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ORIGINAL PAPER

Effect of four local anesthetics (tetracaine, proparacaine, lidocaine, and bupivacaine) on intraocular pressure in dogs

Ali Asghar Sarchahi · Mehdi Eskandari

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Abstract
Purpose To measure IOP in animals, it is often necessary to use topical anesthetics. The use of these drugs may cause changes in IOP and interfere with the final results. To address this issue, the effects of four local anesthetics (tetracaine, proparacaine, lidocaine, and bupivacaine) on IOP were investigated in ten adult dogs.
Methods One drop of tetracaine was instilled in the right eye of half of the dogs and in the left eye of the other dogs; normal saline was instilled in the fellow eyes. The IOP in each dog was measured before and at 0, 5, 10, 15, 20, 25, 30, and 35 min after drug instillation using an electronic rebound tonometer. The effects of the other anesthetics were studied in the same way at intervals of at least 1 week.
Results After instillation of tetracaine, the IOP decreased gradually, such that after 15 min, the IOP was significantly lower than the baseline ($p = 0.022$) and control values ($p = 0.048$). Proparacaine also reduced IOP after 10 min compared to baseline values ($p = 0.046$), but the two other drugs, bupivacaine and lidocaine, had no significant effect on IOP. The duration of eye anesthesia was 16, 20, 22, and 34 min for tetracaine, lidocaine, bupivacaine, and proparacaine, respectively.
Conclusion We recommend using drugs that combine inducing longer anesthesia with producing the smallest change in IOP, such as bupivacaine and, subsequently, lidocaine. Tetracaine and proparacaine have a significant effect on IOP, and if these drugs are used, this effect should be considered.

Keywords Intraocular pressure · Local anesthetic · Tetracaine · Bupivacaine · Lidocaine · Proparacaine

Introduction

Glaucomas are a group of diseases that, at least initially, are caused by increase in intraocular pressure (IOP) and lead to damage to the optic nerve head. To diagnose glaucoma and facilitate its prevention and treatment, intraocular pressure should be measured [1]. Contact and non-contact methods are used for this purpose. Local anesthetic drugs are used in the eye in most contact and non-contact methods in animals [2, 3]. Some researchers believe that the use of anesthetic drugs may affect the intraocular pressure and can make it difficult to diagnose actual IOP; for example, in a study in humans, Baudouin and Gastaud found that bupivacaine reduced the intraocular pressure after 1, 5, and 15 min [4], and Montero et al. [5]

A. A. Sarchahi (✉) · M. Eskandari
Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, PO Box 1793, Mashhad 9177948974, Iran
e-mail: sarchahi@um.ac.ir; aliasgharsarchahi@gmail.com

who studied the effect of tetracaine and oxybuprocaine found that these drugs reduce intraocular pressure in humans. In the case of animals, Sarchahi and Bozorgi [6] showed that tetracaine reduced intraocular pressure in healthy and glaucomatous rabbits. In addition, Boillot et al. [3] showed that tetracaine caused a significant decrease in intraocular pressure 1 min after instillation to the eye in dogs. On the other hand, some researchers believe that topical anesthetics do not affect intraocular pressure. For example, Almubrad and Ogbuehi [2] showed that tetracaine and proparacaine do not reduce intraocular pressure in humans. Likewise, Ehongo et al. [7] showed that oxybuprocaine does not reduce intraocular pressure in humans. In the case of animals, Kim et al. [8] found that proparacaine 0.5% does not reduce intraocular pressure in the rat or dog. The reason for these differences is not exactly clear. One of the reasons may be the type of medication used or the types of animal used, or even the method of measurement [9, 10]. Therefore, it seems that an evaluation of the effect of local anesthetics on IOP would be helpful. Such medication should be able to produce appropriate anesthesia in the eye, and during the time of this anesthetization, should have the least effect on intraocular pressure. Therefore, the main goal of this study was to investigate the effects of four local anesthetics (tetracaine, proparacaine, lidocaine, and bupivacaine) on intraocular pressure in dogs. The duration of anesthesia was also compared in this study.

Materials and methods

Ten clinically and ophthalmologically healthy adult mixed breed dogs with a weight of 20–32 kg (mean ± SD 25 ± 3.4) and aged 18–36 months (mean ± SD 26 ± 4.2) were used. Nine of the dogs were female and one was male. The study was approved by the research council of the Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Iran. The animals were maintained for at least 1 week in the experimental environment to allow adjustment, and were provided with chicken and water ad libitum. All dogs were examined thoroughly, and their eyes were examined using indirect and direct ophthalmoscopes. Before the onset of the study, the intraocular pressure of the dogs was measured several times to habituate the animals to this procedure.

To test the first drug, one drop of 0.5% tetracaine (Anestocaine, Sina Darou, Iran) was instilled in the right eye of five dogs and the left eye of the other five dogs; one drop of normal saline was instilled in the opposite eyes as controls. IOP was measured before and at 0, 5, 10, 15, 20, 25, 30, and 35 min after drop administration using an electronic rebound tonometer (TA01i tonometer, Icare, Finland). The sensation of the eyes was also monitored every 5 min and the time at which the palpebral reflex was observed (return of ocular sensation) was recorded. When measuring IOPs, the dogs were placed on a table and kept in relaxed conditions to avoid any stress (Fig. 1). The eyelids were slowly opened and excessive pressure on the eyelids was avoided to prevent a change in IOP. After an interval of at least 1 week, the effects of 0.5% proparacaine (Alcaine, Alcon, Canada), 2% lidocaine (Lignodig, Caspian Tamin, Iran), and 0.5% bupivacaine (Marcaine® Spinal Heavy, Astrazeneca, Sweden) were studied in the same way. Because IOP may vary throughout the day, IOPs were measured at 14:00–16:00 h in all dogs. In addition, all measurements were taken by a person who was unaware of the medication or placebo used in individual eyes.

The data were analyzed using Shapiro–Wilk's statistical method to verify the normality of the data. As some data had a normal and some had an abnormal distribution, non-parametric methods were used for statistical analysis. The Friedman test was used to evaluate the effect of each drug over time and, if there were significant differences, the Wilcoxon test was used to compare two sets of scores. The Wilcoxon test was also used to compare the IOPs of treated and control eyes. The Wilcoxon method was used to compare intraocular pressure between the four drug groups. The Pearson correlation coefficient was used to test the relationship between IOP and the weight and age of dogs. The Spearman correlation coefficient was used to determine the relationship between IOP and sex. The data are based on the mean ± SD for 10 dogs. p values less than 0.05 were considered as statistically significant.

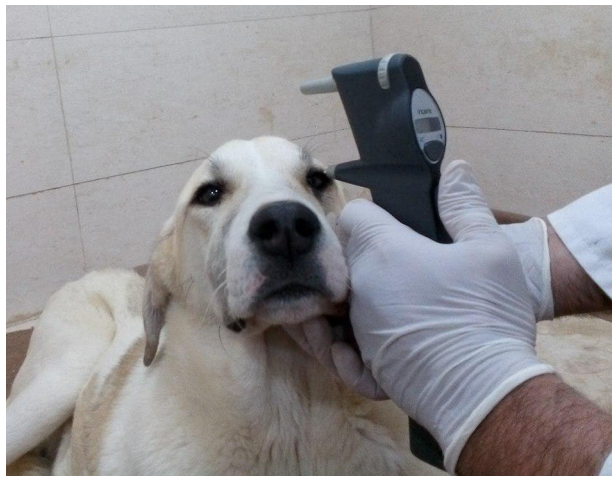

Fig. 1 Restraint of dog and tonometry with rebound Icare tonometer. Probe is in the center of the cornea

Results

Tetracaine

Mean baseline IOP values before drop instillation in treated and placebo eyes of tetracaine group were 11.3 ± 3.9 and 10.2 ± 2.4 mmHg, respectively ($p > 0.05$). As shown in Fig. 2, tetracaine caused a gradual reduction in IOP relative to pre-treated baseline values, which was statistically significant after 15 min (8.6 ± 2.8 mmHg) ($p = 0.012$), after which IOP gradually increased. When compared to placebo eyes (10.6 ± 4.6 mmHg), the IOP reduction in treated eyes was also significant at 15 min after drug instillation ($p = 0.048$).

Bupivacaine and lidocaine

Mean baseline IOP values before drop instillation in treated and placebo eyes of bupivacaine group were 9.9 ± 3.1 and 10.4 ± 4.4 mmHg, respectively ($p > 0.05$). Mean baseline IOP values before drop instillation in treated and placebo eyes of lidocaine group were 9.7 ± 2.6 and 9.9 ± 2.4 mmHg, respectively ($p > 0.05$). As shown in Figs. 3 and 4, these drugs did not significantly reduce IOP in the treated eyes compared to pre-treated baseline values ($p > 0.05$). In addition, there was no significant difference between IOP in treated and placebo eyes ($p > 0.05$). IOP in the treated eyes (13.4 ± 7.3 mmHg) was higher than in the placebo (9.2 ± 3.7 mmHg) eyes at time zero ($p = 0.024$) in the bupivacaine group. There was no relationship between age and IOP changes in the bupivacaine and lidocaine groups ($p > 0.05$).

Proparacaine

Mean baseline IOP values before drop instillation in treated and placebo eyes of proparacaine group were

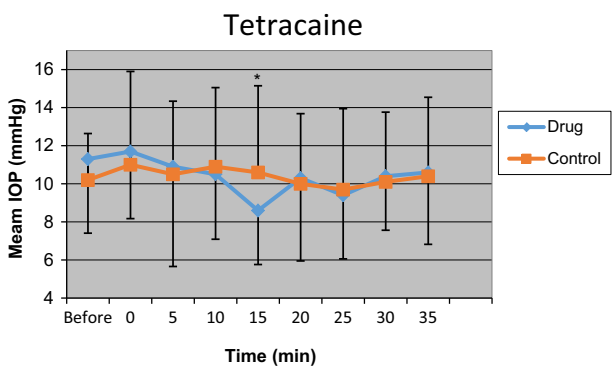

Fig. 2 Mean IOP of treated and control eyes in tetracaine group. IOP in the treated eyes was significantly lower 15 min after the administration of the drug compared to pre-treated baseline and control values ($p < 0.05$). The data are based on the mean ± SD for ten dogs

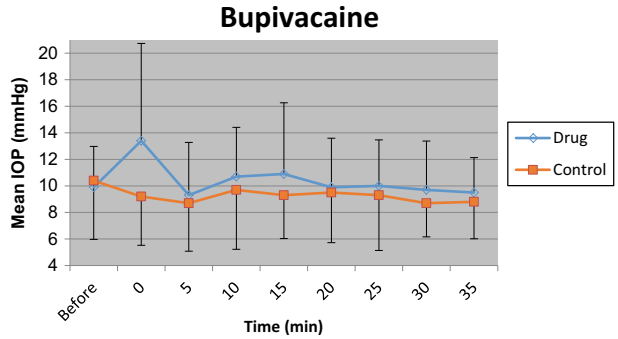

Fig. 3 Mean IOP of treated and control eyes in bupivacaine group. IOP in the treated eyes was higher than in placebo eyes at time zero ($p = 0.024$). The data are based on the mean ± SD for ten dogs

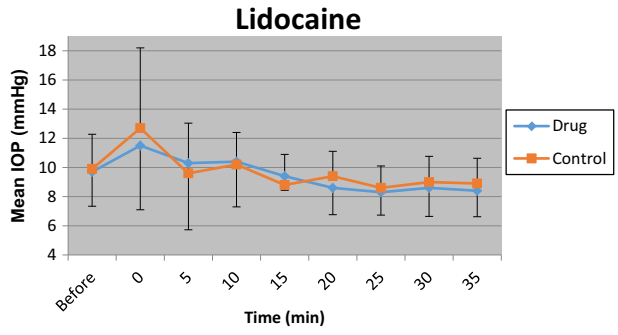

Fig. 4 Mean IOP of treated and control eyes in lidocaine group. There was no significant difference between IOP in treated eyes compared to baseline and placebo values ($p > 0.05$). The data are based on the mean ± SD for ten dogs

8.9 ± 2.8 and 9.5 ± 3.8 mmHg, respectively ($p > 0.05$). As shown in Fig. 5, this drug reduced IOP over time, with this reduction being significant after 10 min compared to the pre-treated baseline values (7.8 ± 2.5 mmHg) ($p = 0.046$). However, there was no significant difference between treated and placebo eyes at any time ($p < 0.05$). There was no correlation between age and pressure change in proparacaine-treated eyes ($p < 0.05$).

Duration of the effect of anesthesia and side effects of drugs

All drugs used in this study caused anesthesia immediately after instillation. This effect was evaluated by assessing the corneal reflex, which was examined by touching a piece of cotton on the surface of the cornea and checking the response of the animal, in the form of blinking. The return of corneal sensation following the disappearance of the drug's effect was also evaluated by assessing this reflex.

The mean duration of anesthesia was 16 min for tetracaine, 20 min for lidocaine, 22 min for

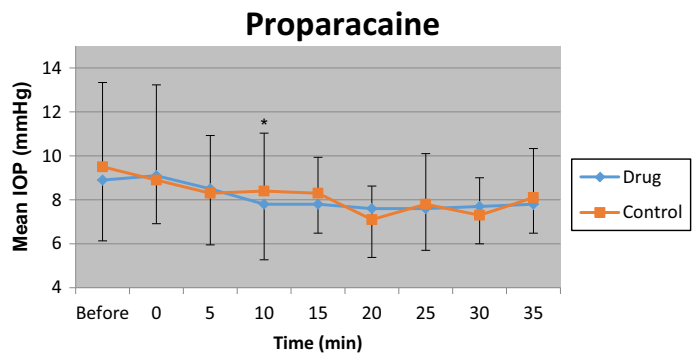

Fig. 5 Mean IOP of treated and control eyes in proparacaine group. IOP in the treated eyes was significantly lower 10 min after administration of the drug compared to pre-treated baseline values ($p = 0.046$). The data are based on the mean ± SD for ten dogs

bupivacaine, and 34 min for proparacaine. Comparison of these times and changes in IOP revealed that the duration of anesthesia was not related to the decrease in IOP. In addition, in this study, dogs were carefully monitored for adverse effects, but no adverse effect was observed, except for a little redness that was observed following the administration of lidocaine, which was quickly resolved and not measurable.

Discussion

Effects on IOP and corneal sensation

Tetracaine

In a study on the effect of tetracaine on IOP in dogs, Boillot et al. [3] found that IOP at 8:00 h was higher than that at 15:00 h. Similarly, in a study that was conducted on healthy and glaucomatous rabbits, we found that the highest IOP was at 9:00 h and the lowest was at 22:00 h [6]. Therefore, IOP may change over the course of the day, and this should be taken into account when examining the effect of drugs. Thus, in the present study, IOPs were measured in all dogs at 14:00–16:00 h, avoiding differences due to the time of the test.

In the present study, tetracaine gradually reduced IOP, with IOP at 15 min being significantly lower than that before drug instillation ($p = 0.012$). After 15 min, IOP gradually increased, and at the end of the study (35 min), it had almost returned to baseline values. Tetracaine had no significant effect on IOP in placebo eyes. This means that the drug does not affect the fellow eye when used topically.

Montero et al. [5] showed that tetracaine decreased IOP 5 min after instillation in humans. We have previously reported that tetracaine reduces the IOP in rabbits too. The reduction in IOP was significant immediately after instillation and persisted for 20 min [6]. Boillot et al. [3] also showed that tetracaine decreases the IOP in dogs from 1 min after instillation. These reports indicate that tetracaine reduces IOP in different species almost immediately after instillation. Ogbuehi [10] showed that tetracaine had no effect on IOP 2 min after instillation, but after 5 min caused a significant decrease in IOP. In the present study, although IOP began to decrease immediately after the use of tetracaine, the reduction was not significant until 15 min. The findings of this study and our previous study as well as those of Ogbuehi indicate that, after using tetracaine, the IOP gradually decreases, and then, after reaching its minimum value, it starts to increase again. We have previously shown that the higher the primary IOP, the greater its reduction by tetracaine [6]. It has also been reported that the IOP measured using different devices may vary [11]. Another important cause of these differences is the animal species. Studies on human, dog, rabbit, and other animals have shown different degrees of IOP reduction by tetracaine [3, 5, 6, 9]. These three reasons may explain the difference between the results obtained in the present study and our previous study [6]. In the present study, we used the TA01i tonometer device, which measures lower pressures than applanation tonometers when the IOP is low [12–16], while, in the previous study, we used the Tonopen Vet device, which measures relatively higher pressures.

Bupivacaine and lidocaine

In the present study, bupivacaine and lidocaine did not significantly decrease the IOP in the treated eyes ($p < 0.05$) compared to the pre-treated baseline and placebo control eyes. Following instillation, IOP in the treated eyes showed an immediate non-significant increase compared to baseline values. Although these increases in IOP were not significant, such increases could be due to irritation of the eyes by the drugs, which were applied in ampoule formulations.

Long-acting local anesthetics such as bupivacaine and lidocaine have been used in local surgeries including oral and dental surgery [17–21]. These medications are amide anesthetics that have also been used in retrobulbar and peribulbar injections for anesthetizing and immobilizing the eyeball [22, 23]. However, there are a few reports that non-topical use of these drugs reduces IOP [22, 23]. Therefore, in this study, the effect of topical anesthesia and its effects on IOP were investigated. In the case of effective topical anesthesia and no effect on IOP, specific drugs can be recommended for future use in the eye for topical anesthesia. Nociti et al. [22] used retrobulbar injections to compare the effects of bupivacaine and ropivacaine, and found that bupivacaine's effect on IOP reduction was much lower than that of ropivacaine. They showed that bupivacaine increased IOP within 1 min after injection, and then started to

decrease the IOP, such that the reduction was significant compared to the control eye after 15 min. They considered the cause of decreased IOP to be relaxation of the eye muscles. Similar results were reported by Shilo-Benjamini et al. [23] in cats when using bupivacaine injections around and behind the eye. In the present study, given the topical use of bupivacaine, there was probably no effect on muscle relaxation and, therefore, no significant reduction in IOP.

Lerman and Kiskis and Abdulla and Flaifil reported that the use of lidocaine as an intravenous injection prevented an increase in IOP due to tracheal intubation and laryngoscopy in children, and even 3 min after intubation, IOP was lower than at time zero [24, 25]. Hassenino et al. [26] also reported similar results during extubation of the tracheal tube.

Proparacaine

In the present study, proparacaine in the treated eyes caused a slight insignificant increase in IOP immediately after drug administration and then IOP started to decrease 5 min after instillation, so that it was significantly lower than that of pre-treated baseline values after 10 min ($p = 0.046$).

Dosunmu et al. [27] examined the effect of 0.5% proparacaine in children, and found that IOP slightly increased after instillation compared to baseline and then decreased slightly, although not significantly, within 8 min after drug administration. The device used by them was similar to the one used in the present study. Herse and Siu [28], Ko et al. [29], and Nam et al. [30] stated that proparacaine causes a transient increase in corneal thickness, thereby temporarily increasing IOP. Almubrad and Ogbuehi [2] showed that proparacaine reduced IOP 2 and 5 min after instillation. Kim et al. [8] found that proparacaine did not change IOP significantly 5–10 min after instillation in dogs and rats. All these studies investigated the effect of proparacaine over short periods of time and their results are inconsistent. The present study showed that proparacaine initially increases and then decreases IOP, such that it reaches its minimum after 10 min and may remain low until 25 min after instillation, after which it begins to increase gradually and returns to its original value.

Topical corneal anesthetics, including tetracaine and proparacaine, reduce IOP by various mechanisms, including corneal relaxation, changes in the thickness of the cornea, loosening of the eyeball, reduction of blink, and effects on the ciliary muscles [5, 31].

Duration of anesthesia

The average duration of corneal anesthesia after instillation of tetracaine in the present study was 16 min. Parchen et al. [32] found that the average duration of corneal anesthesia in dogs was 25 min. The reason for the difference between the two studies is the type of compound used. They used 1% tetracaine associated with 0.1% phenylephrine eye drops. Phenylephrine is a vasoconstrictive agent and may increase the duration of anesthesia. Bartfield et al. [33] found that tetracaine eye drops created corneal anesthesia for an average of 9.4 min in humans.

The duration of corneal anesthesia after instillation of bupivacaine and lidocaine in the present study was 22 and 20 min, respectively. Sun et al. found that bupivacaine and lidocaine and especially their buffer solutions had a longer effect than procaine or benzocaine on topical anesthesia of the eye. In their study, bupivacaine and lidocaine caused corneal anesthesia 1 min after instillation. They also reported that these drugs had a positive effect on the repair of the corneal tissue [34]. Shah et al. [35] stated that lidocaine Akten gel produces longer anesthesia compared to other anesthetic solutions in the eye and, due to containing of hydroxypropyl cellulose, protects the epithelium of the cornea. The antimicrobial effects of lidocaine have also been taken into consideration. Parr et al. [36] showed that lidocaine inhibited bacteria such as *E. coli* and *Staphylococcus aureus* and vancomycin-resistant Enterococci.

The duration of corneal anesthesia after proparacaine instillation in the present study was 34 min. Bartfield et al. [33] showed that the intensity and duration of anesthesia using proparacaine was greater than that using tetracaine in humans. The results of the present study were consistent with this finding. Binder and Herring [37] showed that 0.5% proparacaine induced 25 min of corneal anesthesia in cats, with maximum anesthetic effect lasted 5 min. Herring et al. [38] also found that administering 0.5% proparacaine to dogs caused 45 min of anesthesia with a maximum effect of 15 min. The results of the present study were similar, and the slight difference between them may be due to the difference in dog breeds in the two experiments. Kalf et al. [39] reported that

proparacaine caused anesthesia in the eyes of horses for 25 min. The results of these studies and the present study indicate that local anesthetics, especially tetracaine and proparacaine, produce longer corneal anesthesia in dogs than in humans, cats, and horses. In addition, the results of the present study and others indicate that these drugs cause anesthesia almost immediately after instillation.

Comparison of the reducing effect of drugs on IOP

According to the results, the highest effect of tetracaine on IOP reduction was observed 15 min after drug administration and amounted to a 23.9% reduction. Bupivacaine reduced IOP by 6%, 5 min after instillation. In the case of lidocaine, the highest reduction in IOP was 14.4%, 25 min after drug administration, and for proparacaine, it was 12.3%, 10 min after instillation. This comparison shows that the most effective drug is tetracaine, which is an ester group and is hydrolyzed in the plasma.

In the present study, tetracaine induced an average of 16 min of anesthesia, and during this time, the lowest reduction in IOP compared to baseline values was 3% between 0 and 5 min after instillation. Bupivacaine created an average of 22 min of anesthesia, and during this time, the lowest reduction in IOP compared to baseline values was 0.1% after 20–22 min; lidocaine produced an average of 20 min of anesthesia, and during this time, the lowest reduction in IOP compared to baseline values was 3–7%, 10–15 min after drug administration; finally, proparacaine caused an average of 34 min of anesthesia, and during this time, the smallest reduction in IOP compared to baseline values was 4% after 0–5 min. According to these results, we recommend using drugs that, while inducing a longer period of anesthesia in the eye, produce only a slight change in IOP, such as bupivacaine and, subsequently, lidocaine. Tetracaine and proparacaine have a significant effect on IOP, and if these drugs are used, this effect should be considered.

Most topical anesthetics used in the eye currently are short-acting with a maximum duration of less than an hour, while, in many cases, including eye surgery, the use of a long-acting topical anesthetic is required. In the present study, due to the lack of topical forms of lidocaine and bupivacaine, injection formulations of these drugs were used. Based on the present study results, it is recommended that their droplet formulation be developed and further evaluated.

In conclusion, since bupivacaine and lidocaine induce longer anesthesia and since lidocaine has a positive effect on corneal cells and even has antimicrobial effects, and given that they do not affect IOP, they should be used topically before measuring IOP, although further studies are needed in this regard.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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