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SHORT COMMUNICATION

The Evaluation of Osmotic Pump as Glaucoma Drug Delivery System in Normal Dogs

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A B S T R A C T

The purpose of this study was to examine the effect of continuous release of an antiglaucomatous drug using osmotic pump compared with the effect of conventional eye drop. In group 1, one eye of each dog was treated with artificial tears. In group 2, the right eye was treated with a fixed combination of 2% dorzolamide and 0.5% timolol twice a day. In group 3, an osmotic pump filled with a fixed combination of 2% dorzolamide and 0.5% timolol was subcutaneously implanted over the left eye. In results the mean of intra ocular pressure (IOP) was 12.6±1.8 mmHg in group 3, 15.8±1.8 mmHg in group 2 and 17.3±1.0 mmHg in group 1, respectively. The osmotic pump presents a similar effect on IOP compared to conventional eye drop administration. From the study, it is known that the osmotic pump application can be used as the alternative method for the treatment of canine glaucoma.

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INTRODUCTION

Topical eye drop therapy is the primary form of treatment for various ocular diseases (Lee *et al*., 2010). While eye drop treatment is easy to administer, there are some problems. The most common commercial eye dropper delivers a drop with an average volume of 39 µl. When an eye drop is applied, the human lacrimal sac may momentarily contain a 30 µl volume, but the solution is rapidly removed from the conjunctival sac or drained through the puncta to the lacrimal drainage system (Rathore *et al*., 2010). Drugs are also immediately diluted in the tear film at the time of eye drop administration. To maintain a continuous and sustained level of medication, the frequent, periodic application of eye drops becomes necessary. This supplies the eye with a massive dose of medication, but unfortunately, the higher the drug concentration in the eye drop solution, the greater the amount of the drug that is lost through the nasolacrimal drainage system. Furthermore, the intraocular concentration of medication surges to a peak every time eye drops are applied and drug levels then rapidly decline from that moment until the next application. To overcome these problems, many novel ocular drug delivery systems have been introduced, including microemulsions, nanosuspensions, nanoparticles, and implants (Gaudana, 2009). An osmotic pump is an implantable device composed of a drug pellet coated with polyvinyl alcohol, ethylene acetate and poly sulfone capillary fibers. The generic Alzet® osmotic mini pump is a useful implantable drug delivery system with a constant drug delivery rate (Blair *et al*., 1999). Glaucoma is a degenerative optic neuropathy. It is one of the leading causes of irreversible blindness that is associated with elevated IOP in dogs (Reinstein *et al*., 2009). Especially, canine glaucoma develops secondary to many intraocular diseases such as uveitis, tumor, cataract surgery, and lens dislocation. It has been reported that prevalence of secondary glaucoma with ocular diseases is almost 20 % in hospital patients (Johnsen *et al*., 2006). Recent studies highlighted the fluctuation of IOP, as well as mean IOP, as a risk factor for glaucoma progression (Singh and Shrivastava, 2009). The management of glaucoma needs to not only lower IOP, but also reduce IOP fluctuation (Asrani *et al*., 2000). The purpose of this study is to apply an osmotic pump to normal dogs in order to examine the effect of the continuous release of the dorzolamide-timolol combination anti-glaucomatous drug, compared with the effect of conventional eye drop administration by monitoring IOP, pupil diameter and heart rate.

MATERIALS AND METHODS

Fifteen male beagles weighing 8-12 kg were divided into three groups: 1) control group (n=5), 2) conventional drug application group (n=5) and 3) osmotic pump group

(n=5). All dogs were deemed clinically healthy, especially in the eyes, which were normal for slit lamp biomicroscopy, rebound tonometry, indirect ophthalmoscopy and the Schirmer tear test. The present study was performed in accordance with the rules of the Ethics Committee for Experimental Animals, Chonbuk National University.

In group 1, one eye of each dog was treated with artificial tears. In group 2, the right eye of each dog was treated with a fixed combination of 2% dorzolamide + 0.5% timolol (Cosopt®, Merck, West Point, PA, USA) twice a day (10 a.m. and 10 p.m.) via eye drops. In group 3, an osmotic pump filled with Cosopt® was implanted subcutaneously over the left eye. The opposite (untreated) eyes of each group served as the negative control. The osmotic pumps (model 2004, Alzet®, USA) were filled with a fixed combination of 2% dorzolamide + 0.5% timolol and attached to a flow moderator connected by a polyethylene catheter to release a continuous supply of the drug. The pump was primed for 40 hours. The pumps had an average flow rate of 0.25 µl/h and the drug was applied continuously over a period of 24 days. The pump with flow moderator was weighed before the implantation and at the end of experiment to verify that the drug was released completely. The incision site at the superior orbital rim was aseptically prepared and incised 1cm (Fig. 1A) under general anesthesia. Then, the skin was dissected to make a pocket within which the pump was to be placed deeply around muscle. The pump, connected by a catheter, was then inserted into the subcutaneous pocket while the catheter was placed into the lateral fornix through a stab incision, and cut to a proper length (Fig. 1B). The catheter was then fixed in place and the skin was sutured simple interrupted (Fig. 1C). The pump was removed after 24 days under the general anesthesia and weighed again.

Recorded measurements included IOP by rebound tonometry (TonoVet®, Tiolat, Helsinki, Finland), pupil diameter (PD) by Castroviejo calipers and heart rate (HR) manually by stethoscope. The study parameters were measured five times daily at 8 am(Da), 12 pm(Db), 4 pm(Dc), 8 pm(Dd) and 12 am(De) for the first 2 days and three times at 3 day. Then the parameters were measured one time per day at 5 days, 7 days, 9 days, 16 days and 24 days. All data analyses were performed using SPSS version 19.0 (Chicago, IL, USA) with ANOVA and Tukey tests. Statistical significance was defined as $P<0.05$.

RESULTS AND DISCUSSION

The changes in IOP for each of the groups are described in Fig. 2. The mean IOP throughout the whole time period was 12.6±1.8, 15.8±1.8 and 17.3±1.0 mmHg in group 3, 2 and 1, respectively. The IOP of group 3 was significantly reduced with osmotic pump when compared to the control group. The IOP of group 2 was also significantly reduced with Cosopt® treatment. Another interesting result was the diurnal variation between the three groups. When we compared the highest and lowest point of IOP each day, group 2 showed the highest daily difference (4.8±2.6 mmHg), whereas group 3 presented the least degree of IOP fluctuation (2.2±1.1 mmHg). The difference in group 1 was 4.4±2.2 mmHg. The IOP decrease from baseline was significant for the treated eye as well as for the untreated eye in all groups except the control group. During the entire experimental period, the IOPs of the drug-treated groups, groups 2 and 3, were significantly lower than those of the control group; the IOP of group 3 was 4.6±1.0 mmHg lower than that of the control group and the IOP of group 2 was 1.0±1.0 mmHg lower than that of the control group. The changes in PD for each of the groups are described in Fig. 3. The PD in group 2 was significantly smaller than in the control group, but the difference in PD between group 3 and the control group was not significant. The average PD during the whole monitoring period was 6.8±0.3, 5.4±0.5 and 6.1±0.4 mmHg in group 1, 2 and 3, respectively. The changes in HR for each of the groups are described in Fig. 4. During the whole experimental period, average HR was 98.0±14.1 bpm in group 1, 91.0±8.5 bpm in group 2 and 94.0±29.0 bpm in group 3. These measurements are not significantly different. The mean ± SD weight of osmotic pumps before implantation was 1.22±0.02 g, whereas after removal it was 1.07±0.02 g. The difference in pump weight before and after the experiment was 0.16 g.

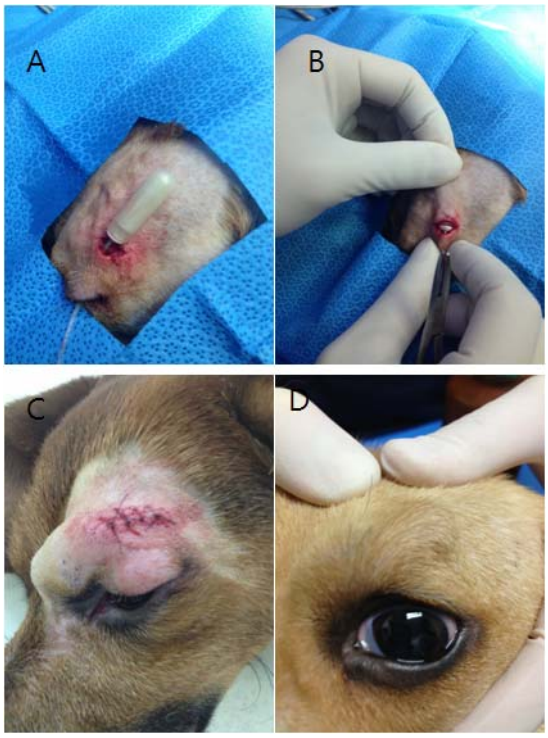

Fig. 1: The procedures of osmotic pump implantation. (A) Preparation of the subcutaneous packet. (B) Placement of the pump. (C) Closure of the skin. (D) Examination on the ocular area at 3 to 4 weeks after implantation.

Glaucoma management is mainly focused on lowering IOP recognized as the highly risk factor (Reinstein *et al*., 2009). Because an unexpected IOP peak may cause pain and visual impairment in glaucoma patients, eye drop administration at accurate time intervals, especially through the night and over the weekend is very important (Boland *et al.*, 2014). However, conventional topical eye drop exposes the eye to a massive dose that may surge to peak drug concentration upon every eye drop application (Rathore *et*

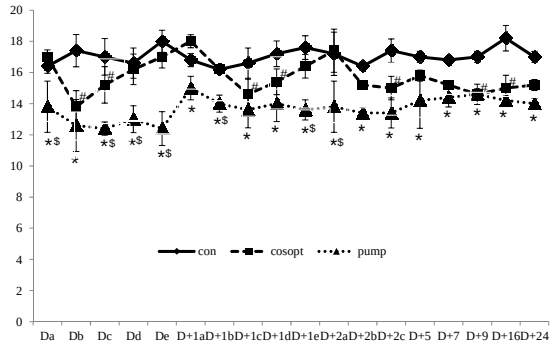

Fig. 2: The changes of intraocular pressure during 24 days. Da: 8 am for the first day; Db: 12 pm for the first day; Dc: 4 pm for the first day; Dd: 8 pm for the first day; De: 12 am for the first day. *Significantly different compared to group 1 as P<0.05; #Significantly different compared to group 1 as P<0.05; $Significantly different compared to group 2 as P<0.05.

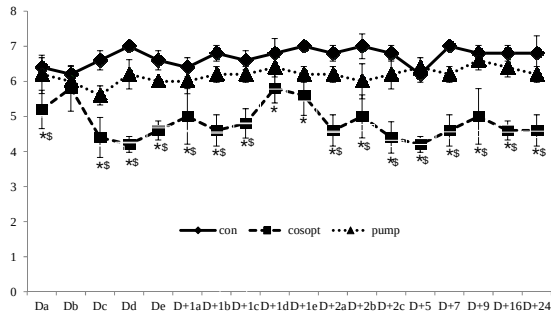

Fig. 3: The changes of pupil diameter during 24 days. Da: 8 am for the first day; Db: 12 pm for the first day; Dc: 4 pm for the first day; Dd: 8 pm for the first day; De: 12 am for the first day. *Significantly different compared to group 1 as P<0.05; #Significantly different compared to group 1 as P<0.05; $Significantly different compared to group 3 as P<0.05.

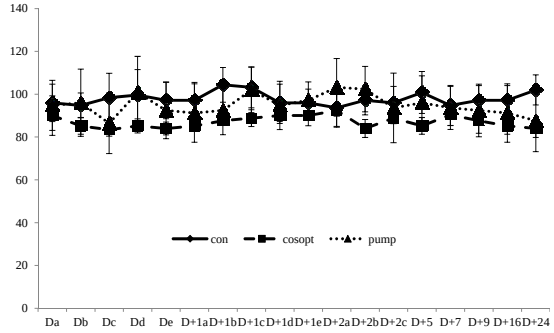

Fig. 4: The changes of heart rate during 24 day. Da: 8 am for the first day; Db: 12 pm for the first day; Dc: 4 pm for the first day; Dd: 8 pm for the first day; De: 12 am for the first days.

al., 2010). Osmotic pump, as one of the constant drug delivery systems, can be placed in the subcutaneous pocket with minimal surgical skills, and continuously administer the wanted drugs into the target regions (Hill *et al.*, 2013). In this study, the osmotic pump was subcutaneously placed without difficulties and IOP level was measured the lowest in the pump group. In addition, the osmotic pump group presented the smallest diurnal IOP alternation when compared with the conventional application group. Recently, the goal of glaucoma treatment has been focused on lowing IOP as well as control of the lowering IOP fluctuation (Song *et al.*, 2014). These results showed that the osmotic pump could be a possible method for the treatments of lowering IOP fluctuation as well as IOP itself. In changes of the PD, it was observed the significant difference between the control group and the conventional application group. Interestingly, the PD of contralateral eye was also changed in conventional application group. This could be the result of increased systemic absorption of the drugs (Plummer *et al*., 2006). However, there was no difference between the control group and the osmotic group. It can be known that the osmotic pump does not have a systemic effect as much as the conventional eye drop application has it. This study was designed to determine the clinical effects of using osmotic pumps as continuous drug-release treatment in normal dogs. Our results show that the osmotic pump exhibited a similar effect on IOP control with lower fluctuation without any changes of PD and HR when compared with conventional eye drop application. In conclusion, it is suggested that the osmotic pump application can be used as the alternative method for the treatment of canine glaucoma.

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