Management of subluxated lenses in the dog: Comparison of phacoemulsification and medical management with prostaglandin analogues in 55 eyes (1999-2011)

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Summary

Primary lens luxation is a common presentation in referral practice. Typically the patient has an anterior lens luxation in one eye for which surgical intervention is required but management of the fellow eye can present a perplexing problem. In this fellow eye there is often evidence of lens subluxation. Treatment options for this subluxated lens may be immediate surgical removal via phacoemulsification surgery or alternatively medical management, commonly with a prostaglandin analogue, to maintain a small pupil and hopefully prevent the lens moving into the anterior chamber.

The aim of this study was to use survival analysis (length of time vision retained) to compare the outcome for the medical and surgical treatment of subluxated lenses. The largely retrospective nature of the study and clinical environment mean that the study was non randomised.

Records of 23 dogs (26 eyes) that were treated medically with prostaglandin analogues for lens subluxation were reviewed and followed up and the outcome compared with that of 26 dogs (29 eyes) in the same time period (1999-2011) that underwent phacoemulsification, for lens subluxation, on presentation.

Results of statistical analysis demonstrated that there was a significant increase in time remaining visual for dogs treated surgically compared to those treated medically when age was not taken into account. When age was included in the model the type of treatment was no longer statistically significant but indicated that the effect of treatment varied with age with younger dogs benefiting most from surgery.
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Introduction / literature review

The lens has a refractive function enabling the sharp focusing of images on the retina. One of the requirements to fulfil this function is that the lens is held in a stable position. It lies, enclosed in its capsule, behind the iris and in front of the vitreous body. It is encircled by the ciliary processes and held in position by the zonular fibres equatorially, the anterior vitreous face posteriorly (patellar fossa) and the iris anteriorly. It receives its nourishment from the aqueous and vitreous humours.\(^1\)

The lens is a relatively large structure within the eye to be held in position, averaging 7mm anterior/ posterior axis and 10 mm equatorial diameter in the dog. The proportion of the lens volume to the entire globe volume varies from 1:8 to 1:10 in dogs.\(^2\)

The ocular zonule is a network of fibres that suspends the lens from the ciliary body. Zonular fibres are believed to originate from the non pigmented epithelium of the ciliary body.\(^3\) In humans the zonules consist of dense glassy bundles 5-30µm in diameter. Each bundle consists of a series of fine fibres (0.35-1µm in diameter) themselves composed of microfibrils 8-12nm in diameter. These microfibrils are tubular in cross section.\(^1\)

In dogs the zonular microfibrils average 13nm diameter.\(^4\) These microfibrils are beaded structures which are highly extensible.\(^5\)

The zonules thus mediate accommodative movement of the ciliary muscle to the lens and their presence is important in lens development. Lack of/abnormal zonules results in lens coloboma formation.\(^6\)

Two distinct types of zonular fibre are discernible: Those passing along the crests of the ciliary processes, arising largely from the pars plana, and inserting at the lens just anterior to the equator and those arising from the walls of the ciliary processes and inserting posterior to the equator. There is a crossing of these two types of fibre roughly at the apex of the ciliary process. At the equator itself zonular material is sparse.\(^4\). In the canine eye the vitreous body is adherent over the whole of the posterior pars plana with fusion of zonular and vitreal elements. The primary component of the microfibrils of the zonular fibres are the structural proteins fibrillin 1 and fibrillin 2.\(^7\)
Lens luxation (ectopia lentis) is the displacement of the lens from its normal position in the eye and implies rupture of the zonule. Subluxation involves only partial zonular breakdown resulting in only minor displacement of the lens from its normal position in the posterior chamber. Lens luxation in the dog can be classified as congenital, primary, secondary or traumatic. Traumatic and congenital luxations are rare. In a normal eye traumatic luxation would generally be associated with major trauma and thus other ocular pathology but in a dog with zonular pathology perhaps more minor trauma could precipitate a luxation. Secondary luxations are associated with zonular damage secondary to other ocular disease such as glaucoma, cataracts, uveitis, neoplasia. Rare systemic disorders such as homocystinuria, sulfocystinuria, hyperlysinemia, Marfans syndrome, Weill-Marchesani syndrome and Weill-Marchesani like disease can be associated with ectopia lentis in man.8 In dogs lens luxation associated with a systemic disorder has been described in a case of Ehlers-Danlos syndrome.9

Primary lens luxation is the most common form of lens luxation in the dog. This is a relatively specific clinical entity, which occurs spontaneously, with no antecedent ocular disease.10 11 12 13 It is a bilateral condition that occurs typically no earlier than 3 years old and no later than 8 years old with a peak age of onset at 4-5 years, and with no sex predisposition.10 12 14

There is a predisposition in the terrier and terrier type but other breeds can also be affected, including the Chinese Shar Pei15 and Border Collie.16

The mutation responsible for the condition in 17 breeds has recently been identified as a single nucleotide substitution in the gene ADAMTS 17. Breeds affected with this mutation are: Australian Cattle Dog, Chinese Crested, Jack Russell Terrier, Jagd Terrier, Lancashire Heeler, Miniature Bull Terrier, Parson Russell Terrier, Patterdale Terrier, Rat Terrier, Sealyham Terrier, Tenterfield Terrier, Tibetan terrier, Toy Fox Terrier, Volpino Italiano, Welsh terrier, Wire Fox Terrier and Yorkshire Terrier. The mode of inheritance appears recessive although <5% of clinically affected dogs only carry a single copy of the mutation. The reasons for this are unknown but possibly other genetic factors are involved.17 18

Mutations other than this can cause primary lens luxation in these breeds (occasionally) and other breeds.

Whilst generally therefore lens luxation in dogs is not associated with systemic disease it is interesting that a splice donor site mutation in the ADAMTS 17 gene causes primary lens
luxation in some breeds of dog and truncating mutation of the human ADAMTS 17 ortholog can cause Weill-Marchesani syndrome like disease. Weill-Marchesani syndrome like disease appears to be a recessive trait that can cause short stature, lenticular myopia, ectopia lentis, spherophakia, and secondary glaucoma. Primary lens luxation in dogs is also a recessive trait and is over-represented in the terrier breeds. Selection for small size in these dogs may have inadvertently contributed to the high frequency of the mutation and possibly therefore there are skeletal and ocular components in dogs as in Weill-Marchesani like disease in humans.\textsuperscript{17}

Previously it has been suggested that inflammation may play a role in zonular breakdown.\textsuperscript{19} More recently it has become apparent that the abnormal zonular material is actually present before clinical signs of subluxation/luxation.\textsuperscript{14, 20}

Light microscopy evaluation of zonular fibre morphology in dogs with glaucoma secondary to lens displacement demonstrated 2 distinct forms of abnormal zonular fibre; Zonular fibre dysplasia and zonular fibre collagenisation. Evidence supported the theory that zonular fibre dysplasia was a heritable condition affecting both eyes equally rather than a condition secondary to a disease process and therefore may play a role in primary lens luxation. Dogs with zonular fibre dysplasia included many of the terrier breeds but also the Shar Pei. They typically were affected at a young age (mean 5.2 years).\textsuperscript{21}

Subtle lens mobility actually precedes zonular rupture.\textsuperscript{20} The lack of tension in the abnormal zonules means the lens can assume a more globoid shape and the lack of zonular tension and resultant inertia of the lens with head movement is thought to actually contribute to zonule breakdown. This tends to occur dorso-laterally initially\textsuperscript{20} and allows vitreous escape into the anterior and posterior chamber which is easily visible in the anterior chamber with a slit lamp or even the naked eye as fluffy greyish material. At this stage as vitreous material is lost the anterior chamber can appear deeper and true iridodenesis (trembling of the iris due to lack of support from the anterior lens face) may be visible.\textsuperscript{11, 14, 20}

Over 50\% of eyes with subluxation may be hypertensive.\textsuperscript{14} It is generally thought now that this is a consequence of the factors associated with subluxation rather than an initiating cause.\textsuperscript{20} Contributing factors include:

- Pupil block due to obstruction with vitreous or the lens itself (physiological iris bombé).
- Vitreous/inflammatory debris in the drainage angle. Inflammation may also cause formation of peripheral anterior synechiae.
- Narrowing of the irido corneal angle due to forward push by the lens.
- Lack of zonular tension as the lens luxates can contribute to ciliary cleft closure.

As the lens starts to move from the patellar fossa an aphakic crescent may be apparent. Once the lens completely luxates approximately 90% move forwards and into the anterior chamber where it will obstruct aqueous flow.\textsuperscript{13} The lens drags vitreous with it. The damaged vitreous face quickly hydrates and contributes to the physical obstruction of aqueous flow. Pupil block glaucoma and compression of the iridocorneal angle and ciliary cleft by the basal iris may ensue. At this point the eye will quickly become hypertensive and acutely painful. Damage to the corneal endothelial cells by the lens will cause a round sub central patch of corneal oedema. The lens may remain in the anterior chamber or move backwards and forwards through the pupil.\textsuperscript{13} Of the 10% of lenses that do not move anteriorly posterior dislocation into the vitreous following vitreal syneresis and disruption of the anterior hyaloid face is possible or the lens itself may wedge in the pupil causing a form of pupil block.\textsuperscript{13}

**Treatment:**

An acute anteriorly luxated lens is a surgical emergency before permanent glaucomatous changes have occurred.

A choice of treatments is possible with a posteriorly luxated lens. It is possible to surgically retrieve these but you will cause some vitreous disruption and thus possible retinal damage. Posteriorly luxated lenses may even actually become adherent to the retina.\textsuperscript{11} Left in situ these posteriorly luxated lenses may cause retinal damage and lens induced uveitis or may migrate anteriorly through the pupil into the anterior chamber. Medical treatment of the potential lens induced uveitis may be warranted and a miotic to prevent anterior displacement.

The subluxated lens, which is usually an incidental finding, at presentation for the other eye with the anterior luxation provides the clinician with a dilemma. Small incision phacoemulsification surgery to remove the lens at the same time as the intra-capsular lendectomy on the fellow eye is one option. This allows a planned surgery hopefully before many pathological changes associated with gross lens instability can occur. Statistical analysis has demonstrated a significant improvement in the median survival probability
(vision) with lens extraction by phacoemulsification compared with intra-capsular extraction.\textsuperscript{22} Retinal detachment and glaucoma are the most common reasons for vision loss after phacoemulsification surgery on subluxated lenses. Over 75\% of eyes that had phacoemulsification surgery for subluxated lenses were visual 2.75 years later.\textsuperscript{22} If left in situ however luxation of the second lens may not occur for many months and intervals as great as 4 and 5.5 years have been recorded.\textsuperscript{11}

The other treatment option is medical with a miotic agent to trap the lens behind the pupil. A study using the parasympathomimetic acetylcholinesterase inhibitor demecarium bromide 0.25\% topically twice daily on eyes with posterior lens instability (subluxated or posteriorly luxated) showed a median vision retention time of 1,313 days. Those without miotic treatment had a median vision retention time of 1,454 days. Miotic treatment did not therefore significantly effect the time to vision loss compared to non treated eyes. Miotic treatment did however significantly delay the time to anterior luxation in eyes with subluxated lenses.\textsuperscript{23} In another study in the dog the prostaglandin analogue travaprost (Travatan®; Alcon) was applied once daily in the evening to 100 dogs with posterior lens luxations. These dogs were followed up for 6 months and in 93\% the lens remained posterior.\textsuperscript{24}

Possible complications associated with topically administered miotics include the exacerbation of pupil block and breakdown of the blood aqueous barrier.

As yet no data have been presented comparing success rates i.e. length of time remaining visual, after phacoemulsification surgery for subluxated lenses with conservative medical management of a subluxated lens with a topical prostaglandin analogue and this is the purpose of this study.
Materials and Methods

The clinical records of dogs that had been referred to the Eye Veterinary Clinic, Leominster, U.K., usually for anterior lens luxation in one eye, but with a subluxated lens in the fellow eye, between 1999 and 2011 were reviewed. Cases were excluded where there was evidence that the subluxation was secondary or where there was any other significant ocular disease. Signalment was noted and ocular examination, including assessment of visual responses, slit lamp biomicroscopy, direct and indirect ophthalmoscopy as well as applanation tonometry were carried out routinely and results recorded. Gonioscopy was also carried out in some cases and results recorded. The position of the lens at presentation, presence/absence of phacodenesis and presence of any anterior vitreous prolapse were also noted. The eyes with a subluxated lens were then either started on medical treatment with a prostaglandin analogue (latanoprost (Xalatan®; Pfizer) or travaprost (Travatan®; Alcon)) usually twice daily or underwent phacoemulsification surgery on the subluxated lens. This was not randomised but dependent on the owners circumstances and request after discussion of the two treatment options.

Dogs undergoing surgery were routinely sedated with acepromazine maleate (0.03mg/kg; ACP™ injection 2mg/ml; Novartis Animal Health) and buprenorphine (0.03ml/kg; Vetergesic 0.3mg/ml; Alstoe Ltd) and induced with propofol (0.4ml/kg; Propoflo™; Abbott Animal Health) followed by anaesthetic maintenance with isoflurane (Isoflo®; Abbott Animal Health). Once anaesthetised and prepped for surgery intravenous vecuronium bromide (0.05mg/kg; Norcuron®; MSD) was used for paralysis and globe positioning. The surgery was via a standard 3mm corneal incision through which phacoemulsification was carried out and the empty capsular bag delivered. No sulcus fixated intra-ocular lenses were used. Ophthalmic viscosurgical devices were used as required (surgeons preference) and vitrectomy carried out as necessary. The corneal wound was sutured with 9-0 polyglactin 910 (9-0 Vicryl; Ethicon). Routine post operative treatment consisted of topical dexamethasone, polymyxin b sulphate, neomycin sulphate suspension (Maxitrol®; Alcon) QID for one month reduced to BID for up to 6 months. Oral carprofen (Rimadyl®; Pfizer) or meloxicam (Metacam®; Boehringer Ingelheim) for one month and clavulanic acid potentiated amoxicillin (Synulox™; Pfizer) for 1 week. Usually a topical anti-hypertensive drug such as brinzolamide (Azopt®; Alcon), dorzolamide (Trusopt®; Merck Sharp & Dohme) or one of
the prostaglandin analogues (surgeons preference) were also used post operatively. Patients wore an Elizabethan collar for up to a month post operatively. Post operative checks were routinely at one day post surgery then 1 week, 1 month, 3 months, 6 months and a year then normally at 6 month intervals after this. Some cases were seen more frequently than this if there were complications and some less frequently (owner compliance).

Dogs on medical management had less of a set follow up regime and follow up time periods depended on how stable they appeared on medication. Follow up exams in general included visual responses, slit lamp biomicroscopy, direct and indirect ophthalmoscopy and applanation tonometry. Initial follow up exams were carried out at the Eye Vet Clinic. Two cases (two eyes) were then followed up by fellow ophthalmologists and in longer standing cases information from referring vets (five eyes) or owners (eight eyes) was used. Reliable evidence of the presence of vision (chasing balls, squirrels) by owners was only assumed in one eyed dogs and in two cases of bilaterally visual dogs; one where the owner was a veterinary receptionist and therefore the dog was frequently seen by her own vets and one other case following detailed communication with the owner.

Statistical Analysis:

In all analyses the outcome was loss of vision. Time was measured from date of treatment to either the date the animal left the study or the study ended. (i.e. censored) or the average date between the examination when last visual (minimum time in study) and subsequent examination when blind (maximum time in study). The effect of surgical treatment versus medical treatment was assessed using univariable regression with life data. Subsequently the confounding effect of age was investigated in a multivariable regression with life data which included both treatment types and age (in years). The effect of the type of treatment was evaluated by plotting age versus the estimated time remaining visual for each treatment group.
## Results

49 dogs (55 eyes) were included in the study. Of these 23 dogs (26 eyes) were in the medical group and 26 dogs (29 eyes) in the surgical group. Two dogs in the medical group had only one visual eye at the start of the study and four dogs in the surgical group had only one visual eye.

<table>
<thead>
<tr>
<th>Breed</th>
<th>Age Years</th>
<th>Eyes affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jack Russell Terrier</td>
<td>6</td>
<td>Right</td>
</tr>
<tr>
<td>Miniature Poodle</td>
<td>10</td>
<td>Left</td>
</tr>
<tr>
<td>Lancashire Heeler</td>
<td>4</td>
<td>Both</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>5</td>
<td>Right</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>5</td>
<td>Left</td>
</tr>
<tr>
<td>Border Collie</td>
<td>13</td>
<td>Right</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>4</td>
<td>Left</td>
</tr>
<tr>
<td>X breed</td>
<td>11</td>
<td>Left</td>
</tr>
<tr>
<td>X breed</td>
<td>6</td>
<td>Left</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>9</td>
<td>Left</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>5</td>
<td>Left</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>5</td>
<td>Left</td>
</tr>
<tr>
<td>German Shepherd Dog</td>
<td>9</td>
<td>Left</td>
</tr>
<tr>
<td>X breed</td>
<td>13</td>
<td>Left</td>
</tr>
<tr>
<td>Border Terrier</td>
<td>7</td>
<td>Both</td>
</tr>
<tr>
<td>German Shepherd Dog</td>
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</tr>
<tr>
<td>German Shepherd Dog</td>
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<tr>
<td>X breed</td>
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<td>Left</td>
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<td>Right</td>
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<td>Left</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>3</td>
<td>Left</td>
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<tr>
<td>Lancashire Heeler</td>
<td>6</td>
<td>Right</td>
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*Table 1 Medical group breeds and ages of dogs*
<table>
<thead>
<tr>
<th>Breed</th>
<th>Age Years</th>
<th>Eyes affected</th>
<th>Breed</th>
<th>Age Years</th>
<th>Eyes affected</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Jack Russell Terrier</td>
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<td>Right</td>
<td>Tibetan Terrier</td>
<td>4</td>
<td>Both</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>4</td>
<td>Right</td>
<td>Jack Russell Terrier</td>
<td>4</td>
<td>Right</td>
</tr>
<tr>
<td>Miniature Bull Terrier</td>
<td>3</td>
<td>Both</td>
<td>Jack Russell Terrier</td>
<td>7</td>
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<td>Both</td>
<td>Lancashire Heeler</td>
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<td>Both</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>6</td>
<td>Left</td>
<td>Border Collie</td>
<td>4</td>
<td>Left</td>
</tr>
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<td>2</td>
<td>Right</td>
<td>Miniature Bull Terrier</td>
<td>4</td>
<td>Right</td>
</tr>
<tr>
<td>Terrier x</td>
<td>6</td>
<td>Right</td>
<td>Jack Russell Terrier</td>
<td>5</td>
<td>Right</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>3</td>
<td>Right</td>
<td>Jack Russell Terrier</td>
<td>3</td>
<td>Right</td>
</tr>
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<td>Jack Russell Terrier</td>
<td>6</td>
<td>Right</td>
<td>Jack Russell Terrier</td>
<td>5</td>
<td>Right</td>
</tr>
<tr>
<td>Cairn Terrier x</td>
<td>7</td>
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<td>x Breed</td>
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<td>Patterdale Terrier</td>
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<td>Patterdale Terrier</td>
<td>5</td>
<td>Left</td>
<td>Staffordshire Bull Terrier</td>
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<td>5</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Surgical group breeds and ages of dogs

In the medical group there were ten Jack Russell Terriers, four cross breeds, three German Shepherd Dogs, two Lancashire Heelers, one Patterdale Terrier, one Miniature Poodle, one Border Terrier and one Border Collie.

In the surgical group there were ten Jack Russell Terriers, two Tibetan Terriers, two Lancashire Heelers, two Patterdale Terriers, two Miniature Bull Terriers, two cross breeds, one Cairn Terrier cross, one Staffordshire Bull Terrier, one Yorkshire Terrier, one Terrier cross, one Border Collie and one non specified Terrier type.

The breeds involved were those in which we commonly see primary lens luxation.
8 eyes of the medical group of 26 eyes were still visual when they left the study. 13 eyes of the surgical group of 29 eyes were still visual when they left the study.

18 eyes of the medical group were non visual and 16 eyes of the surgical group were non visual when they left the study.

Where the reason for vision loss was known this was recorded (tables 3 & 4). In the medical group reasons for vision loss included glaucoma (five eyes—one of these cases had pathology carried out and iris bombé recorded), glaucoma and retinal detachment (one eye), presumed glaucoma (one eye-high intra-ocular pressure noted at previous visit), cataract (one eye), uveitis and hyphaema (one eye), corneal opacity (one eye), corneal opacity, imperceptible pupil (one eye) and retinal detachment (one eye). In six eyes the reason for vision loss was unknown. In the surgical group the reasons for vision loss were glaucoma (eight eyes) and presumed glaucoma (five eyes with previous high intra-ocular pressure and optic nerve cupping) in three eyes in this group the cause of vision loss was unknown.
<table>
<thead>
<tr>
<th>Breed</th>
<th>Gender</th>
<th>Eyes affected</th>
<th>Reason for vision loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jack Russell Terrier</td>
<td>Female neutered</td>
<td>Right</td>
<td>Pupil occluded, Iris Bombé and glaucoma</td>
</tr>
<tr>
<td>Miniature Poodle</td>
<td>Female</td>
<td>Left</td>
<td>Retinal detachment, glaucoma</td>
</tr>
<tr>
<td>Lancashire Heeler</td>
<td>Male</td>
<td>Right</td>
<td>Cataract</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>Male</td>
<td>Right</td>
<td>Retinal detachment.</td>
</tr>
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<td>Jack Russell Terrier</td>
<td>Male neutered</td>
<td>Left</td>
<td>Corneal changes. Remained permanently blind</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>Male neutered</td>
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<td>Glaucoma</td>
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<td>Jack Russell Terrier</td>
<td>Male</td>
<td>Left</td>
<td>Presumed glaucoma</td>
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<td>Glaucoma</td>
</tr>
<tr>
<td>Patterdale Terrier</td>
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<td>Right</td>
<td>Corneal scarring and pupil size (imperceptible)</td>
</tr>
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<td>Jack Russell Terrier</td>
<td>Female neutered</td>
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<td>Glaucoma</td>
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<tr>
<td>Lancashire Heeler</td>
<td>Male</td>
<td>Right</td>
<td>Uveitis/hyphaema</td>
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Table 3 Medical group breed and cause of vision loss
<table>
<thead>
<tr>
<th>Breed</th>
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<th>Eyes affected</th>
<th>Reason for vision loss</th>
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<tbody>
<tr>
<td>Terrier</td>
<td>Male</td>
<td>Right</td>
<td>Presumed glaucoma as previous high IOP in this eye</td>
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<td>Right</td>
<td>Glaucoma</td>
</tr>
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</tr>
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<td>Jack Russell Terrier</td>
<td>Female</td>
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<td>Presumed glaucoma</td>
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<td>Presumed glaucoma</td>
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<tr>
<td>Lancashire Heeler</td>
<td>Female</td>
<td>Right</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Terrier X</td>
<td>Male</td>
<td>Right</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>Male</td>
<td>Right</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Jack Russell Terrier</td>
<td>Female</td>
<td>Right</td>
<td>Presumed glaucoma</td>
</tr>
<tr>
<td>Staffordshire Bull Terrier</td>
<td>Female</td>
<td>Left</td>
<td>Presumed glaucoma</td>
</tr>
</tbody>
</table>

Table 4 Surgical group breed and cause of vision loss

During the course of the study five dogs in the medical group died (seven eyes) and three dogs in the surgical group (three eyes).

Three eyes (different dogs) in the medical group were still visual at the time of death. One eye was still visual and two non visual in the surgical group at time of death.

Univariable regression with life indicated that the median time to loss of vision was 28 months for the medical group (s=0) and 55 months for the surgical group (s=1).

This outcome was statistically significant. (p=0.025).

In contrast when age was included in the model, the type of treatment received was no longer significant (p=0.16) but age did influence the time to vision loss (p=0.038). This means that
although the treatment type was significant when included by itself in the model when age was included it was no longer significant. This is likely because age affected the outcome.

Figure 5: Age versus time remaining visual for medical and surgical treatment groups

In a larger study it may be possible to detect a significant effect of treatment, when age is included, but this was not statistically significant here. The results suggested however that the effect of treatment varies with age and the greatest variation between the two groups being with younger dogs (younger dogs having surgery appeared to stay visual for longer than those of a similar age receiving medical treatment) hence treatment type may affect the time to blindness in younger dogs but have limited effect in older dogs.

It may be that age confounded the relationship between treatment and outcome; the apparent effect of treatment was due to more younger dogs having a particular treatment (i.e. not randomised) or that age itself modifies the effect of treatment.

A randomised trial therefore would be required to eliminate the confounding effect of age.
Discussion

Previous studies have shown that success rates for vision retention post surgery for primary lens displacement vary according to several factors including the position of the lens prior to surgery. Glover et al (1995) reported success rates at 4-6 weeks after intra-capsular lens removal via cryo extraction through a clear 160 degree corneal incision of:

- 65% if the lens was anterior at presentation
- 75% if the lens was posterior
- 77% if the lens was subluxated.

The overall longterm success rate declined however to 53% at 12 months. In a study by Manning et al (2006) survival curves for luxated and subluxated lenses treated by intracapsular lendectomy (ICLE) were similar however whereas longterm success rate (vision) for subluxated lenses removed by phacoemulsification surgery when compared with subluxated lenses removed by ICLE was significantly better. Surgical technique utilised therefore also affects the longterm outcome. The small incision surgery possible with phacoemulsification moves towards a closed system where there is less fluctuation in intraocular pressure and less vitreous disruption. Vitreous displacement has been attributed both to causing glaucoma via obstruction at the level of the trabecular meshwork or at the level of the pupil (pupil block). In a large survey of secondary glaucoma in the dog in North America Gelatt and MacKay (2004) reported the risk of secondary glaucoma after cataract surgery was highest after intra-capsular lens extraction (10.6%), less with extracapsular lens extraction (7.4%) and lowest with phacoemulsification/phacofragmentation (2.5%). Vitreous displacement is also associated with an increased likelihood of retinal detachment. Rhematogenous detachments occur due to traction on the vitreous base as the lens and its associated vitreous move. The peripheral detachments that ensue then allow subretinal fluid migration between the retinal pigment epithelium and neurosensory retina and further detachment follows. The incidence of retinal detachment in humans has been reported as 0.4-3.6% post ICLE, 0.55-1.65% post extracapsular cataract extraction and 0.75-1.65% post phacoemulsification. Manning et al (2006) reported a retinal detachment incidence of 28% post ICLE and 5.6% post phacoemulsification. Some people also now advocate
phacoemulsification of anteriorly displaced lenses in the anterior chamber using a topical cholinergic, parasympathomimetic, miotic 0.01% carbachol (Miostat®; Alcon). Complications with this technique include corneal endothelial damage and the possibility of residual cortical lens fragments which can cause a persistent immunological response in the short term and pre-iridal fibrovascular membranes in the longer term which are themselves often implicated in glaucoma. The miotic pupil also makes vitreous management difficult.

Small incision phacoemulsification surgery on a subluxated lens would therefore be preferable to large incision surgery on a fully luxated lens. However the problem exists that the time period from initial signs of subluxation of a lens to complete luxation is variable and difficult to predict. In a study on Tibetan terriers Curtis (1983) reported the shortest interval between the onset of ocular disturbance and clinical luxation in the first eye was 12 months. Time periods from subluxation to complete luxation of 4-5.5 years have been recorded. If surgery had been carried out on these eyes at initial presentation with subluxation these dogs at best would probably be aphakic and thus hyperopic for this time period and potentially developed sight threatening problems such as glaucoma and retinal detachment.

In the dog eyes with replacement intra-ocular lens (IOL) placement after cataract surgery have been reported to have a significantly lower risk for glaucoma (10%) compared to eyes without an IOL (33%). It may be influenced however by the fact that eyes that do not have IOLs placed have intra-operative complications that preclude lens placement but may themselves increase the post operative glaucoma risk. Other papers on the development of glaucoma in dogs after cataract surgery have reported no statistical difference between aphakes and pseudophakes in the development of glaucoma after surgery. Primary posterior chamber IOL implantation post cataract surgery in children decreased the incidence of open angle glaucoma (0.27%) compared to those eyes that remained aphakic (11.3%) after cataract surgery. Two methods have been proposed for this difference; loss of support to the trabecular meshwork in aphakia and a proposed vitreous chemical component that is toxic to the trabecular meshwork. The placement of an IOL minimises these effects.

The problems with large corneal incision and increased intra-ocular manipulation mean that sulcus fixated intraocular lenses to restore emmetropia are not commonly used in dogs. Usually an ab interno approach is required to suture the sulcus fixated IOL as this can be done at the same time as the removal of an anteriorly luxated or subluxated lens. This requires blind placement of the sutures and severe intra-ocular haemorrhage or inaccurate
suture placement and thus refractive error are possibilities. Endoscopic guidance would be of benefit. One study on luxated and subluxated lenses removed via intra-capsular cryoextraction and a sulcus fixated intraocular lens placed using a modified ab interno approach reported vision retention in 70 % of eyes with a mean time to vision loss of 41 months. A modified ab externo approach has been described by Wilkie et al (2008) which enables more accurate suture placement on an inflated eye and can be carried out at the same time as the phacoemulsification or ICLE surgery. In this paper a 8mm incision is required but a foldable lens would mean not needing to enlarge the incision beyond 4mm. If zonular dehiscence is less than or equal to 180 degrees a capsular tension ring may be utilised to allow an IOL to be placed in the remaining lens capsule. However even though the replacement intraocular lens is much lighter than the true lens further zonular dehiscence may occur and it is possible that luxation of the artificial lens and capsule remnants may occur.

Because of the unpredictability of time to complete luxation from the subluxated state, potential sight threatening problems post surgery, difficulty in restoring the emmetropic state with a sutured IOL and in some cases owners preference to avoid surgery also there has been some argument to treat a subluxated lens with a topical miotic to maintain the lens in the posterior chamber; The study carried out by Binder et al (2007) was using the parasympathomimetic acetylcholinesterase inhibitor 0.25% demecarium bromide twice daily to maintain a small pupil. Included in this study were cases of lens subluxation and posteriorly luxated lenses. These were collectively categorised as having a posterior lens instability. In this study miotic treatment did not significantly effect the time to loss of vision compared to non treated eyes. It did however significantly delay the time to anterior luxation in eyes with lens instability.

Demecarium bromide 0.25% given topically may cause systemic side effects in some individuals, gastro-intestinal disturbance being the most frequently reported. In another study of 100 dogs with posterior lens dislocation topical travoprost was applied once daily in the evening. Follow up was at one and four weeks and then by contact with the referring vet or the owner further follow up for at least six months. In 93% anterior dislocation was prevented but there was no specification of vision retention. Neither of these studies solely involved subluxated lenses nor was a direct comparison made with the outcome from phacoemulsification at the subluxation stage.
Results of our study indicate that the group treated surgically retained vision for a significantly longer median time than the group treated medically. Causes for vision loss, where known, also varied between the medical and surgical group. In the surgical group in all but three cases, where the cause of vision loss was not known, blindness was due to glaucoma. (eight definite and five presumed). In the medical group causes of vision loss were more variable. These included six definite glaucoma cases (one with confirmed iris bombé) and one presumed case but other reasons for vision loss noted included cataract (one eye), uveitis and hyphaema (one eye), retinal detachment (one eye), corneal opacity (one eye), corneal opacity and imperceptible pupil (one eye). In five eyes the reason for vision loss in this group was not known.

Latanoprost 0.005% and travoprost 0.004% are structural analogues of the naturally occurring PGF2α. PGF2α has a large intraocular pressure lowering efficacy. This effect is primarily due to increasing uveoscleral flow although latanoprost may also reduce aqueous humor production.35 36 By increasing the area of the ciliary cleft there is also a potential for increased outflow by the conventional route.37 Latanoprost and travoprost are ester prodrugs that are hydrolysed by esterases in the cornea to the active free acid. The free acid is a synthetic prostaglandin F2α analogue that is highly selective for intraocular prostaglandin F (FP) receptors. The natural prostaglandin F2α molecule is less selective and also activates the prostaglandin E (EP) receptors. It is activation of these EP receptors that causes ocular irritation. The selectivity for the FP receptor allows separation of effect (IOP lowering) and side effect (ocular irritation/inflammation). In order to stimulate other prostaglandin receptors latanoprost has to be given in a concentration that is at least a thousand fold compared to that which is required to stimulate FP receptors.38

Latanoprost is lipophilic and becomes trapped within the cornea where it becomes hydrolysed and released into the anterior chamber in the active free acid form. This allows sustained release of the active form of the drug from the cornea for approximately 24 hours.39 Latanoprost in humans is recommended as a once daily dose and a second dose will not increase the effect but may actually reduce the effectiveness.38 The canine uveal tract is thought to metabolise latanoprost at a higher rate than in humans. The IOP lowering effect is profound but only lasts 12-15 hours so twice daily dosing in often necessary.40 In 2 studies in clinically normal dogs the greatest mean reduction in IOP was detected at 6 hours post treatment.35 39 The mean IOP reduction effect from baseline in normal dogs on once daily treatment was estimated at 20-40% for latanoprost41 and 22.45 +/- 7.9 % for latanoprost39 and
22-45% for travoprost. Previous studies indicate that glaucomatous dogs are more sensitive to the drugs and IOP reductions of 45-60% have been reported in these dogs.

Although once daily application of latanoprost or travoprost can significantly reduce IOP, morning application only results in daily pressure spikes. Evening application or twice daily application help to smooth out diurnal spikes and provide the least daily fluctuations in IOP. Twice daily application giving the greatest decline in IOP with the least daily fluctuations but longer duration miosis. Variation in pupil size tends to correspond with variation in IOP. In Gelatt and MacKay’s (2001) report on the effect of different dose schedules of latanoprost on IOP and pupil size in the glaucomatous beagle twice daily administration gave a relatively constant pupil size reflecting the more stable IOP control. In both normal and glaucomatous dogs the highest IOP is in the morning. In studies of the effect of prostaglandin analogues in both normal and glaucomatous dogs there is reported to be an intense miosis starting as early as one hour after the initiation of treatment. In a study by Pirie et al relative mydriasis was noted 24 hours post latanoprost dose. If we are relying on iris support for the unstable lens therefore twice daily administration may be advisable. However intense miosis with these prostaglandin analogues has been reported. In humans a miotic pupil can be visually debilitating particularly at night and we could perhaps expect a similar effect on vision in dogs. In one case, in the medical group, in our study epicapsular stars in the lens were noted at presentation. The lens opacity progressed during the course of the study and the small pupil size combined with the developing cataract probably significantly affected vision. Another dog in the medical group had the reason for vision loss recorded as imperceptible pupil and corneal scarring.

There is a marked species difference in the effect of prostaglandins on the iris sphincter and dilator muscles. Topical application of prostaglandins does not alter the pupil diameter in humans. Prostaglandin F2α is very potent at contracting the dog iris sphincter muscle however. The prostaglandin acting directly on the muscles rather than through the release of adrenergic or cholinergic neurotransmitters. Reported side effects of prostaglandin analogues in humans include hypertrichosis as well as darkening of the lashes, increase in iris pigmentation, increase in eyelid skin pigmentation, conjunctival hyperaemia, ocular surface problems, corneal erosions (9.6% of eyes on chronic latanoprost medication), blepharitis, ocular pain, visual disturbance, conjunctival hyperaemia, damage to the blood aqueous barrier and cystoid macular oedema. Conjunctival hyperaemia has been noted in studies of prostaglandin analogues in dogs. The hyperaemia is not an inflammatory reaction but
caused by release of nitric acid and neuropeptides which cause vasodilation.\textsuperscript{48, 49} Studies using prostaglandin analogues in dogs and cats have not reported blepharospasm\textsuperscript{39, 41} nor signs of substantial ocular pain.\textsuperscript{35} In our study two eyes in the medical group had corneal erosions noted during the time on medication. Corneal sensitivity decreases temporarily after the application of travoprost, latanoprost and bimatoprost. This may be due to other factors, such as benzalkonium chloride, present in the preparations rather than the drug itself however. Alterations noted in the tear film may mean artificial tear supplementation would be of benefit when using these preparations.\textsuperscript{50}

In three eyes on medical treatment evidence of the breakdown of the blood ocular barrier manifested as uveitis was noted. One was severe with hyphaema and given as the reason for eventual vision loss. In a fourth medical case flare and a red eye plus pupil occluded by a membrane were noted clinically and histopathology of this specimen revealed an occluded pupil, iris bombé and glaucoma. In previous studies in dogs uveitis has not been recognised.\textsuperscript{35} Carvalho \textit{et al} (2006) did report a single case of anterior chamber flare in one latanoprost treated eye during the first and second days of treatment.\textsuperscript{41} A study using fluorophotometry indicated topical latanoprost may cause blood aqueous barrier disruption in normal dogs.\textsuperscript{51}

In our study the treatment was relatively longterm compared to other reported studies in dogs. This may have relevance or the uveitis may be incidental and associated with other pre-existing subclinical ocular pathology. The dogs that developed these complications were relatively young dogs however; two eyes with uveitis in one dog a four year old Lancashire Heeler, one eye in a six year old Lancashire Heeler with uveitis and hyphaema, and one eye in a six year old Jack Russell terrier with uveitis, occluded pupil and iris bombé, and thus they were all typical cases for primary uncomplicated lens luxation.

Younger dogs in our study appeared to benefit most from the surgical approach whereas the older dogs did not seem to remain visual for so long whichever the treatment option taken.

The clinical environment of the study means that the trial was non randomised. There will therefore be several variables including client and clinician preference, breed, general health and age of the dog and owner compliance with medications.

The non randomised effect of age could influence the results in several ways. People with older dogs may be more likely to elect for medical treatment-The mean age of the dogs in the medical group was 6.76 years with a range of 3-13 years and in the surgical group 4.86 years
with a range of 2-10 years. Older dogs may be more likely to have undetected other ocular pathology which perhaps would influence the results. Pre-iridal fibrovascular membranes (PIFVM) can be difficult to detect clinically in dogs due to the dark iris colour. Clinical signs suggestive of PIFVM formation include loss of normal surface architecture of the iris, ectropion uveae and peripheral anterior synechiae. These membranes probably form in response to angiogenic factors released by ischaemic retina, neoplasms or leucocytes involved in ocular inflammation.\textsuperscript{52}

The rate of production of the glycoprotein fibrillin 1 which is a primary component of zonular fibres also decreases with age.\textsuperscript{53}

Light microscopy has been used to identify two distinct types of abnormal zonular morphology, in cases of canine glaucoma caused by primary lens displacement, zonular fibre dysplasia and zonular fibre collagenization. In zonular fibre dysplasia protein was tightly adherent to the non pigmented ciliary body epithelium and had a distinct lamellar and cross hatched pattern. It was Periodic Acid Schiff (PAS) (stains glycoproteins) and Masson’s trichrome (stains collagen blue and protein red) stain positive and Verhoeff’s elastin (stains elastic fibres black) negative. In zonular fibre collagenization excessive zonular fibre was not tightly adherent to the ciliary body epithelium. It stained positively with PAS, trichrome and elastin stains. In both of these abnormalities the abnormal zonular fibres have increased amounts of collagen. Normal zonular fibres stain positively with PAS and elastin stain and only minimally with trichrome. The structural changes noted with zonular fibre collagenization are seen in a number of ocular abnormalities and may therefore be an ageing change or tissue reaction rather than specific disease. The mean age of dogs with zonular fibre collagenisation was 8.9 years whereas the mean age of dogs with zonular fibre dysplasia was 5.2 years.\textsuperscript{21} It may be that zonular fibre morphology abnormality resulting in lens luxation in younger and older dogs also varied in our study and perhaps if zonular fibre collagenization represents a more generalised ageing/ tissue reaction this could also perhaps contribute to the less successful outcome for vision retention in older dogs.

In summary there was a significant increase in the time remaining visual for the dogs treated surgically compared to those treated medically when age was not taken into account.

Reasons for vision loss were more variable in the medical group.
When age was included in the model the type of treatment was no longer significant but indicated that the effect of treatment varied with age with younger dogs benefiting most from surgery. A larger study, ideally randomised would be required to confirm this.

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