RESEARCH ARTICLE

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Effects of Intracameral Injection of Phenylephrine - Cyclopentolate and Tropicamide-Lidocaine Hydrochloride Combinations on Ophthalmologic and Cardiovascular Parameters in Healthy Cats

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Abstract

In this study, it is aimed to investigate the effects of intracameral mydriatic combinations on the pupil dilation (PD), intraocular pressure (IOP), heart rate (HR) and mean arterial pressure (MAP). In this study 35 animals were divided into 5 groups. The first group (MSic) was phenylephrine hydrochloride (Mydfrin) and cyclopentolate hydrochloride (Sikloplejin), the second group (TLic) was tropicamide (Tropamid) and 2% lidocaine, the third group (BSS) was balanced salt solution. Cats were anesthetized, and all solutions were injected intracamerally. The fourth group (MSt) was phenylephrine hydrochloride (Mydfdrin) and cyclopentolate hydrochloride (Sikloplejin) and the fifth group (TLt) tropicamide (Tropamid) and 2% lidocaine were given by topically. During this research, the fastest onset of the mydriasis was numerically formed by first group. All intracameral groups were seen having longer duration of mydriasis compared to topical groups. Intraocular pressure decreased after anterior camera paracentesis in all intracameral procedures. In our study, time dependent changes of heart rate were found to be statistically significant in all groups. Our research observed that first and second group successfully created enough mydriasis (>10mm). In terms of pupil diameter, it has been proven that first and second group are usable alternatives administration, and no side effects on intraocular pressure, heart rate or mean arterial pressure.

Keywords: Heart rate, intraocular pressure, mean arterial pressure, mydriatics, pupil diameter.

INTRODUCTION

Cataract plays a vital role in intraocular lens administration and intraocular medical procedures such as vitrectomy (Stadtbaumer et al., 2006). The size of the pupil increases the success rate of such procedures (Ayintap et al., 2011). At the same time, the use of midriatics reduces the formation of posterior synechia which may occur after cataract surgery (Bilgin and Demir, 2015). As same as other animals, pupil dilation is achieved with topical agents such as parasympatholytic agents like tropicamide and atropine; sympathomimetic agents like cyclopentolate hydrochloride and phenylephrine hydrochloride in cats (Nuijts et al., 2017).

Phenylephrine hydrochloride is a sympathomimetic agent consisting of an alpha 1 adrenergic receptor agonist (Stavert et al., 2015). It's effectiviness increases when used with other midriatics (Ayintap et al., 2011). It shows its effect by stimulating α receptors at the iris dilator. Cyclopentolate hydrochloride is a passive anticholinergic agent and shows its effect by inhibiting acetylcholine receptors in the iris (Lundberg et al., 2008). Its effects starts and ends faster than atropine and scopolamine (Agin et al., 2008). Tropicamide causes mydriasis by preventing the cholinergic stimulation of iris muscles and blocking the M4 muscarinic receptors (Deeks, 2019). Lidocaine is a local anesthetic that blocks neural links by connecting itself to voltage-covered sodium passages. It shows mydriatic effect by causing anesthesia and akinesia of the iris (Deeks, 2019; Park et al., 2009). Topical mydriatics may lose their effectivineness in case of a preoperative inflammation and may cause problems such as delay in the onset of mydriasis, weakening of its effect over time and reoccurrence frequency during the administration (Nikeghbali et al., 2008; Soong et al., 2006). Besides, it also might cause varius side effects like tachycardia, arrhythmia, toxication in the cornea and rise of blood pressure in the cardiovascular system (Bilgin and Demir, 2015; Stadtbaumer et al., 2006). Therefore, various studies have been tried to provide mydriasis in addition to topical procedures (Myers and Shugar, 2009). There are countless studies in progress on intracameral injections in order to achieve preoperative mydriasis in humans (Liou and Chen, 2001). For intracameral mydriasis, lidocaine was the first to be tried; afterwards, Lundberg and Behndig (2003) was reported the phenylephrine hydrochloride and lidocaine combinations (Myers and Shugar, 2009). Intracameral tropicamide, lidocaine and phenylephrine hydrochloride administrations are known as the most current and accepted intracameral mydriatics on humans (Deeks, 2019). On cats and dogs, it is known that intracamaral lidocaine and epinephrine combination produces the most effective mydriasis (Amorim et al., 2019). Due to a lack of research and testing of effective intracameral combinations on animals and unknown side effect, in this study it is aimed to investigate the effects of mydriasis performed with intracameral phenylephrine hydrochloride–cyclopentolate hydrochloride and tropicamide-lidocaine combinations on PD, IOP, and cardiovascular system.

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MATERIALS AND METHODS

Animals

This study involved brought to private veterinary clinics in the Bodrum/Mugla region on mix breed cats. The ethical approval of the study was provided by the University's Institutional Animal Care and Use Committee (approval number: 2021/026). In this study, a signed information confirmation form was obtained from the patient owners.

The average weight of cats was between 1-4 kgs (averaging around 3.5 kgs), and ages differed between 1-3 (averaging around 2.1) years. Cats with healthy physiological parameters such as cardiovascular system, respiratory system, body temperature, skin structure; and ophthalmological parameters such as pupil diameter (PD), menace and palpebral reflex values, intraocular pressure (IOP), schirmer tear test, and fluorescein test were also included in the study.

Treatment Groups

Cats were divided into five groups, and each group was assigned seven cats. The first group (MSic) was given an intracameral injection of 0.1 mL of phenylephrine hydrochloride (Mydfrin®) and 0.1 mL cyclopentolate hydrochloride combination (Sikloplejin®), the second (TLic) group was given an intracameral injection of 0.1 mL tropicamide (Tropamid®) and 0.1 mL 2% lidocaine combination. Third (BSS) group as the negative control group, was injected 0.2 mL of balanced salt solution was used as placebo. The intracameral procedures of the third group were performed by administering the amount of aspirated aqueous humour after anterior camera paracentesis under general anesthesia. The fourth group (MSt) was topically given a phenylephrine hydrochloride (Mydfrin®) and cyclopentolate hydrochloride (Sikloplejin®) combination. The fifth group (TLt) was topically injected a tropicamide (Tropamid®) and 2% lidocaine combination. Cats in these groups were not taken under general anesthesia and were designated as the positive control group. These topical combinations were performed to the cats with 1 -minute intervals, 2 drops each time for a total of three times. All experiments were applied in a room with 37 lux luminosity, 70% relative humidity, and 25°C of temperature.

Procedures

In the study were noted heart rates (HR), mean arteriel pressure (MAP), intraocular pressure (IOP), and PD of every cat. PD of cats were determined as a result of measurements performed with photographs taken under a slitlamp biomicroscope, and HR were recorded by electrocardiography. The most effective mydriasis diameter in the experimental procedure was identified as more than 10 mm. While MAP of cats were determined with an oscillometric blood pressure machine that was placed on 1/3 of the distal antebrachium, their IOP was displayed with an intraocular rebound tonometer (Tonovet). In the study, food and water intake was stopped 24 hours before the general anesthesia in the cats who underwent intracameral procedures. General anesthesia induction was done with propofol (10 mg/kg), and they were connected to an anesthesia machine after endotracheal intubation, and anesthesia was maintained with a 1.5% concentration of isoflurane. Intracameral procedures in cats were performed in sternal position. Before intracameral procedures, the eyes of cats were sterilized with 3% acid boric solution and anterior chamber paracentesis was performed with a 27-gauge cannula at 12 o'clock. 0.2 mL aqueous humour was aspirated after accessing the frontal chamber. The same amount of drug combinations as aspirated aqueous humour was injected into the anterior camera. Post-injection parameters were determined as T0 and were recorded and observed repeatedly at 0, 5, 10, 20, 30, 45, and 60th minutes until anesthesia lost its effect (T60). Vital functions of cats were monitored and kept under control during anesthesia.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22. The variables were investigated using Shapiro-Wilk's test to determine whether or not they are normally distributed. Pulse count, HR, IOP, and PD measurements were not normally distributed the Kruskal-Wallis tests were conducted to compare these parameters. The Mann-Whitney U test was performed to test the significance of pairwise differences for multiple comparisons. Friedman tests were conducted to compare whether there is a significant change in HR, pulse count, IOP, and PD variables, due to violations of parametric test assumptions (non-normal distribution). The Wilcoxon test was performed to test the significance of pairwise differences for multiple comparisons. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

Pupil Diameter

In the study, mydriasis activity formed by BSS, topical and intracameral procedures in the PD shown in table 1. Except for BSS, all procedures have increased the PD at T10 compared to baseline ($P<0.001$). The earliest mydriasis at T5 with MSic and the latest mydriasis was reached with group TLt at T30. There was no observed change in initial PD ($P<0.05$). Nonetheless, while differences in PD was determined at all minutes, it was observed that the narrowest pupillary occured with the BSS groups ($P<0.001$). In terms of mydriasis, intracameral procedures were seen to present a higher effectivity compared to topical procedures at T0 ($P<0.001$). It was established that MSic for 20 minutes and TLic between T30-60 minutes show higher activity compared to each other ($P<0.001$).

Intraocular Pressure

Intraocular pressure has been seen to decrease at T0 and T5 minutes with BSS and intracameral procedures. It was observed that the decrease in IOP continued at T10, T20, T30, T45 in in BSS and TLic compared MSic ($P<0.001$). In the case of IOP, there haven't been any differences at T60 between topical and intracameral methods ($P<0.05$). While intraoculer pressure was found lower than baseline in intracameral procedures at TO, this decrease continued up to T30 in the MSic groups and up to T45 in the TLic groups. Furthermore, in topical procedures respectively, seen a decrease at T0 and T5 for Mydfrin-Sikloplejin and Tropamide-Lidocaine, decrease kept on until T10 for Mydfrin-Sikloplejin, and T45 for other topical groups until baseline (Table 2).

Heart Rate

Time dependent changes in HR were statistically significant in all groups ($P<0.001$). Heart rate of all groups were statistically lower than baseline at T5, T10 and T20. It was determined that this decrease continued until T45 for BSS and T60 for intracameral groups. Along with this, all groups have been observed to have the same HR value as baselines at T60 (Table 3).

Comparison of HR between groups pointed out important differences in all evaluation times except at T60. According to this, it was observed that HR in TLic were higher at T0 and T5 compared to MSic and TLt, HR in MSic were significantly lower compared to the rest at T10, T20 and T30. İn addition, the difference between the HR of the MSic, group at T45 and the HR of all groups except MSt group was statistically significant (Table 3).

Table 1. Effects of topical and intracameral procedures on pupil diameter

	Mydfrin-Siklоplejin Intracamaral (MSic)	Tropamid-Lidocain Intracamaral (TLic)	Balanced salt solution (BSS)	Mydfrin-Siklоplejin Topical (MSt)	Tropamid-Lidocain Topical (TLt)	P value
Baseline	5.77±0.18	6.17±0.06	5.84±0.17	5.79±0.17	5.84±0.19	0.148
T0	8.71±0.34^{a}	8.56±0.19^{a}	4.46±0.10^{c}	5.91±0.18^{bc}	6.03±0.16^{b}	0.000
T5	10.20±0.10^{a}	9.76±0.27^{ab}	3.10±0.21*^{d}	6.20±0.14^{cd}	7.01±0.89^{bc}	0.000
T10	11.57±0.22*^{a}	10.90±0.31*^{ab}	3.00±0.25*^{d}	8.06±0.09*^{cd}	8.56±0.22*^{bc}	0.000
T20	11.99±0.13*^{a}	12.07±0.11*^{a}	2.70±0.17*^{c}	10.01±0.11*^{b}	9.60±0.18*^{bc}	0.000
T30	12.14±0.10*^{ab}	12.46±0.08*^{a}	2.76±0.17*^{d}	10.69±0.07*^{bc}	10.36±0.18*^{cd}	0.000
T45	12.43±0.04*^{ab}	12.61±0.06*^{a}	2.94±0.14*^{d}	10.94±0.09*^{bc}	10.54±0.06*^{cd}	0.000
T60	12.43±0.04*^{ab}	12.60±0.06*^{a}	3.27±0.17^{d}	11.26±0.24*^{bc}	10.63±0.09*^{cd}	0.000
P value	0.000	0.000	0.000	0.000	0.000	

^{a,b,c,d}: Statistical significance was determined between different letters on the same line (P<0.05).
*: Differs significantly from baseline (P<0.05).

Table 2. Effects of topical and intracameral procedures on intraocular pressure

	Mydfrin-Siklоplejin Intracamaral (MSic)	Tropamid-Lidocain Intracamaral (TLic)	Balanced salt solution (BSS)	Mydfrin-Siklоplejin Topical (MSt)	Tropamid-Lidocain Topical (TLt)	P value
Baseline	18.29±0.36	16.29±0.52	17.86±0.51	17.43±0.57	17.14±0.26	0.062
T0	8.29±0.56*^{b}	7.29±0.42*^{b}	7.71±0.42*^{b}	15.14±0.59*^{a}	16.00±0.31^{a}	0.000
T5	12.00±0.44*^{a}	6.86±0.26*^{b}	6.57±0.37*^{b}	14.43±0.65*^{a}	13.71±0.42*^{a}	0.000
T10	10.57±0.37*^{bc}	6.57±0.30*^{cd}	5.43±0.43*^{d}	15.57±0.57^{a}	12.00±0.38*^{ab}	0.000
T20	12.00±0.31*^{bc}	8.00±0.31*^{cd}	5.57±0.48*^{d}	16.00±0.58^{a}	12.43±0.53*^{ab}	0.000
T30	15.00±0.44^{a}	9.29±0.29*^{bc}	7.14±0.46*^{c}	16.71±0.64^{a}	13.86±0.51*^{ab}	0.000
T45	16.43±0.53^{a}	12.86±0.40^{bc}	7.86±0.46*^{c}	17.43±0.57^{a}	15.57±0.57^{ab}	0.000
T60	17.71±0.47^{a}	16.43±0.37^{a}	8.71±0.61*^{b}	17.71±0.64^{a}	17.14±0.59^{a}	0.001
P value	0.000	0.000	0.000	0.000	0.000	

^{a,b,c,d}: Statistical significance was determined between different letters on the same line (P<0.05).
*: Differs significantly from baseline (P<0.05).

Table 3. Effects of topical and intracameral procedures on heart rate

	Mydfrin-Siklоplejin Intracamaral (MSic)	Tropamid-Lidocain Intracamaral (TLic)	Balanced salt solution (BSS)	Mydfrin-Siklоplejin Topical (MSt)	Tropamid-Lidocain Topical (TLt)	P value
Baseline	144.14±3.34	152.86±2.09	147.14±2.86	144.00±3.15	148.57±2.72	0.206
T0	140.86±2.50^{b}	152.00±2.09^{a}	146.00±2.54^{ab}	141.71±2.91^{b}	147.14±2.58^{ab}	0.040
T5	135.57±2.31*^{b}	146.86±2.34*^{a}	142.86±2.26*^{ab}	138.00±2.22*^{b}	143.14±2.92*^{ab}	0.031
T10	125.43±2.30*^{b}	144.00±2.27*^{a}	140.57±2.17*^{a}	138.86±2.34*^{a}	144.00±2.76*^{a}	0.002
T20	124.57±1.73*^{b}	140.00±2.51*^{a}	142.57±2.42*^{a}	138.86±2.38*^{a}	145.43±2.82*^{a}	0.001
T30	126.00±1.95*^{b}	142.00±2.27*^{a}	143.14±2.34*^{a}	140.57±2.38^{a}	146.57±2.68^{a}	0.001
T45	130.00±2.47*^{b}	145.00±2.17*^{a}	145.71±2.41^{a}	141.14±2.38^{ab}	147.43±2.53^{a}	0.003
T60	138.00±2.86	148.86±2.38	148.43±3.21	143.14±2.42	148.86±2.54	0.053
P value	0.000	0.000	0.000	0.000	0.000	

^{a,b,}: Statistical significance was determined between different letters on the same line (P<0.05).
*: Differs significantly from baseline (P<0.05).

Mean Arterial Pressure

Depending on the duration and the time of the procedure, MAP decreased in the groups compared to the baseline. In the BSS groups, the MAP decreased at T0 and returned to normal at T10 (P<0.001). The duration of this decrease was determined to be least in the TLic group and the maximum in the MSic group (P<0.001) (Table 4).

Table 4. Effects of topical and intracameral procedures on the mean arterial pressure

	Mydfrin-Sikloplejin Intracamaral (MSic)	Tropamid-Lidocain Intracamaral (TLic)	Balanced salt solution (BSS)	Mydfrin-Sikloplejin Topical (MSt)	Tropamid-Lidocain Topical (TLt)	P value
Baseline	76.00±0.87	75.14±0.74	75.43±0.84	75,14±0.74	74.86±0.96	0.872
T0	72.00±0.62	73.43±0.72	71.43±1.13*	73.14±0.86	73.43±0.84	0.392
T5	70.00±0.62*	71.86±0.77*	72.57±0.84*	71.14±0.96*	71.43±0.84*	0.265
T10	70.71±1.49*^{b}	71.14±0.46*^{ab}	73.71±0.81^{a}	69.14±0.86*^{b}	70.00±0.62*^{b}	0.016
T20	68.00±0.62*^{c}	72.29±0.56*^{ab}	75.14±0.96^{a}	70.29±1.11*^{bc}	70.86±0.74*^{bc}	0.001
T30	67.71±0.81*^{c}	73.43±0.61^{ab}	76.29±0.68^{a}	71.43±1.04*^{bc}	72.29±0.68*^{b}	0.000
T45	69.14±0.59*^{c}	75.00±0.65^{ab}	77.71±0.81^{a}	72.57±0.84^{bc}	73.43±0.84^{b}	0.000
T60	72.29±0.52^{c}	75.86±0.80^{ab}	78.86±0.74^{a}	74.29±1.02^{bc}	74.86±0.59^{bc}	0.001
P value	0.000	0.000	0.000	0.000	0.000	

^{a,b,c}: Statistical significance was determined between different letters on the same line (P<0.05).
*: Differs significantly from baseline (P<0.05).

DISCUSSION AND CONCLUSION

Topical mydriatic agents are known to be often used in ocular fundus examinations and intraocular surgical procedures. In these procedures, the pupil must be dilated enough, and they should activate as soon as possible and maintain until the operations end with minimal side effects. However, topical mydriatic agents show various side effects, especially on the cornea. Also, on animals and primarily on humans, it may cause differences in blood pressure and HR, which may alter the start of the effect and cause it to get delayed and decrease its effects over time. In order to get rid of all these local and systemic undesirable side effects, intracameral mydriatic practices were created as alternatives to topical mydriatic methods.

The vast number of studies conducted on humans (Lundberg and Behndig, 2003; Pypendop and Ilkiw, 2005; Williams et al., 2012) showed us the usage of intracameral mydriatics results in a capable and effective mydriasis in operations that require pupil dilation such as cataract surgeries. In the study, Nuijts et al., (2017) performed on rabbits, they have reported that no side effects were seen while or after achieving successful and adequate mydriasis with intracameral mydriatics. With our study we went through, after operating on cats with intracameral mydriatics, effective mydriasis (more than 10 mm) has been achieved without any side effects reported.

Behndig and Korobelnik (2015) on humans, Kim et al., (2010) on rabbits, Park et al., (2009) on dogs, and Amorim et al., (2019) on their work on cats reported maximum effect on pupil dilation after using intracameral mydriatics compared to topical mydriatics. In our studies, intracameral usage of the combination made by local anesthetic agent lidocaine and mydriatic agent tropicamide has positively affected pupil dilation compared to the topical usage. With the intracameral tropicamide-lidocaine combination, mydriasis was achieved at the 10th minute after anterior parasynthesis and created a mydriasis that did not lose its effect during the operation.

Pupil dilation on cats is achieved by parasympatholytic topical agents like atropine, tropicamide and topical sympathomimetic agents like phenylephrine hydrochloride (Mydfrin) and cyclopentolate hydrochloride (Osinchuk et al., 2020). Lidocaine produces mydriasis effect by causing acinesia in the iris (Deeks, 2019). In studies of intracamaral mydriatic procedures (cyclopentolate hydrochloride 1%, phenylephrine hydrochloride 1.5%, lidocaine 2%) performed on humans, it was reported that pupil dilation occurred 95% of the cases within 20 seconds after injection (Lundberg and Behndig, 2003). Intracameral lidocaine procedures performed on dogs observed the start of mydriasis as between 1-10 minutes and kept its effect for approximately an hour. It was reported that the effect is correlated with the amount of injected lidocaine and its concentration (Osinchuk et al., 2020). The study on cats stated the usage of intracameral epinephrine and lidocaine, which resulted in more effective and long duration mydriasis in the pupil. Nonetheless, it was noted that intracameral lidocaine forms quicker mydriasis than intracameral epinephrine (Amorim et al., 2019). In our study, the fastest mydriasis was numerically formed by MSic among groups, which formed longer duration mydriasis in all intracameral procedures compared to topical procedures. By numbers except for the first 10 minutes, TLic groups have formed the largest mydriasis groups. Moreover, in the BSS groups, it was concluded that miosis was formed with the release of prostaglandins after anterior camera paracentesis, and it was observed that injected material didn't affect the PD.

After anterior camera paracentesis, IOP values in intracameral procedures, fell under 10 mmHg and tend to return to normal compared to baseline after T5 in intracameral procedures. In MSic procedures, it was observed that it was statistically and numerically proven to go back to their baseline references earlier than the other intracameral procedures. It was noted that after intracameral procedures on cats, the reason for the inocular pressure increase had been identified as relaxation of sillier muscles which cause mechanical blockage at the aqueous humour exit towards the iridocorneal angle (Srinavasan, 2018). Intracameral epinephrine and lidocaine methods were tried on humans, and change in inocular pressure was observed; however, no statistical differences with topical methods were found (Nikeghbali et al., 2007). Park et al., (2009) study on dogs, different concentrations of intracameral lidocaine, and Osinchuk et al., (2020) reported the intracameral epinephrine not making a significant change in inocular pressure. It was notified that operations made with intracameral epinephrine and lidocaine cause a decrease in inocular pressure in intracameral groups until T20, which then tends to climb back up to baseline reference levels (Amorim et al., 2019).

It has been reported that after intravenous injection of lidocaine, it can cause cardiovascular depression under general anesthesia with isoflurona in cats (Pypendop and Ilkiw, 2005). In a study of intracameral administration of epinephrine and lidocaine in cats, it was reported that epinephrine increased the HR in the first 20 minutes, but didnt cause significant changes in HR and MAP in all groups according to the time (Amorim et al., 2019). There were no ocular or systemic complications after the process

in any groups in our research. In our studies, all changes in the HR speed among the groups were found to be ideal, and no statistical differences between T60 and baseline values were found. Depending on the time of the process, with the exception of BSS, there has been a decrease in pulse compared to baseline reference after T5, recovery for the baseline starts at T20 for TLic, and T45 for MSic methods.

In our studies, it was observed that MSic and TLic result in enough mydriasis with healthy cats. The fastest midriasis formed by MSic groups, and the largest PD was reached by the TLic groups. All intracameral groups were observed to achieve longer mydriasis compared to topical methods. Because of this MSic and TLic were decided on as usable alternatives to other topical and intracameral practices with no side effects on IOP, HR and MAP.

Conflict of Interest

The authors declare that they have no competing interests.

Authorship contributions

Concept: O.B., Design: O.B., Data Collection or Processing: O.B., Analysis or Interpretation: O.B. Literature Search: O.B., Writing: O.B

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