The effect of postoperative oral antibiotic therapy on the incidence of postoperative endophthalmitis after phacoemulsification surgery in dogs. 320 eyes (1997-2006)

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Purpose. To assess the effectiveness of postoperative administration of oral antibiotics at reducing the incidence of endophthalmitis following phacoemulsification cataract extraction in dogs.

Methods. Medical records of the University of Tennessee College of Veterinary Medicine were reviewed for cases having undergone phacoemulsification and divided according to whether or not they had received oral antibiotics postoperatively. Records were then evaluated for a diagnosis of endophthalmitis and incidence rates between the group receiving postoperative oral antibiotics and the group not receiving postoperative oral antibiotics were compared.

Results. A total of 185 patients (320 eyes) were identified by the search. 113 patients (197 eyes) were treated with oral antibiotics postoperatively. 72 patients (123 eyes) were not treated with oral antibiotics postoperatively. Two cases of endophthalmitis were identified, with 1 in each group ($P>0.05$, Fisher's exact test).

Conclusions. The overall incidence of endophthalmitis in this study was 0.63%. The rate of postphacoemulsification endophthalmitis was unaffected by the postoperative administration of oral antibiotics.

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The effect of postoperative oral antibiotic therapy on the incidence of postoperative endophthalmitis after phacoemulsification surgery in dogs: 320 eyes (1997-2006)

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Abstract

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Introduction

Infectious endophthalmitis is one of the most devastating complications of phacoemulsification cataract extraction in both human and veterinary ophthalmology. In humans, post-phacoemulsification endophthalmitis results in visual acuity of 20/200 or worse in 15-30% of cases, and 10% are left with no useful vision (20/800 or less) (Behndig et al, 2013; Durand 2013). The rate of post-cataract extraction endophthalmitis ranges from 0.012% to 0.56% in the human literature, with two large studies reporting averages of 0.03% and 0.128% (Liesagang, 2001; Ciulla, Starr & Masket, 2002; Kamalarajah et al, 2004; Li et al, 2004; Taban et al, 2005; Wejde et al, 2005; Ou & Ta, 2006; Rosha et al, 2006; Cao et al, 2013; Rudnisky, Wan & Weis, 2014). Rates from 0 - 1.4% have been published in dogs (Sigle & Nasisse, 2006; Johnstone & Ward, 2005; Azoulay et al, 2013). The presumed sources of ocular infection and risk factors for veterinary patients appear to be similar to those in human medicine. Although variations do exist, standards of care for prevention of infection during cataract surgery among human medical institutions have been suggested (Rosha et al, 2006; Rudnisky, Wan & Weis, 2014; Behndig et al, 2013). Many veterinary practices likely have been extrapolated from this data. However, there is still much opportunity to investigate the best practices for prevention of endophthalmitis in veterinary patients undergoing cataract surgery.

The only strategy proven to decrease the rate of endophthalmitis is the preoperative use of 5% povidone-iodine on the periocular and ocular surfaces (Taylor et al, 1995; Liesagang, 2001; Ciulla, Starr & Masket, 2002; Mayer et al, 2003; Ou & Ta, 2006; Rosha et al, 2006). Although postoperative systemic antibiotic administration has not been shown to reduce the incidence of postoperative endophthalmitis, many veterinary ophthalmologists list postoperative systemic antibiotic administration as part of their perioperative protocol (Paulsen et al, 1986;

Boldy, 1988; Taylor et al, 1995; Ledbetter, Millichamp & Dziezyc, 2004; Sigle & Nasisse, 2006; Hazra et al, 2008; Gift et al, 2009). Postoperative oral antibiotics are not used routinely following catarct extraction in humans; in one study of endophthalmitis prophylaxis practices, postoperative oral antibiotics were not used in any of the 75,318 cataract extractions that were reviewed (Rudnisky, Wan & Weis, 2014). Prophylactic use of postoperative systemic antibiotics is particularly problematic due to the potential for antibiotic resistance, adverse side effects, additional cost and additional medication for owners to administer. Up to 50-60% of operations in human general surgery are estimated to be associated with over-use, under-use or misuse of antibiotics (Bratzler et al, 2005; De Almeida et al, 2018). Recent guidelines made by the American Journal of Veterinary Internal Medicine have been made in response to recognition of the importance of veterinarians' role in reducing antimicrobial resistance whenever possible (Weese et al, 2015).

The purpose of this retrospective study was to determine whether prolonged post-operative oral antibiotic is effective in reducing the incidence of endophthalmitis after phacoemulsification in dogs, and we hypothesized that a statistically significant effect would not be found.

Materials and Methods

Medical records of patients that had phacoemulsification performed at the University of Tennessee Veterinary Teaching Hospital (UTVTH) between 1997 and 2006 were reviewed for procedure codes of "cataract surgery" or "phacoemulsification" and a diagnosis code of "endophthalmitis." This period of time was evaluated because in that timeframe some of the cataract patients at UTVTH received oral antibiotics following cataract extraction while others did not. Cases with evidence of post-operative corneal ulceration and patients that did not return for at least three post-operative follow-up appointments were excluded from the study. Surgeries were performed by a Diplomate of the American College of Veterinary Ophthalmologists (ACVO), a third year veterinary ophthalmology resident, or a first or second year veterinary ophthalmology resident under the guidance of an ACVO diplomate. Surgery was standard one- or two-handed phacoemulsification, per surgeon's preference. In general, pre-operative protocols consisted of treatment with topical anti-inflammatory medication (steroidal and/or nonsteroidal) for approximately 7 days prior to surgery. With slight variation in timing, treatment protocols for the evening prior to and morning of surgery consisted of topical prednisolone acetate, topical flurbiprofen, topical antibiotics (neomycin-bacitracin-polymixin B or chloramphenicol), topical phenylephrine, and systemic flunixin meglumine. Cefazolin (22mg/kg IV) was administered intraoperatively beginning at anesthetic induction and continued every 90 minutes until the end of surgery. Polymethylmethacrylate (PMMA) intraocular lenses (IOLs) were inserted within the lens capsule when appropriate at the discretion of the surgeon. Post-operative protocols generally consisted of topical anti-inflammatories, antibiotics, parasympatholytics, and artificial tears. In addition, some patients received subconjunctival or systemic corticosteroids. Oral post-operative antibiotics (either amoxicillin or cephalexin 20-30 mg/kg PO q 8-12 hrs for 1-2 weeks) were used in some cases but not in others based upon surgeon preference.

Recheck examinations were performed at approximately 1, 3, 8, and 26 weeks postopertaively, and then annually thereafter. Patients that did not return to UTCVM for at least the first three scheduled rechecks were not included in the study. Post-operative endophthalmitis was diagnosed based upon clinical examination findings of severe anterior uveitis with hypopyon, decreased vision, and ocular pain beyond what would be expected postoperatively, with or without a positive aqueous humor culture, as per Rudnisky et al (Rudnisky, Wan & Weis, 2014). Each eye that underwent phacoemulsification was considered the experimental unit for the purpose of statistical analysis. Fisher's exact test was used to compare the rate of endophthalmitis in dogs that did receive postoperative systemic antibiotics with those that did not using commercially available software[a]. $P < 0.05$ was considered statistically significant.

Results

A total of 185 patients and 320 eyes were identified by the medical records search as satisfying inclusion and exclusion criteria. One-hundred and thirteen patients were treated and 72 patients were not treated with systemic oral antibiotics post-operatively. Among the 113 antibiotic-treated patients, 84 were operated bilaterally and 29 were operated unilaterally for a total of 197 eyes in the antibiotic-treated group. Among the 72 patients not treated with postoperative oral antibiotics, 51 were operated bilaterally and 21 were operated unilaterally for a total of 123 eyes in this group. During the study period two eyes of two different patients, one eye from each group, developed post-operative endophthalmitis. There was no statistically significantly difference in incidence rates between the two groups ($p = 0.478$; power at $\alpha=0.05$: 0.11).

Cases

The first affected patient (from the antibiotic treated group) was a 12 year old nondiabetic female spayed mixed breed dog with bilateral immature cataracts. Apart from the cataracts, ocular examination was within normal limits. Flash electroretinography and ocular ultrasonography were normal, and the dog underwent uneventful bilateral phacoemulsification. This patient was left aphakic OU; the reason for that decision was not elucidated in the medical record, but the surgery report did not indicate lens instability nor posterior capsular tears. Immediate postoperative treatment consisted of a single subconjunctival injection of 0.4 mg dexamethasone sodium phosphate, prednisolone acetate (1gtt OU q 4 hours), triple antibiotic solution (1 gtt OU q 8 hrs), prednisone (1 mg/kg PO q 12 hrs) and cephalexin (25 mg/kg PO q 8 hrs). On postoperative day 1 (POD 1) an incisional wound leak was present and cyanoacrylate tissue adhesive was applied. The incision was still leaking on POD 2, so the patient was taken back to surgery and the sutures were removed and replaced without complication. The dog was discharged on POD 3 on a regimen of prednisolone acetate (1 gtt OU q 6 hours), triple antibiotic solution (1 gtt OU q 8 hrs), tropicamide (1 drop OU q 12 hrs), oral prednisone at a tapering dose (1 mg/kg PO q 12 hrs X 4 days, then q 24 hrs), and cephalexin (25 mg/kg PO q 8 hrs for 10 days). On POD 15, recheck examination was within normal limts OU, with no aqueous flare, no wound leaks, and good vision OU. Prednisolone acetate was decreased to 1 gtt OU q 8 hrs, triple antibiotic solution was continued at 1 gtt OU q 8 hrs, and tropicamide was decreased to q 24 hrs. Oral prednisone was decreased to 1 mg/kg PO q 48 hrs for another week and then discontinued.

On POD 19, the patient returned after the owner noticed acute onset redness, cloudiness, pain, and periocular swelling OS. Exam findings OD were within normal limits. The OS had conjunctival and episcleral injection, aqueous leakage at the incision site, 3+ diffuse corneal edema, 4+ aqueous flare and cells, hypopyon, fibrin in the anterior chamber and miosis OS. The dog was blind OS. The IOP was 30 mmHg OS. The presumptive diagnosis was endophthalmitis and secondary glaucoma. Aerobic, anaerobic and fungal cultures were obtained from the wound leak and from an aqueous humor aspirate. Both sites yielded positive growth of *Enterococcus faecalis* that was sensitive to all antibiotics tested (ampicillin, chloramphenicol, penicillin, vancomycin, gentamicin and streptomycin); anaerobic and fungal cultures were negative. An ultrasound OS identified a complete retinal detachment with cellular infiltrate in the vitreal chamber. Due to the ocular pain and poor prognosis for vision, the left eye was enucleated. The eye was submitted for histopathologic examination, which revealed corneal edema, large numbers of neutrophils admixed with fibrin in the anterior and posterior chambers, neutrophilic infiltration of the iris, ciliary body and choroid, retinal detachment, degeneration of the photoreceptor layer, and retinal pigment epithelial hypertrophy. No microorganisms were identified on histopathology.

The second affected patient (from the non-antibiotic treated group) was a 12 year old diabetic male castrated mixed breed dog with mature cataracts OU. In addition to the cataracts, lens instability due to zonular disruption was noted OD. Therefore an intracapsular extraction was performed OD and an IOL was not placed. Surgery OS was uneventful and a PMMA IOL was placed in that eye. Post-operatively, the patient was started on prednisolone acetate (1gtt OU q 4 hours), triple antibiotic solution (1 gtt OU q 4 hrs), and ocular lubricating gel (1/4" OU q 4 hrs). The dog was discharged on POD 2 on a regimen of prednisolone acetate (1 gtt OU q 6 hours), triple antibiotic solution (1 gtt OU q 6 hrs), tropicamide (1 drop OU q 8 hrs), and ocular lubricating gel (1/4" OU q 4 hrs). Systemic antibiotics were not prescribed. Recheck exams on days 9 and 23 were relatively normal with the exception of retinal hemorrhage OS, which was attributed to diabetic retinopathy (Landry, Herring & Panciera, 2004). The tropicamide and triple antibiotic solution were discontinued and the prednisolone acetate was decreased to q 24 hrs.

On POD 30, the patient was re-presented for a scheduled recheck and had aqueous flare and hypopyon OS. The intraocular pressure was 5 mmHg. The patient was diagnosed with anterior uveitis and presumptive endophthalmitis OS. The patient was discharged on enrofloxacin (5mg/kg PO BID), prednisolone acetate (1 drop up to QID OS) and atropine (1 drop OS TID). On POD 35 flare and hypopyon were reduced, though fibrin and hyphema were present. The intraocular pressure OS was too low to read. All medications were continued. The endophthalmitis OS continued to show subjective improvement and on POD 44 the enrofloxacin was discontinued while the prednisolone acetate and atropine were continued as previously prescribed. By POD 65 the endophthalmitis was considered resolved with no hyphema, fibrin, flare or hypopyon present. The prednisilone acetate was decreased (TID X 2 weeks and then BID X 2 weeks) and the atropine was decreased (BID). All medications were discontinued on POD 86, at which time menace reponses were positive OU and functional vision was deemed to be excellent. The patient was lost to follow-up after this visit.

Discussion

Our data indicate that endophthalmitis following phacoemulsification cataract extraction is a rare event in dogs, occuring in 2 out of 320 at risk eyes in this study (0.63%). This is in general agreement with previous studies in dogs (Johnstone & Ward, 2005; Sigle & Nasisse, 2006; Azoulay et al, 2013) but higher than most studies in humans (Liesagang, 2001; Ciulla, Starr & Masket, 2002; Kamalarajah et al, 2004; Li et al, 2004; Taban et al, 2005; Wejde et al, 2005; Ou & Ta, 2006; Rosha et al, 2006; Cao et al, 2013; Rudnisky, Wan & Weis, 2014). Furthermore, postoperative administration of systemic antibiotics was not protective against endophthalmitis as 1 case occurred in each group. With the diagnosis of endophthalmitis being so rare in both groups, one must be wary of statistical serendipity hiding significant differences, with the possibility that a single additional case could push the results into the realm of statistical significance (as indicated by the exceedingly low power of 0.11). However, based on the group sizes in our study it can be calculated that an additional 5 cases would have had to occur in the group not receiving systemic antibiotics to demonstrate a protective effect of systemic antibiotics, making it unlikely that our conclusions would change if the study were extrapolated to thousands of cases.

Both cases developed more than a week postoperatively, analagous to the human designation of "chronic post-phacoemulsification endophthalmitis" (Durand, 2013). Most cases of endophthalmitis following phacoemulsification probably occur following introduction of infectious agents from the conjunctiva and eyelid margins (Sherwood et al 1989; Tervo et al, 1999; Liesegang, 2001; Ledbetter, Millichamp & Dziezyc, 2004). In humans the most common offending organisms are coagulase negative *Staphylococci* in acute cases (i.e., POD 2-7) and *Propionibacterium acnes* in more chronic cases.(Durand, 2013) The single culture-proven case in the present study was an *Enterococcus*, but the number of reported cases of post-phacoemulsification endophthalmitis in dogs is too limited to make any conclusions about predominance of any specific organism (Johnstone & Ward, 2005; Sigle & Nasisse, 2006). It has been shown that introduction of organisms into the eye during phacoemulsification is rather common in dogs and humans, yet development of endophthalmitis is rare (Dickey, Thompson & Jay, 1991; Taylor et al, 1995; Tervo et al, 1999; Ledbetter, Millichamp & Dziezyc, 2004). This indicates that the eye has effective mechansisms for clearing organisms prior to the development of infection, and Durand has suggested that simple turnover of aqueous humor is important in this regard (Durand, 2013).

Reported risk factors for developing post-phacoemulsification endophthalmitis have been identified in humans include posterior capsule disruption, incisional wound leak, concurrent diabetes mellitus, concurrent periocular disease, immunoincompetence, and advanced age (Aaberg et al, 1998; Liesegang, 1999; Liesagang, 2001; Li et al, 2004; Wejde et al, 2005; Ou &

Ta, 2006; Cao et al, 2013; Rahmani & Eliot, 2018). It is interesting to note that our cases each had one of these risk factors (wound leak in case 1 and diabetes in case 2). Choice of surgical technique, corneal incision and intraocular lens type have also been shown to influence the rate of post-cataract surgery endophthalmitis in humans (Mayer et al, 2003; Miller et al, 2005; Ou & Ta, 2006; Rosha et al, 2006; ESCRS Endophthalmitis Study Group, 2007).

Among methods of reducing the incidence of post-phacoemulsification endophthalmitis, surgical preparation with 5% povidone-iodine is most consistently supported in the literature (Speaker & Menikoff, 1991; Leisegang, 1999; Schmitz et al, 1999; Liesegang, 2001; Ciulla, Starr & Masket, 2002; Ang & Barras, 2006; Ou & Ta, 2006). Preoperative topical antibiotics are also widely used as endophthalmitis prohylaxis, and while reports of efficacy are conflicting the preponderance of evidence is in favor of their routine use (Lehmann et al, 1997; Leisegang, 1999; Ta et al, 2002; de Kaspar et al, 2004; Ou & Ta, 2006). Some studies have also shown a protective effect of subconjunctival antibiotics and intracameral antibiotics (Schmitz et al, 1999; Rosha et al, 2006; ESCRS Endophthalmitis Study Group, 2007), while other studies have found no benefit from these measures (Ciulla, Starr & Masket, 2002). There is no evidence that prolonged postoperative systemic antibiotics are beneficial in humans (Liesegang, 2001; Ang & Barras, 2006), and our data indicate the same is true in dogs. The numerous untoward effects of injudicious use of antibiotics makes is clear that without evidence of active infection systemic antibiotics should not be administered after phacoemulsification in dogs. For preoperative antimicrobial prophylaxis in general surgery, the Surgical Infection Prevention Guideline Writers Workgroup advocates administering a first intravenous antimicrobial dose within 60 minutes before surgical incision and discontinuing anitmicrobials no more than 24 hours of the end of surgery (Bratzler & Houck, 2005). It seems prudent to follow these recommendations for phacoemulsification in dogs.

In some particular respects our data must be viewed with caution. Conclusions drawn in retrospective studies are only as reliable as the medical record entries that give rise to them; this variable cannot be controlled after the fact. Additionally, while 320 operated eyes would appear to be a relatively large sample size, it is suboptimal when studying a condition of extreme rarity and similar studies in the human literature usually include 10,000 - 100,000 subjects; meta-analyses may include millions (Aaberg et al, 1998; Mayer et al, 2003; Li et al, 2004; Wejde et al, 2005; Cao et al, 2013). It would also be more convincing if all suspected cases could be culture-proven, but it has been established in the human endophthalmitis literature that many cases proven to be associated with bacterial infection on PCR testing are negative on microbiological culture. Thus, bacterial endophthalmitis following phacoemulsification is often a clinical diagnosis based on ocular signs and time to occurrence (Durand, 2013; Rudnisky, Wan & Weis, 2014), and Kamalarajah *et al* even refer to the syndrome as "presumed infectious endophthalmitis" (Kamalarajah et al, 2004). Similarly, post-phacoemulsification endophthalmitis must be differentiated from toxic anterior segment syndrome (TASS). The two conditions have similar clinical signs, but TASS is marked by peracute onset (usually within 24 hours of surgery).

Conclusions

Despite the study limitations, we feel our data support the hypothesis that prolonged postoperative antibiotic adminstration does not demonstrably reduce the rate of post-phacoemulsification endophthalmitis, and we recommend against this practice.

Footnotes

[a]SigmaPlot 14, Systat Software, San Jose CA

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