to 6 weeks, although the cornea had healed within a short period of time. Subsequently it faded and the cornea became completely clear, without any opacities.

Healing time

The healing time was considered to be the time necessary for the cornea to become completely fluorescein negative. This parameter could be determined for patient nos. 1, 2, 4, 5, 8, 9 and 10. In these seven patients the mean healing time was 8.4 days (± SD 4). Three horses (nos. 3, 6 and 7) left the clinic before they became completely fluorescein negative. Patient nos. 3 and 6 returned for follow-up (at 45 and 35 days, respectively) and their corneas had completely healed. Of the other case (no. 7) further information is unavailable.

Postoperative pain

Most horses did not show obvious discomfort following the keratotomy. In only two patients (cases nos. 2 and 7) the eyes were painful during the first few postoperative days, but these patients were already suffering from ocular discomfort before treatment. They showed moderate lacrimation and blepharospasm. On ophthalmic examination mydriasis was present in both cases as a consequence of atropine administration prior to referral.

Neovascularization and scarring

Five patients (nos. 1, 2, 3, 5 and 6) showed some degree of superficial corneal vascularization after grid keratotomy. In three of these patients (nos. 1, 3 and 6) vascularization of the cornea was already present at the time of referral. In all five patients the vascularization did not increase after the grid keratotomy. In two cases (nos. 5 and 6) the vascularization reached the ulcer and resulted in the formation of scar tissue. In all five cases the blood vessels completely withdrew after the cornea had healed.

Postoperative complications

In patient nos. 9 and 10, grid keratotomy was performed on the left eye. Both patients recovered well and did not show postoperative ocular discomfort.

However, on the eighth postoperative day (day 8) horse no. 9 suffered from an acutely painful left eye. Ocular examination revealed conjunctival hyperemia. In the cornea small vesicles and multifocal punctuate fluorescein-positive spots and fissures with focal anterior stromal edema were present. An acute viral keratitis was suspected, but not confirmed.[2] Based upon the clinical findings, antiviral treatment with acyclovir ointment (Glaxo Smith and Kline, Zeist, the Netherlands; q6 h) was initiated. On day 15 postoperatively the eye was no longer painful and fluorescein staining was negative, whereupon the horse was released from the clinic. The owner was advised to continue the medication with acyclovir (q6 h) for another 2 weeks. The acyclovir therapy was combined with the administration of 0.1% dexamethasone and tobramycin ointment (Alcon Nederland, Gorinchem, the Netherlands; q8 h) for 1 week. Six months later the horse was readmitted because of recurrent ocular problems. The left eye showed signs of corneal degeneration. The eye was not painful. Edema, superficial blood vessels and white-colored scar tissue with deposits of brown–black colored pigment were present in the cornea. Any further treatment was discontinued and a poor prognosis was given.

The cornea of patient no. 10 was fluorescein negative on the third postoperative day (day 3) and the horse was discharged on day 7. Approximately 4 weeks later the horse was readmitted. In the left eye a superficial punctate viral keratitis was diagnosed. Treatment with acyclovir was prescribed, with subsequent full remission.

DISCUSSION AND CONCLUSION

The etiopathogenesis of indolent, superficial corneal ulcers has been described to be an alteration in the function of the corneal basement membrane. The adherence of the epithelium to the stroma is disrupted and there are everting, loosened edges of the epithelium around the ulcer.[3–5,7] According to Cutler,[4] the disrupted adherence between epithelium and stroma can be due to the following mechanisms: formation of an abnormal membrane between the stroma and epithelium, alteration in the homeostasis of growth factors and neurotransmitters, and a disrupted balance of degradative enzymes.

Stanley *et al*.[8] described the presence of a thin superficial acellular zone of hyaline collagen in the corneal stroma in dogs with indolent corneal ulcers. This layer is suspected to act as a barrier to epithelial healing. This finding is in line with the theory of Willeford *et al*.,[3] Cutler[4] and Bentley.[9] In addition, Bentley[9] showed that indolent corneal ulcers in dogs are characterized by the complete absence of a corneal epithelial basement membrane at the site of the defect.

Willeford *et al*.[3] described two different pathophysiologies for superficial nonhealing corneal ulcers in dogs: (1) as described above, a thin layer acellular layer of hyaline works as a barrier for epithelial healing. (2) The 'normal' healing of a corneal defect starts with preparation of the epithelial cells for migration. Fibronectin, fibrin, laminin and other extracellular matrix proteins form a matrix creating a scaffold for the migrating epithelial cells. During this migration, these epithelial cells release plasminogen activator in the presence of fibronectin and fibrin. Plasminogen is then converted into plasmin, causing the newly formed scaffold to detach from its surrounding. This enables the epithelial cells to form permanent anchoring fibrils to the underlying basement membrane. This cascade continues until the defect is covered with firmly attached epithelial cells. However, this cascade can be over-activated causing disruption of newly attached epithelial cells or even ultimately degradation of the basement membrane. In this situation the healing process is hindered and consequently a superficial nonhealing corneal ulcer is the result. This theory is supported by the results on superficial nonhealing corneal ulcers treated

with protease inhibitors (polysulfated glycosaminoglycans) by Willeford *et al*.[3]

Ollivier *et al*.[12] and Strubbe *et al*.[13] made investigations into the levels of matrix metalloproteinases (MMP) in the tear film of horses with ulcerative keratitis. In these horses, a decreased concentration of MMP was associated with clinical improvement.[12] The beneficial effect of a topically applied autologous serum supports the role of MMP in cases of indolent corneal ulcers.[4]

Many therapeutic options have been described.[4–6,14] The therapy of choice is based on clinical signs, the experiences of the veterinarian, the efforts to be made by the owner, and financial aspects. Medical therapy is often the first choice, as differentiation between simple superficial corneal erosions and superficial nonhealing corneal ulcers may be difficult at the onset of ocular problems. As medical treatments generally give disappointing results with superficial nonhealing corneal ulcers, the absence of response after a period of time may be a sign of the presence of such ulcers.[3,5–7]

A soft contact lens can be used to protect the cornea.[14] In a horse that was medically treated because of an indolent ulcer, the affected eye became significantly less painful as soon as the soft contact lens was applied. The contact lens allowed the horse to undergo training during the time of treatment.

When loosened epithelial margins are present, debridement is advised using a cotton tip or small curette.[4] Michau *et al*.[6] described 23 horses with indolent corneal ulcers. Out of the 16 horses in which only debridement was performed, 10 healed (63%) with a mean healing time of 15 days. In the patients treated by grid keratotomy (initially or not responding to debridement alone) the success rate was 78% with a mean healing time of 16 days. Similar to our definition, Michau *et al*.[6] determined complete healing of the cornea as soon as fluorescein dye staining was negative.

Supported by all the positive results with grid keratotomy published by several authors, together with the promising results of our second author (Professor M. H. Boevé) with grid keratotomy in his canine patients, we decided in only one case to perform debridement alone. The other nine patients were directly submitted to debridement and grid keratotomy.

When a superficial corneal ulcer is present for more than 2 weeks (despite medical treatment and/or debridement) superficial keratectomy or grid keratotomy is indicated.[4] The choice between these techniques is based on several factors. A superficial keratectomy requires general anesthesia, a well-experienced ophthalmic surgeon, and a well-equipped surgery room (including an operating microscope). A grid keratotomy is easier to perform; only simple equipment is needed, and the procedure can be performed in the standing (sedated) horse, provided safe conditions can be maintained. The results of both procedures are favorable, but the mean healing time after grid keratotomy is shorter than that after superficial keratectomy according to Michau *et al*.[6] Delayed healing, infection and recurrence of the initial lesion may occur after both procedures. However, after superficial keratectomy more severe complications such as descemetocele, corneal perforation, and excessive scar formation have been described as well.[11]

Based on the etiopathogenesis, there are two theories concerning the efficacy of grid keratotomy: (1) it increases contact of the epithelium with the underlying stroma by disrupting the basement membrane, and (2) it alters the superficial stromal collagen, thereby allowing better adherence with the epithelium.[5,8]

Because of the simplicity of the procedure, the shorter healing time, the small amount of discomfort after surgery, the slight risk of serious complications and the minimal scar formation, grid keratotomy is preferred to superficial keratectomy in superficial indolent ulcers.

Punctate keratotomy is a variant of grid keratotomy. Using a hypodermic needle small punctures are made in the cornea at the site of the ulcer, as well as in the healthy cornea around the lesion.[5] The risk of corneal perforation is estimated to be higher for punctate keratotomy than for grid keratotomy. This is because the needle is positioned perpendicular to the cornea during a punctate keratotomy, whereas in grid keratotomy the needle is held in an oblique position. Stanley *et al*.[8] reported a lower success rate after punctate keratotomy than after grid keratotomy in dogs.

The disadvantages of conjunctival (pedicle) grafts or flaps, such as the requirement of a well-experienced ophthalmic surgeon, excessive scar formation, and in some cases the need for a second operation, make this therapeutic option less attractive for an indolent, superficial corneal ulcer.[5] Only in cases of deep ulcers or in cases in which other therapies are not successful are conjunctival grafts a good choice of therapy.[5]

Bentley and Murphy[7] described eight dogs and two horses in which thermal cautery was successfully used in order to treat spontaneous chronic corneal epithelial defects. It was suggested that this procedure would alter the superficial portion of the corneal stroma as it burns the stromal layer, thereby causing disruption of the stromal lamellae through contraction of collagen fibrils and keratocytic injury and death.

In the presented cases the occurrence of indolent corneal ulcers tended to be age-related. The prevalence appeared to be higher in very young and in old horses. Three horses were rather young (2–4 years). Young horses tend to get simple superficial corneal erosions more often, as they may be hot headed and inexperienced in working with humans. In these horses superficial corneal ulcers may evolve into indolent corneal ulcers. There were six horses of average age (10–17 years) and two old horses (24 and 27 years). The finding of a tendency for older horses to be more susceptible to indolent corneal ulcers is also in line with those of Michau *et al*.[6] and Barnett *et al*.[2] In our patients there was no indication for a breed and sex predisposition, also in agreement with Michau *et al*.[6]

A viral keratitis probably developed some time after the grid keratotomy in two of our patients. This is not a known complication of grid keratotomy or of any other therapy for indolent corneal ulcers. Therefore, it is unclear whether there was a causal relationship between grid keratotomy and viral keratitis in these patients.

In patient no. 6, signs of chronic uveitis were also present at the time of referral. The patient was treated with grid keratotomy in a standing (sedated) position and was discharged the same day. The horse was sent home with advice to the owner to treat the ulcer with antibiotic ointment and atropine as long as it was visible. The horse returned for follow-up after 35 days. At that time the cornea had completely healed while the signs of chronic uveitis (slight cataract and some inflammatory detritus in the vitreous body) had not changed. An ultrasonographic examination of the eye was performed, as clinical examination of the fundus of the eye did not provide sufficient information. Ultrasound of the eye revealed retinal detachment, which is a common complication of recurrent chronic uveitis.[2] In our opinion the retinal detachment was not directly related to the indolent corneal ulcer.

The results of grid keratotomy for the treatment of a superficial indolent corneal ulcer in our cases are very promising. It is a simple procedure to perform and overall it provides good, nonpainful, uncomplicated and rapid healing with few side effects and little scar tissue formation.

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