Mydriasis plays an important role in most intraocular surgeries, including phacoemulsification, intraocular lens implantation, and vitreoretinal surgery to expose the lens and posterior segments. The effect is mainly achieved through topical administration of parasympatholytics such as atropine and tropicamide. Topically administered phenylephrine is also used sometimes as an adjunct medication to facilitate mydriasis. However, the mydriatic effects of topically administered mydriatics occasionally wear off during surgery, and the mydriatic effects of tropicamide are hindered or nonexistent when preoperative inflammation is present. Systemic cardiovascular adverse effects have been reported with the topical administration of sympathomimetics in human and dog eyes and of parasympatholytics in human eyes.

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##### ABBREVIATIONS

<table>
<thead>
<tr>
<th>BSS</th>
<th>Balanced salt solution</th>
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<tr>
<td>IOP</td>
<td>Intraocular pressure</td>
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<tr>
<td>P\textsubscript{\textit{et}}CO\textsubscript{2}</td>
<td>End-tidal partial pressure of CO\textsubscript{2}</td>
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Numerous studies in humans have been performed to investigate intracameral (in the anterior chamber of the eye) injection of mydriatics as a possible alternative for achieving preoperative mydriasis. Intracameral injection of epinephrine has been used as an adjunct to preoperative mydriatics or as the sole dilating agent in humans and other animals. In humans, intracameral injection of lidocaine is considered effective at yielding adequate mydriasis and analgesia without considerable systemic or ocular adverse effects. Intracameral injection of preservative-free lidocaine is reportedly safe in humans, rabbits, and pigs. In dogs, the suspected analgesic effect of intracameral injection of lidocaine has been assessed, and the safety of intracameral injections of preservative-free 1% or 2% lidocaine hydrochloride solution has been established. However, to the authors’ knowledge, no study has been conducted to evaluate the mydriatic effect of intracameral injected lidocaine in dogs. The purpose of the study reported here was to evaluate the mydriatic effect of intracameral injection of preserva-
tive-free 1% and 2% lidocaine hydrochloride solutions and determine the onset and duration of mydriasis according to the concentration and volume of lidocaine administered.

Materials and Methods

Animals—Both eyes of 5 healthy Beagles (2 females and 3 males), aged 2 to 4 years old and weighing 7 to 10 kg, were included in this study. Before the experiment began, complete ophthalmic examinations were performed with a slit lamp, an indirect opthalmoscope, and an applanation tonometer to verify that the dogs had healthy eyes. All procedures adhered to the standards for the care and use of laboratory animals of Seoul National University and were approved by the Institutional Animal Care and Use Committee of Seoul National University.

Study design—A double-blinded, randomized, 9-session crossover trial was performed, with a minimum 7-day washout period between treatments. Nine treatments were used: 0.1, 0.2, and 0.3 mL of 2% lidocaine hydrochloride solution; 0.1, 0.2, and 0.3 mL of 1% lidocaine hydrochloride solution; and 0.1, 0.2, and 0.3 mL of BSS. Lidocaine solutions used in this study were preservative-free, and the BSS was administered as a placebo. Ten eyes of the 5 dogs were assigned to receive all 9 treatments with a minimum 7-day interval between treatments. The order of treatments in each eye was randomly assigned. Only 1 eye/dog was treated in any given session, so each dog underwent a total of 18 treatment sessions.

Experimental procedure—Each dog was administered physiologic saline (0.9% NaCl) solution (10 mL/kg, IV) and anesthetized with acepromazine (0.05 mg/kg, IV), propofol (6 mg/kg, IV), and isoflurane (1.0% to 1.5% in oxygen). After endotracheal intubation, dogs were monitored via ECG and respiratory gas analysis by use of an anesthesia monitor. Dogs were positioned in dorsal recumbency, with the head stabilized with a vacuum pillow as is routine for intraocular surgery. The eye chosen for treatment was aseptically prepared with 0.2% povidone-iodine solution. After initial measurements were obtained (baseline), paracentesis of the anterior chamber of the eye was performed slightly to the right side of the 12 o’clock position of the limbus under an operating microscope, and a volume of aqueous humor equal to that of the treatment to be injected was aspirated with a 30-gauge needle and a 1-ML syringe. Immediately after aspiration, a second paracentesis was performed with the same size needle and syringe, slightly to the right of the position of the first paracentesis, and the test treatment was injected into the anterior chamber of the eye.

Evaluation of mydriasis—Two perpendicular pupil diameters were measured on the surface of the cornea under the operating microscope by means of a caliper, and the mean pupil diameter was calculated. Measurements were obtained before injection, then every minute for 10 minutes after injection, every 5 minutes from 15 to 30 minutes after injection, every 10 minutes from 40 to 60 minutes after injection, and every 30 minutes until the pupil diameter was 4 mm. Sufficient mydriasis was defined as a pupil diameter > 10 mm. When sufficient mydriasis did not take place, measurements were performed for only 30 minutes after injection. The interval to onset and duration of sufficient mydriasis were recorded once mydriasis was achieved. Anesthesia was maintained until all measurements were completed.

Intraocular pressure was measured with an applanation tonometer before injection, 5 minutes after injection, and every 30 minutes during each of the 9 treatment sessions. Heart rate, respiratory rate, ECG readings, and P_{ETCO}_2 were recorded every 5 minutes throughout each session.

Statistical analysis—Results are expressed as mean ± SD. Statistical analysis was performed by construction of a linear mixed model, with the Scheffe method used as a multiple-comparison (post hoc) test, by use of a commercially available statistical software program. To evaluate differences in mean pupil diameter, IOP, heart rate, and respiratory rate at each time point, as well as differences in interval to onset and duration of sufficient mydriasis, linear mixed models were created for each of these outcome variables by including all potential experimental variables as follows:

\[ y_{ijk} = \beta_0 + \alpha_{i} + \beta_{j,\text{treatment}} + \beta_{k,\text{eye}} + \beta_{l,\text{treatment} \times \text{eye}} + \epsilon_{ijk} \]

in which \( \alpha_{i} \) represents a random-subject effect, \( \beta_0 \) is the intercept (representing the mean response in the absence of covariate effect), \( \beta_{j,\text{treatment}} \) is the effect of each of the 9 treatments, \( \beta_{k,\text{eye}} \) is the variability (right vs left eye) effect, \( \beta_{l,\text{treatment} \times \text{eye}} \) represents the interaction effect between treatment type and laterality, and \( \epsilon_{ijk} \) represents random error, which is identically and independently distributed.

To evaluate differences in IOP, heart rate, and respiratory rate over time for each treatment, the following linear mixed models were used:

\[ y_{ijk} = \beta_0 + \alpha_{i} + \beta_{j,\text{time}} + \beta_{k,\text{eye}} + \beta_{l,\text{time} \times \text{eye}} + \epsilon_{ijk} \]

in which \( \alpha_{i} \) represents a random-subject effect, \( \beta_0 \) is the intercept, \( \beta_{j,\text{time}} \) is the time effect, \( \beta_{k,\text{eye}} \) is the variability effect, \( \beta_{l,\text{time} \times \text{eye}} \) represents the interaction effect between treatment type and laterality, and \( \epsilon_{ijk} \) is random error. A value of \( P < 0.05 \) was considered significant for all analyses.

Results

Pupil diameter—Changes in the mean pupil diameter before and after each treatment were summarized (Table 1). At baseline, there were no significant differences in pupil diameter among the treatments. The pupils of dogs after all lidocaine treatments dilated > 10 mm. A significant (\( P < 0.05 \)) treatment effect on pupil diameter was detected at each measurement point between 1 and 150 minutes after treatment. No significant effect of dog or laterality (right vs left eye) on pupil diameter was evident.

Multiple-comparison testing revealed the mean pupil diameters after all lidocaine treatments were significantly (\( P < 0.05 \)) greater than that after all BSS treatments at each measurement point between 1 and 30
minutes after treatment. The mean pupil diameter after 0.3 mL of 2% lidocaine solution was significantly (P < 0.05) greater than that after 0.1 mL of 1% lidocaine solution was injected from 1 to 150 minutes after treatment, except at 30 minutes.

Onset and duration of sufficient mydriasis—The interval to onset and duration of sufficient mydriasis after each type of lidocaine treatment were summarized (Table 2). Sufficient mydriasis was achieved after all lidocaine treatments; however, BSS did not induce mydriasis, regardless of volume. The mean interval to onset of mydriasis was < 5 minutes after all lidocaine treatments, except for injection of 0.1 mL of 1% lidocaine solution. Injection of 0.3 mL of 2% lidocaine solution resulted in the fastest onset (1.4 ± 0.7 minutes) and longest duration (142.6 ± 23.0 minutes) of sufficient mydriasis. Choice of treatment was significantly (P < 0.001) associated with interval to onset and duration of mydriasis; a significant (P < 0.05) effect of dog on interval to onset was also detected. No significant relationship between laterality and interval to onset or duration of mydriasis was detected.

Multiple-comparison testing revealed that onset of sufficient mydriasis after 0.1 mL of 1% lidocaine solution was injected took place significantly (P < 0.05) later than it did after the other lidocaine treatments. The duration of sufficient mydriasis after 0.1 mL of 1% lidocaine solution was injected was significantly (P < 0.05) shorter than after 0.2 and 0.3 mL of 1% lidocaine solution and after 0.3 mL of 2% lidocaine solution was injected.

IOP and other variables—When IOP, heart rate, and respiratory rate were compared at each measurement point, no significant effect was evident with regard to treatment, dog, or laterality. Heart rate, IOP, or respiratory rate did not vary significantly with time after any treatment. There were no detectable differences in ECG readings or PetCO₂ before versus after injection.

Discussion

Intracameral injection of lidocaine hydrochloride is reportedly a rapid, effective, and safe means of induc-
ing iris paralysis and mydriasis in human eyes.\textsuperscript{10} When lidocaine is intracameral injected, it acts on nerve fibers in the iris and blocks conduction of nerve impulses through its effects on voltage-gated sodium channels.\textsuperscript{2,5} There have been many clinical studies\textsuperscript{3,4,10} of the mydriatic effect of intracameral injection of lidocaine for human cataract surgery, and various volumes of 1% lidocaine solution have been used in those studies. Results of the present study indicated that intracameral injection of 1% or 2% lidocaine solutions in volumes of 0.1 to 0.3 mL can induce sufficient mydriasis that persists for 74 to 142 minutes, depending on the volume and concentration of lidocaine, in clinically normal dogs.

In human clinical studies\textsuperscript{10,8} in which the mydriatic effect of intracameral lidocaine injection was evaluated, lidocaine was injected into the anterior chamber of the eye through a 3-mm corneal incision or a side-port incision. However, we injected lidocaine intracamerally with a 30-gauge needle to prevent leakage of lidocaine before it was distributed to the iris. We removed an equal volume of aqueous humor from the anterior chamber of the eye before intracameral injection was performed to eliminate the possibility of mechanical mydriasis caused by ocular hypertension (a potential confounding factor). There was no apparent drug leakage or ocular hypertension (as assessed via applanation tonometry) before or after drug injection in our study.

Topically applied mydriatics are absorbed systemically.\textsuperscript{5} Atropine, with reported systemic absorption of 63%, has adverse effects similar to those of topically applied anticholinergics, including dry mouth, dry eyes, and disturbances in cardiac function.\textsuperscript{3,8,10} Cardiovascular adverse effects of topically applied phenylephrine are also reported for humans\textsuperscript{5,30} and dogs.\textsuperscript{8} Systemic adverse effects of lidocaine administration, such as cardiovascular and respiratory depression and CNS signs, are usually associated with a high plasma concentration of the drug.\textsuperscript{5,21} The systemic absorption rate of intracameral injected drugs is limited by the rate of aqueous humor turnover, and the risk of systemic adverse effects is low.\textsuperscript{8} In a study in humans, intracameral injection of 0.5 mL of 1% lidocaine solution yielded no therapeutically systemic concentration and no detectable change in heart rate or ECG readings.\textsuperscript{29} The study reported here revealed no apparent changes in ECG readings and PET\textsubscript{CO}_{2} and no significant effect of lidocaine on heart rate or respiratory rate after intracameral injection of various concentrations and volumes of lidocaine in dogs.

Another concern related to intracameral injection of lidocaine is its effect on the corneal endothelium.\textsuperscript{24} Long-term and short-term clinical studies\textsuperscript{3,23,26} in humans have revealed no significant endothelial cell loss after intracameral injection of preservative-free 1% lidocaine solution, compared with endothelial cell loss in a control group. A study in dogs\textsuperscript{27} revealed that intracameral injection of preservative-free 1% or 2% lidocaine solution can yield adverse effects in the anterior aspect of the eye. Bupivacaine, another type of local anesthetic that has a theoretically longer duration than does lidocaine, has been compared with lidocaine with regard to efficacy and safety when injected intracameraly.\textsuperscript{27} In a study\textsuperscript{27} in humans, there were no significant differences in analgesic effect between intracameraly injected 1% lidocaine solution and intracameraly injected 0.5% bupivacaine, but the bupivacaine caused corneal endothelial damage attributable to its lipid solubility.

Reports\textsuperscript{29,30} exist of temporary loss of visual activity after intracameral injection or inadvertent intravitreal injection of lidocaine in humans. The electroretinographic b-wave amplitude reportedly decreases and b-wave implicit time increases after intracameral injection of lidocaine in humans, and these effects are no longer evident 24 hours after injection.\textsuperscript{30} Although results of other studies\textsuperscript{30,31} suggest the retinal toxic effects are transient,\textsuperscript{30,31} careful monitoring is needed when a patient has a clinical condition that allows diffusion of lidocaine to the posterior segment of the eye such as luxation of the lens and rupture of the posterior aspect of the lens capsule or when a patient undergoes surgery of the posterior segment of the eye.

Reports of objective studies of the interval to onset and duration of the mydriatic effects of intracameral lidocaine injection in humans and other animals are limited. In humans, mydriasis was induced immediately after intracameral injection of 0.2 to 0.5 mL of 1% lidocaine solution, and this effect was still evident at the end of 25 minutes of ocular surgery.\textsuperscript{3,22} However, the full duration of mydriasis was not measured. In a cat, intracameral injection of 0.2 mL of 2% lidocaine solution reportedly caused immediate mydriasis, and when the affected eye was examined 18 hours after injection, the pupil reacted as it would without lidocaine administration.\textsuperscript{29} However, that study was not controlled with respect to the effect of injection-induced ocular hypertension on the onset of mydriasis, and pupil diameter was not monitored continuously until the mydriatic effect was no longer evident.

In the present study, the mean interval to onset and duration of sufficient mydriasis were recorded after intracameral injection of 0.1, 0.2, and 0.3 mL of lidocaine at concentrations of 1% and 2%, which are reportedly safe in dogs.\textsuperscript{27} The interval to onset and duration of sufficient mydriasis appeared adequate for intraocular surgery for most volumes and concentrations of lidocaine, except for 0.1 mL of 1% lidocaine solution. The mean duration of action was 1 to 2 hours and varied with the concentration and volume of lidocaine administered. Therefore, in clinical settings, the concentration and volume of lidocaine used should be chosen on a case-by-case basis.

Some studies\textsuperscript{3,34} have been conducted to evaluate the analgesic effects of intracameral injection of lidocaine in humans undergoing cataract surgery. Clinical trials\textsuperscript{3,34} in humans have revealed that patient cooperation increases when topical application of an analgesic to the eye is supplemented with intracameral injection of lidocaine prior to intraocular surgery. In the present study, we were primarily concerned with the mydriatic effect of intracameral injection of lidocaine on canine eyes, but it is likely such a treatment also has an analgesic effect in dogs undergoing intraocular surgery. Therefore, evaluation of the intraoperative and postoperative analgesic effect of intracameral injection of lidocaine in dogs will be necessary.

In the eyes of clinically normal dogs in the study reported here, intracameral injection of lidocaine had
a significant mydriatic effect that began 1 to 10 minutes after injection and persisted for approximately 1 to 2 hours, depending on the volume and concentration used. This technique could serve as an alternative to topical administration of mydriatics for intraocular surgery in dogs and could be particularly beneficial in dogs that are at risk of the systemic adverse effects associated with administration of sympathomimetic and anticholinergic drugs. Furthermore, additional mydriatic effects may be achieved with use of intracameral injection of lidocaine when the mydriasis induced by topically applied drugs before intraocular surgery is not sufficient to permit commencement of surgery or when intraoperative miosis develops.

References