Equine Veterinary Journal

Equine Veterinary Journal ISSN 0425-1644
DOI: 10.1111/evj.12098

Feasibility of aqueous shunts for reduction of intraocular pressure in horses

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Presented in part in abstract form at the 4th Annual Conference of the International Equine Ophthalmology Consortium, Stirling, Scotland, June, 2012.

Summary

Reasons for performing study: Based on the current literature, neither medical, surgical nor combination therapy adequately controls equine glaucoma for many horses. Aqueous shunts have been useful in other species to control glaucoma.
Objectives: To determine whether aqueous shunts in normal equine eyes significantly reduce intraocular pressure (IOP) without causing vision threatening complications.
Study design: Prospective experimental trial.
Methods: Aqueous shunts were placed in 7 normal eyes of 4 horses. The shunts were placed dorsotemporally. Examinations were initially performed daily for 7 days and after that every 3 days through 4 weeks after implantation. Horses were then subjected to euthanasia and globes enucleated for routine histological examination. The IOPs for each day post operatively were compared to the preoperative value (Day -1) using a Wilcoxon signed ranks test. Significance was set at $P<0.05$.
Results: The mean IOP preoperatively (20.7 ± 3.0 mmHg) was significantly higher than on any post operative day (P values ranged from 0.018 to 0.048). The aqueous shunts remained *in situ* for the entire study. Two eyes developed corneal ulcers that resolved. Shallow anterior chambers were noted in 2 eyes after shunt placement, which normalised after placement of full eye cup masks. Histologically, 7/7 eyes had fibrosis surrounding the implant. Minimal peripheral neovascularisation and neutrophilic keratitis were noted in 5/7 eyes. Corneal damage was scored as none in 3/7, mild in 2/7, moderate in 1/7 and marked in 1/7 eyes.
Conclusions: After placement of aqueous shunts, a significant decrease in IOP was noted from preoperatively (Day -1) to Day 28 despite fibrosis surrounding the implants. No vision threatening complications were noted.
Potential relevance: Aqueous shunts may represent a feasible therapeutic option for equine glaucoma. The results of this study suggest that further studies in glaucomatous horses would be warranted.

The Summary is available in Chinese – see Supporting information.

Keywords: horse; glaucoma; eye; valve; shunt; aqueous shunt

Introduction

Equine glaucoma was considered a rare condition prior to the development of a tonometer that enabled easy and accurate assessment of a horse's intraocular pressure (IOP) [1]. The improved diagnostic capabilities resulted in increasing numbers of horses being diagnosed with glaucoma [1,2]. Failure to preserve vision and/or relieve discomfort frequently resulted in evisceration and the placement of intrascleral prostheses, enucleation or euthanasia [1,2].

Current glaucoma therapies reduce IOP medically or surgically [3]. Medical therapy consists of topical beta blockers [4] and/or topical carbonic anhydrase inhibitors [5,6] applied 2–3 times daily to reduce aqueous humour production, and concurrent systemic and topical anti-inflammatory therapy to control any underlying equine recurrent uveitis [7]. However, based on 2 retrospective case studies on equine glaucoma, the long-term success of medical management appears poor [1,2].

Surgical management is initiated if medical therapy fails to maintain a normal IOP or the horse's temperament precludes instillation of topical medications. Laser trans-scleral cyclophotocoagulation (TSCP) is the preferred surgical method [3]. The TSCP induces coagulation necrosis of the nonpigmented ciliary body epithelium, thereby reducing aqueous humour production [8]. Although coagulation necrosis occurs within 60 min of TSCP [9], the IOP does not diminish for 2–4 weeks post operatively [10]. The sustained elevation in IOP can cause further optic nerve compression and retinal ganglion cell death [11]. In a recent retrospective study, after TSCP 64% of eyes required long-term topical medical therapy to maintain a normal IOP [7]. Over the post operative period, only 59% of eyes maintained vision [7]. Based on the current literature, neither medical therapy, surgical therapy or combination therapy adequately controls equine glaucoma for many horses.

An alternate approach to IOP reduction is restoration of aqueous humour outflow [12]. Circulating aqueous humour provides nutrients to the cornea and lens [13]. Disruption of aqueous humour flow can result in cataract formation and corneal decompensation [12]. Aqueous shunts restore aqueous outflow. The shunt consists of a silicone tube placed within the anterior chamber that extends subconjunctivally and terminates beneath an explant plate sutured to the sclera [14]. Aqueous humour drains into the space created by the explant plate, moves into the surrounding tissue and clears via conjunctival venous capillaries [14]. In human patients, placement of aqueous shunts is clearly indicated for patients that fail to respond to medical or laser therapy [14]. In canine patients receiving aqueous shunts as the sole surgical therapy, the success rate was 80% at 9 months post operatively [15]. These results demonstrate the utility of aqueous shunts for maintenance of normal IOP and vision in man and dogs.

A single case report describes placement of a silicone drainage implant in the eye of a horse with chronic glaucoma [16] and reports excellent IOP control with minimal inflammation. The implant was dislodged after one week. However, the results suggest aqueous shunts may be a successful treatment modality in the horse. Therefore, the current study was designed with the purpose of determining whether aqueous shunts in normal equine eyes significantly reduce IOP without causing vision threatening complications.

Materials and methods

Number of animals

Aqueous shunts were planned to be placed in 8 normal eyes of 4 horses donated to the Purdue University College of Veterinary Medicine. The number of horses used was based on possible results for the binomial exact 95% confidence interval (CI). Four horses (8 eyes) were determined to be the smallest viable number of horses. Had fewer eyes of fewer horses been selected, for example 3 horses, then, if there was one complication, the 95% CI would have been 0.4–64.1%. Those rates were deemed unacceptable. This study was approved by the Purdue University Animal Care and Use Committee and conformed to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.

Experimental design

Each horse was acclimatised to the surroundings for at least 7 days, during which a complete ocular examination, including Schirmer tear testing, fluorescein staining, IOP measurement (TonoPen XL)[a], slit-lamp biomicroscopy and indirect ophthalmoscopy, was performed by a single investigator (WMT). Vision was assessed by the menace response and observing the horse as it walked in the stall and aisleway. Horses were not sedated and akinesia of the regional nerves was not performed. Horses with significant ocular abnormalities were excluded from the study. A routine physical examination was also performed. Horses with systemic conditions, such as significant lameness or pulmonary disease that would interfere with general anaesthesia or require therapy, were excluded.

Prior to surgery, ofloxacin 0.3% ophthalmic solution and prednisolone acetate 1% ophthalmic solution were applied to each eye every 30 min for a total of 3 applications. An i.v. jugular catheter was placed. Flunixin meglumine (1.1 mg/kg bwt, i.v.), potassium penicillin (10,000 iu/kg bwt, i.v.) and gentamicin (6.6 mg/kg bwt, i.v.) were administered 1 h prior to anaesthetic induction. General anaesthesia was induced, maintained and monitored using the standard procedures for the Purdue Veterinary Teaching Hospital anaesthesia service. Each horse was placed in dorsal recumbency with the head turned laterally so that the right eye was directed upward and parallel to the surface of the surgical table. At completion of surgery on the right eye, the head was repositioned for the left eye. Routine preparation of each globe and ocular surface for surgery was performed. An operating microscope was used for magnification.

Stay sutures of 4-0 silk were placed dorsally and ventrotemporally to facilitate globe manipulation and positioning. A conjunctival incision was made 10 mm posterior to the limbus dorsotemporally. Haemostasis was achieved through the use of wet field cautery. Caudal dissection along the scleral surface created a subconjunctival pocket for the explant plate of the aqueous shunt (Ahmed Model VFP7)[b]. The tubing was flushed normograde with 50 μg of tissue plasminogen activator (tPA) (25 μg/100 μl) to prime the tube, open the valve and reduce fibrin deposition within the lumen. The explant plate was then placed in the pocket and secured to the sclera with 4 simple interrupted sutures of 8-0 nylon (CaraNylon)[b]. The tubing was cut at a 45° angle and short enough so it would not cross the pupillary margin or contact the *corpora nigra*. A 20 gauge needle was used to create a scleral tunnel into the anterior chamber. Viscoelastic material (CaraVisc)[b] was injected into the scleral tunnel as the needle was withdrawn. The tubing was inserted through the tunnel into the anterior chamber and aqueous flow visualised at the explant plate. The conjunctival incision was closed with simple continuous sutures of 6-0 polyglycolide (CaraGlyde)[b]. Dexamethasone sodium phosphate (1 mg) was injected subconjunctivally. Atropine 1% ophthalmic ointment was applied to the globe at the conclusion of surgery. A ventral subpalpebral lavage system (eye lavage kit – subpalpebral)[c] was placed. Ofloxacin 0.3% ophthalmic solution and prednisolone acetate 1% ophthalmic solution were applied to the ocular surface 4 times daily for 7 days, followed by prednisolone acetate 1% ophthalmic solution as needed to control inflammation. Flunixin meglumine was administered (1.1 mg/kg bwt, i.v. or *per os* q. 12 h for 3 days and then q. 24 h for 4 days).

Complete ocular examinations, including fluorescein staining, IOP measurement, slit-lamp biomicroscopy and indirect ophthalmoscopy, were performed daily for the first week and then every third day until the end of the study. Aqueous flare was scored as 0 = absent, 1 = barely detectable, 2 = relucency equal to that of the lens, 3 = iris detail hazy and 4 = not able to view the iris.

Four weeks after implantation of the aqueous shunt, each horse was used in a terminal surgery laboratory, subjected to euthanasia and the globes collected for histological evaluation. The globes were placed in 10% formalin for fixation, then paraffin-embedded, sectioned and stained with haematoxylin and eosin for routine light microscopic evaluation. The following features were graded histologically by one investigator (IML): thickness of fibrous wall surrounding the explant plate (0 = none, 1 = <0.5 mm, 2 = 0.5–1 mm, 3 = >1 mm), degree of inflammation (0 = none, 1 = mild, 2 = moderate, 3 = severe), degree of corneal damage (0 = none, 1 = mild, 2 = moderate, 3 = severe), scleral thinning (absent, present), retinal degeneration (absent, present) and cataract (absent, present).

Data analysis

Scores for aqueous flare and the histological parameters were reported as the median and range. Descriptive data for the IOP were reported as mean ± s.d. (median and range). As the IOP values were nonparametrically distributed, each globe's IOP preoperatively (Day -1) and on Days 1–7, 10, 13, 16, 19, 22, 25 and 28 were compared using a Wilcoxon signed ranks test. The significance level was set at $P<0.05$.

Results

Study population

Aqueous shunts were placed in 7 eyes of 4 adult horses. One horse experienced complications under general anaesthesia that precluded continued general anaesthesia and placement of an aqueous shunt in the left eye. There were 3 mares and one gelding, 2 Dutch Warmbloods, one Quarter Horse and one Trakehner. The median age was 17.5 years (range 17–20 years).

Intraocular pressures

The mean IOP on the day prior to surgery was 20.7 ± 3.0 mmHg (median 19, range 18–26 mmHg) (Table 1) (Fig 1). The mean IOP on Day 28 was 12.6 ± 2.4 mmHg (median 13, range 9–15 mmHg). The IOP was significantly lower on all post operative days (P values ranged from 0.018 to 0.048) than the IOP on the day prior to surgery (Fig 1). Increases of IOP above the baseline were noted in 2 cases. In *Case 2*, left eye (OS), the IOP elevation (24 mmHg) occurred the day following surgery. Wisps of fibrin were noted obstructing the tip of the shunt tubing. The fibrin retracted by the following day and the IOP decreased to 14 mmHg. In *Case 4*, right eye (OD), IOP elevations were noted on Days 5 (23 mmHg, tPA injected intracamerally), 13 (20 mmHg) and 19 (24 mmHg).

Clinical findings

All shunts remained *in situ* for the entirety of the study (Fig 2a). No retinal detachments were identified. Minimal intraocular inflammation was detected. The median aqueous flare score on Day 1 post operatively was 2 (range 1–2). The maximum aqueous flare score recorded on any day was also 2. Aqueous flare was absent in all eyes in week 4.

Some complications occurred (Table 1). *Case 1* OD had dehiscence of conjunctival sutures at the limbus dorsotemporally where the conjunctiva had torn during shunt placement. This area generated marked granulation tissue by week 4 post operatively. *Case 1* OS had hyphaema and anterior vitreal haemorrhage noted during shunt placement that resolved by Day 7 post operatively. Incipient anterior capsular opacities were observed after the haemorrhage resolved. Additionally, in *Case 1* OS, a shallow anterior chamber and scleral indentation were noted due to hypotony on Day 3 post operatively. After placement of a full eye cup mask, the anterior chamber returned to normal depth and the scleral indentation resolved. The mask was worn for 10 days.

Case 2 OD had keratic precipitates observed at Day 23 post operatively. These lesions improved, but failed to completely resolve by the end of the

TABLE 1: Summarised data including the preoperative intraocular pressure (IOP); post operative Day 28 IOP; histological scores and complications encountered after placement of the aqueous shunt

ID	Eye	IOP preop mmHg	IOP 28 days mmHg	Histological scores F	I	C	Complications
1	OD	26	15	3	3	1	Marked granulation tissue along the drainage tube in area where previous conjunctival incision dehisced
1	OS	22	13	1	1	1	Hyphaema at surgery, haemorrhage in anterior vitreous at surgery, shallow anterior chamber and scleral indentation due to hypotony Days 3–7, resolved with placement of a mask, incipient cataract in area of previous hyphaema
2	OD	23	9	2	2	1	Keratic precipitates on Days 23–28
2	OS	19	10	2	0	1	Wisps of fibrin noted in anterior chamber Days 1–2
3	OD	18	10	1	0	1	Corneal ulceration Days 4–10, wisps of fibrin noted in anterior chamber
3	OS	19	10	1	1	0	Corneal ulceration Days 5–10 and 16–19, hyphaema at surgery, shallow anterior chamber Day 3, resolved with placement of mask, incipient cataract in area of previous hyphaema
4	OD	18	15	2	0	1	Hyphaema on recovery, tubing plugged with fibrin, intracameral tPA D.5, marked chemosis Days 1–13
*		20.7	12.6	2	1	1	

*Denotes the mean for IOP and median for the histological scores in each category.
OD = right eye, OS = left eye, IOP = intraocular pressure, F = thickness of fibrous wall surrounding the explant plate (0 = none, 1 = <0.5 mm, 2 = 0.5–1 mm, 3 = >1 mm), I = degree of inflammation (0 = none, 1 = mild, 2 = moderate, 3 = severe), C = degree of corneal damage (0 = none, 1 = mild, 2 = moderate, 3 = severe).

study despite the application of topical prednisolone acetate and systemic flunixin meglumine. *Case 2* OS had fibrin strands present within the anterior chamber on Days 1 and 2 post operatively. The strands subsequently resolved.

Case 3 OD developed a 4×5 mm corneal ulcer on Day 4 that resolved in 6 days. *Case 3* OS had hyphaema noted at the time of shunt placement. Upon resolution of the fibrin and haemorrhage, incipient anterior capsular opacities were noted. *Case 3* OS also developed a shallow anterior chamber on Day 3 that resolved with placement of a full eye cup mask. The mask was worn for 3 days. *Case 3* OS developed a 4×6 mm corneal ulcer on Day 5 that resolved in 5 days. On Day 16 post operatively, *Case 3* OS developed multiple, pinpoint additional areas of corneal ulceration ventronasally that resolved in 3 days.

Case 4 OD haemorrhaged into the anterior chamber during recovery from anaesthesia (Fig 2b). On Day 5 post operatively, 50 μg of tPA was injected intracamerally to lyse the remaining fibrin, some of which occluded the tip of the shunt, and to restore shunt function. The same eye also had marked chemosis that persisted for 13 days post operatively before resolving.

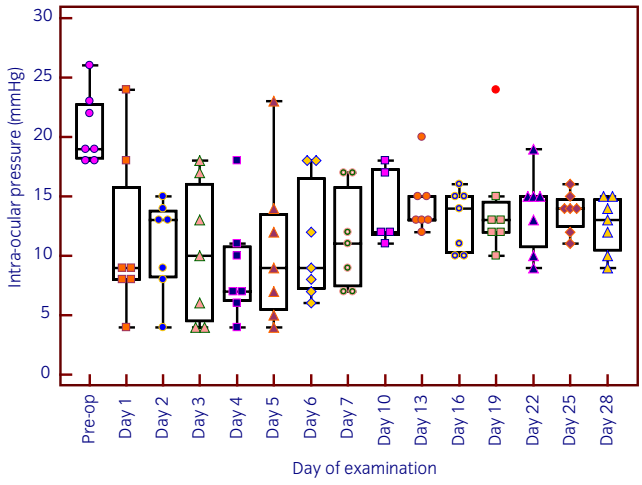

Fig 1: The intraocular pressures preoperatively and each day they were measured post operatively are displayed as box and whisker plots. Each datapoint is displayed but the datapoints are not identified by case or eye. Outside values (those greater than the upper quartile plus 1.5 times the interquartile range) are not connected to the box by the vertical line. The red circle on Day 19 represents a far out value (greater than the upper quartile plus 3 times the interquartile range).

Histological findings

The nature and severity of the histological lesions observed in the eyes after termination of this study are listed in Table 1. All eyes (7/7) had fibrosis surrounding the implant. The median fibrosis score was 2 (range 1–3) (Fig 3). In 4/7 eyes inflammation was detected surrounding the implant. The

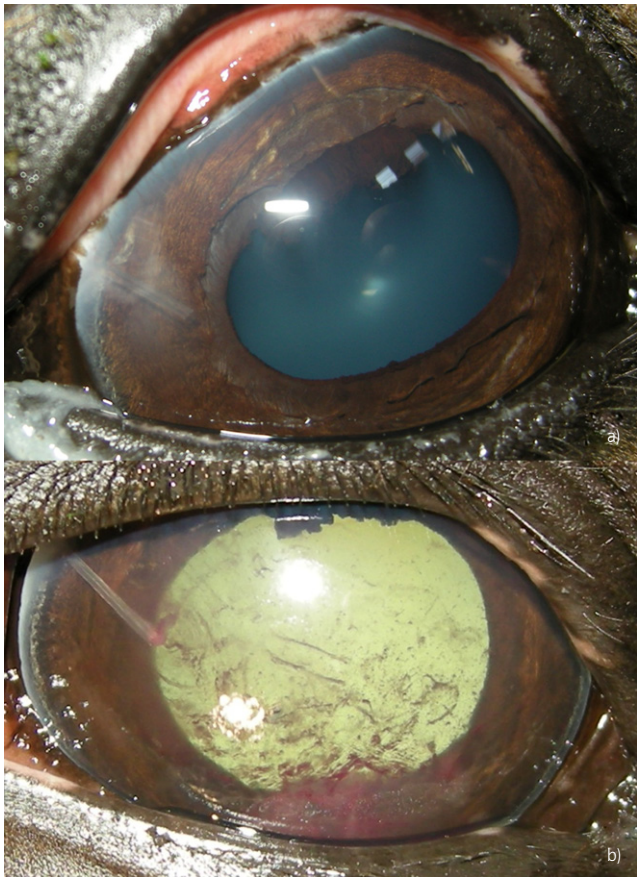

Fig 2: a) The right eye of *Case 1* one week post operatively with the tubing well positioned within the anterior chamber. b) The right eye of *Case 4* with hyphaema and fibrin, some of which occludes the tip of the shunt tubing.

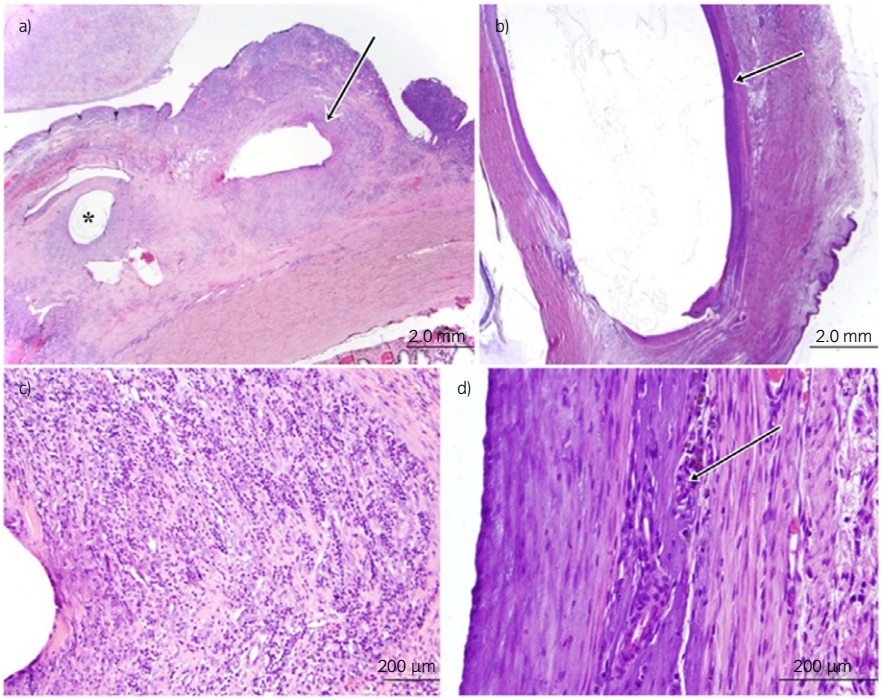

Fig 3: a) Histological section stained with haematoxylin and eosin from the right eye of *Case 1* taken at 12.5 × magnification with the arrow denoting the area of fibrosis scored as 3 (>1 mm). The asterisk denotes the shunt tubing coursing through the tissue. b) Histological section stained with haematoxylin and eosin from the left eye of *Case 3* taken at 12.5 × magnification with the arrow denoting the area of fibrosis scored as 1 (<0.5 mm). c) Histological section stained with haematoxylin and eosin from the right eye of *Case 1* taken at 100× magnification demonstrating the degree of inflammation scored as 3 (severe). d) Histological section stained with haematoxylin and eosin from the left eye of *Case 3* taken at 100 × magnification with the arrow denoting the area inflammation scored as 1 (mild).

median inflammation score was 1 (range 0–3) (Fig 3). In 6/7 eyes minimal peripheral neovascularisation and neutrophilic keratitis were detected. Additionally, one of these eyes had small inflammatory cell aggregates on the corneal endothelium (keratic precipitates). The median corneal damage score was 1 (range 0–1). There was no evidence of corneal ulceration. There were 0/7 eyes with scleral thinning, 0/7 eyes with histologically noted cataract formation and 0/7 eyes with retinal damage.

Discussion

In this study, placement of aqueous shunts in normal equine eyes resulted in a significant decrease in IOP from one day preoperatively to week 4 post operatively. This decrease in IOP occurred despite fibrosis around the implants. All eyes retained vision and the shunts remained *in situ* for the entire 4 week period of the study.

It has been previously suggested that in horses with glaucoma shunts are less likely to be successful owing to the propensity of the equine eye to develop a marked inflammatory response and intraocular fibrin [10]. However, in this study, the degree of post operative inflammation in all eyes was mild. The highest aqueous flare score recorded one day post operatively was 2 (iris detail hazy). Difficulties with fibrin obstructing the shunt were not encountered, except for *Case 4* OD, which developed hyphaema during anaesthetic recovery. In that eye, injection of intracameral tPA lysed the fibrin and the shunt regained function.

As the eyes in this study were all normal at the beginning, greater inflammation might be experienced when placing aqueous shunts in clinical patients, as equine glaucoma often develops secondary to equine recurrent uveitis [2]. Therefore, patients could already have intraocular inflammation at the time of surgery. More aggressive pre- and post operative anti-inflammatory therapy might therefore be required in those patients. Future studies should ascertain whether intraocular inflammation is increased after aqueous shunt placement in glaucomatous equine eyes.

Other investigators have noted that fibrosis or drainage tube blockage causes failure of the aqueous shunts [3]. In this study, the median histological fibrosis score at 4 weeks post operatively was 2 (0.5–1.0 mm fibrous wall surrounding the explant plate). Despite the fibrosis, each eye had a lower IOP recorded 4 weeks post operatively than on the day prior to surgery, suggesting that the shunts in this study remained functional for 4 weeks. Future studies with longer follow-up are required to determine the maximum time that aqueous shunts can remain functional. Eyes ought then also to be monitored for complications such as implant extrusion, tube displacement from the anterior chamber and episodic inflammation over a longer period of time.

One horse, *Case 1* OD, developed marked granulation tissue over the drainage tube and extensive fibrosis over the explant plate. The conjunctiva had torn during placement of the drainage tube. The conjunctival tear was repaired at the time of surgery, but later dehisced. The marked inflammatory response despite the use of topical corticosteroids highlighted the need for meticulous conjunctival closure. Although the eye did not seem painful, the marked fibroproliferative response due to the incisional dehiscence probably contributed to the increased fibrosis surrounding the explant plate [17]. However, the fibrosis did not appear to influence the post operative IOP, as the IOP at 4 weeks post operatively was markedly decreased from the preoperative value and similar to that in the contralateral eye.

A variety of aqueous shunts are produced. They vary in size, shape and composition. An Ahmed Model VFP7 glaucoma valve was selected for this study for several reasons. First, the explant plate has a large surface area (184 mm^2) which has been shown to diminish fibrosis [18]. Second, the entire aqueous shunt is constructed of silicone. Recent papers have demonstrated lower long-term IOP with silicone explants [19,20]. Finally, the shunt is valved to prevent hypotony [18], with an opening pressure of 8–10 mmHg [21]. Nonetheless, despite using such a valved implant, 2 eyes (*Case 1* OS and *Case 3* OS) developed hypotony and shallow anterior chamber depths during the first post operative week. Both horses were noted to be rubbing the affected eye. The pressure from rubbing probably compressed the globe, thereby elevating the IOP, overcoming the valve's outflow pressure and expressing aqueous humour leading to hypotony. Placement of a full eye cup mask prevented rubbing and the hypotony resolved. The masks were removed later in the study and the hypotony did not recur.

One limitation of the study was housing the horses in stalls to facilitate post operative monitoring. While the horses were hand-walked several times daily, none had access to daily turnout. Clinical patients receiving aqueous shunts would probably return either to work or to pasture, or both. Therefore, in future studies, horses should be returned to their normal routines to ensure the shunts do not become dislodged by increased activity, physical contact with other horses, or objects in the environment.

The results of this study are promising. Placement of aqueous shunts diminished IOP compared to preoperative values and all horses maintained vision throughout the study. Nevertheless, complications did occur, indicating the need for frequent monitoring for corneal ulceration, inflammation and a shallow anterior chamber throughout at least the first month post operatively. Future studies will be required to determine the long-term efficacy of aqueous shunts in clinical patients.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

This study was approved by the Purdue University Animal Care and Use Committee and conformed to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.

Source of funding

State of Indiana and the Purdue Veterinary Medicine Research account funded by the total wager tax.

Acknowledgements

The authors would like to thank Cara Life, Inc. for donation of the aqueous shunts, viscoelastic agent and suture material.

Authorship

Wendy Townsend was responsible for study design, study execution and preparation of the manuscript. Ingeborg Langohr was responsible for all histological analysis and interpretation, prepared the histological portions of the manuscript and contributed all histological images for the study. Meredith Mouney was responsible for study execution and review of the manuscript. George Moore was responsible for study design, data interpretation, statistical analysis and review of the manuscript.

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[c]Mila International Inc., Erlanger, Kentucky, USA.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Summary in Chinese.