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Effects of atropine used as eye drops on tears, pupil diameter and intraocular pressure in rabbits

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Abstract

Objective: It was aimed to determine the effects of using atropine as eye drops on tear amount (Schirmer tear test, STT), pupil diameter (PD), and intraocular pressure (IOP).
Method: STT, PD and IOP measurements were made before instillation of atropine and 30 minutes after instillation of single dose atropine for seven days in the six (6) male New Zealand Rabbits. Measurements were evaluated in Wilcoxon Signed Ranks Test.
Results: The STT, PD and IOP measurement values of both left and right eyes of the atropine group were statistically significantly different compared to those who did not receive atropine ($P<0.05$).
Conclusion: Atropine increase the PD values in the eye, decrease the STT values and increase the IOP values if it use in long-term.
Keywords: Atropine, Schirmer tear test, intraocular pressure, pupil diameter

INTRODUCTION

It is necessary to ensure adequate pupillary dilatation, especially in the examination of the lens, optic nerve and posterior segment (1). At the present time, there are many mydriatic agents such as tropicamide, phenylephrine, atropine, and cyclopentolate in routine use for pupil dilation (2, 3). It is important to ensure adequate pupillary dilation in fundus examinations, retinal laser photocoagulation, and cataract extractions in ophthalmic diseases because there may be a weak pupillary reaction to mydriatic drugs (4). This study is unique because it demonstrates the effects of mydriatic atropine usage on pupil diameter, intraocular pressure, and tear volume.

Clinical evaluation of tear production is performed with the Schirmer tear test (STT) (5). While Gelatt (6) reported the STT value in rabbits as 4.85 mm/min, the Schiötz tonometer intraocular pressure (IOP) value was not reported. There is no study examined the effect of atropine used in fundus examination on STT in the literature.

Mughannam et al. (7) used 1% atropine in horse eyes and reported that there was no significant IOP change. Wu et al. (8) reported that increasing atropine dose (0.1% and 1% doses) did not affect the treatment duration and IOP elevation. Liang et al. (9) revealed that topical atropine eye drops did not induce ocular hypertension and effectively slowed the progression of myopia. There are also studies reporting different results regarding the effects of atropine use on IOP. Instilling 1% atropine as eye drops may cause pupil dilation, stinging sensation, eye pain, photophobia, and blurred vision (10,11). Atropine causes increased intraocular pressure (IOP) due to pupil dilation (10). Atropine eye drops at a concentration of 0.01% have been reported not to cause an increase in IOP (7,8,12,13).

In this study, İt was aimed to determine the effects of eye drop atropine usage on STT, pupil diamater (PD) and IOP.

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METHOD

Ethics Committee permission was obtained for the study from Hatay Mustafa Kemal University, Experimental Animals Local Ethics Committee with the decision numbered 2023/03-03 and dated June 26, 2023. Six male New Zealand rabbits with a live weight of 550-650 grams were used in the study. The study was carried out in the Hatay Mustafa Kemal University Experimental Animal Laboratory between 09:00 and 11:00 in the morning. 0.1 milligram atropine sulfate solution (7,8) was topically administered as a single dose in the eye of each rabbit on seven day (14). STT, PD and IOP measurements were made before instillation of atropine and 30 minutes after instillation of atropine for seven days. PD was measured with a millimetric ruler, STT with strips, and IOP with Schiötz tonometer. The millimetric ruler was placed on the cornea, and the distance between the two irises was determined as PD in mm. STT strips were placed in the middle area of the lower eyelid and waited for one minute. At the end of one minute, the wetted amount on the strip was recorded as STT. For IOP measurement, the rabbit was laid on its back and its head was positioned appropriately. The Schiotz tonometer foot plate was placed on the cornea, and the value shown on the scale by the needle moving with the pressure applied by the plunger to the cornea was recorded. Since the Schiotz tonometer does not directly measure IOP, the scale values were converted to IOP values in mmHg using the conversion table provided with the device. These procedures were repeated for seven days.

Statistical Analysis

In this study, data were analyzed using SPSS 25 (Armonk, NY: IBM Corp.). Mean, standard deviation, minimum and maximum values were used for descriptive statistics. Wilcoxon signed-rank test, one of the non-parametric tests, was used in the statistical comparison of the measurements taken at two different times and situations of the dependent sample groups. Nonparametric Friedman's two-way analysis of variance was used for statistical comparison of measurement values on different days, meaning more than two dependent groups. The significance level for all tests was determined as $p<0.05$.

RESULTS

In this study, the effect of atropine used as eye drops on STT, PD and IOP was investigated; no systemic or ophthalmic symptoms or diseases were detected in the subjects. Atropine was used as eye drops for a week, and as a result of daily measurements, the seven-day average STT was 12.90±2.21 without atropine and 9.23±2.17 with atropine, respectively. The seven-day average PD was 0.26±0.06 without atropine and 0.71±0.15 with atropine, respectively. The seven-day average IOP was 13.95±1.60 without atropine and 17.60±2.25 with atropine, respectively.

In the daily statistical evaluation of daily measurements; There was a statistically significant difference in the STT measurement values of both left and right eyes of the atropine group compared to those who did not use atropine ($P<0.05$) (Table 1). Statistically significant differences were determined between the PD measurement values of both the left and right eyes of the groups with and without atropine ($P<0.05$) (Table 2).

In the IOP evaluation, although there was no statistically significant difference between the groups with and without atropine on days 2, 3, 4 and 5 regarding the left eyes ($P>0.05$), there was a significant difference on days 1, 6 and 7 regarding the left eyes. ($P<0.05$) (Table 3). In the IOP evaluation of the right eyes, there was a statistically significant difference between the groups with and without atropine on all days ($P<0.05$) (Table 3).

When the Friedmen test results were evaluated, in which we compared the days (comparing many dependent groups) in terms of relevant variables, no statistically significant difference was found between the days for the STT and PD measurement values of both left and right eyes without or with atropine ($P>0.05$).There was no statistically significant difference between the days in the IOP values of the right eyes with and without atropine ($P>0.05$). While there was no statistically significant difference between days in the IOP values of the left eyes with atropine ($P>0.05$), there was a significant difference between the days in the IOP values of the left eyes without atropine ($P<0.05$) (Table 4).

DISCUSSION

Atropine, an ophthalmic parasympatholytic drug, is widely used in both human and veterinary medicine. Mydriatic drugs are used for therapeutic purposes in a wide variety of ocular diseases and help prevent pupillary constriction (15). In this study, it was aimed to reveal the effect of atropine use for diagnostic purposes on the eye parameters STT, PD and IOP. The use of atropine as eye drops has complications such as pupil dilation, stinging sensation, eye pain, photophobia, and blurred vision (10,11). While STT, PD and IOP were evaluated in detail during the study, no other clinical symptoms such as pain or photophobia were observed. It has been reported that the use of atropine as eye drops has no effect on IOP (7, 8, 13). However, atropine or other anticholinergic agents may cause IOP elevation and are contraindicated in glaucoma

Table 1. Comparison of Schirmer tear test values (mm/min) of eyes with and without atropine administration*						
			Mean±Standart Deviation	Minimum-Maximum	Z	P
1st day	Left eye	Atropine	6.50±1.05	6-8	-2.214	0.027**
		Non-atropine	13.33±1.37	12-15		
	Right eye	Atropine	7.83±1.17	6-9	-2.201	0.028**
		Non-atropine	12.67±1.21	11-14		
2nd day	Left eye	Atropine	9.83±1.33	8-12	-2.264	0.024**
		Non-atropine	13.33±1.37	12-15		
	Right eye	Atropine	10.17±0.98	11-14	-2.041	0.041**
		Non-atropine	12.67±1.21	7-15		
3rd day	Left eye	Atropine	9±2.83	6-14	-1.892	0.058
		Non-atropine	12.00±3.10	9-11		
	Right eye	Atropine	8.67±2.34	5-11	-2.333	0.020**
		Non-atropine	11.17±2.71	7-14		
4th day	Left eye	Atropine	9.50±2.43	7-14	-2.023	0.043**
		Non-atropine	12.83±3.13	7-15		
	Right eye	Atropine	9.67±0.52	9-10	-2.207	0.027**
		Non-atropine	12.50±1.05	11-14		
5th day	Left eye	Atropine	8.67±2.16	6-12	-2.214	0.027**
		Non-atropine	13.33±1.86	11-15		
	Right eye	Atropine	10.17±0.98	9-11	-2.060	0.039**
		Non-atropine	12.50±1.05	11-14		
6th day	Left eye	Atropine	9±1.79	7-12	-2.214	0.027**
		Non-atropine	14.33±2.66	12-19		
	Right eye	Atropine	10.50±3.51	8-17	-2.207	0.027**
		Non-atropine	13.67±3.08	11-18		
7th day	Left eye	Atropine	10.17±1.94	7-12	-2.232	0.026**
		Non-atropine	14.00±1.55	12-15		
	Right eye	Atropine	9.67±2.16	7-11	-1826	0.068
		Non-atropine	12.33±1.03	11-14		
*Wilcoxon Signed Ranks Test. **p<0.05						

patients (16). Atropine used as eye drops may have a potential complication such as IOP elevation (10,11). Topical or intramuscular use of atropine sulfate increases IOP (17). On the other hand, other studies reported that atropine reduced IOP (15,16). The existence of different reports that atropine use has no effect on IOP, increases or decreases it, reveals the importance of this study. It is thought that these different notifications are related to the application times of atropine. It was reported that mydriasis lasted more than 14 days after administration of a single dose of 1% atropine sulfate ophthalmic solution to the normal horse eye (14). Therefore, it was thought that longer-term studies were needed to fully reveal the effect of atropine on IOP. In this study, atropine increased IOP. Although no difference was expected between the right and left eyes, there was an increase in IOP on all days in the right eye, while there was an increase on days 1, 6 and 7 in the left eye. More generalizable data may be obtained in repeated studies with larger sample sizes.

It has been reported that maximum PD occurs 30-60 minutes after topical atropine use in dogs, cats and cattle (17). In the literature review, pupillary dilation time was evaluated, yet no data on PD measurement were found. In this study, PD was determined as 0.26±0.06 without atropine and 0.71±0.15 with atropine.

Atropine has been reported to cause statistically significant

Table 2. Comparison of PD values (mm) of eyes with and without atropine administration*

			Mean±Standart Deviation	Minimum-Maximum	Z	P
1st day	Left eye	Atropine	0.65±0.10	0.5-0.8	-2.201	0.028**
		Non-atropine	0.32±0.11	0.2-0.4		
	Right eye	Atropine	0.63±0.08	0.5-0.7	-2.232	0.026**
		Non-atropine	0.28±0.04	0.2-0.3		
2nd day	Left eye	Atropine	0.65±0.10	0.5-0.8	-2.214	0.027**
		Non-atropine	0.27±0.05	0.2-0.3		
	Right eye	Atropine	0.63±0.08	0.5-0.7	-2.271	0.023**
		Non-atropine	0.27±0.05	0.2-0.3		
3rd day	Left eye	Atropine	0.57±0.08	0.5-0.7	-2.226	0.026**
		Non-atropine	0.23±0.05	0.2-0.3		
	Right eye	Atropine	0.83±0.24	0.5-1	-2.207	0.027**
		Non-atropine	0.23±0.05	0.2-0.3		
4th day	Left eye	Atropine	0.67±0.12	0.5-0.8	-2.226	0.026**
		Non-atropine	0.27±0.05	0.2-0.3		
	Right eye	Atropine	0.78±0.18	0.6-1.1	-2.201	0.028**
		Non-atropine	0.30±0.09	0.2-0.4		
5th day	Left eye	Atropine	0.68±0.18	0.5-1	-2.207	0.027**
		Atropinsiz	0.25±0.05	0.2-0.3		
	Right eye	Atropine	0.78±0.25	0.5-1.2	-2.214	0.027**
		Non-atropine	0.27±0.05	0.2-0.3		
6th day	Left eye	Atropine	0.70±0.14	0.5-0.9	-2.232	0.026**
		Non-atropine	0.25±0.05	0.2-0.3		
	Right eye	Atropine	0.83±0.19	0.6-1.1	-2.207	0.027**
		Non-atropine	0.23±0.05	0.2-0.3		
7th day	Left eye	Atropine	0.78±0.25	0.5-1.2	-2.207	0.027**
		Non-atropine	0.23±0.05	0.2-0.3		
	Right eye	Atropine	0.72±0.04	0.7-0.8	-2.233	0.020**
		Non-atropine	0.30±0.00	0.3-0.3		

*Wilcoxon Signed Ranks Test. **p<0.05

changes in various anterior segment parameters (13). It has been stated that the use of atropine inhibits aqueous humor flow in the Schlemm canal (16). It has been reported that atropine in dogs causes a statistically significant decrease in tear production in both eyes, and no statistically significant difference was detected in Schirmer tear test values between the left and right eyes (18). In this study, the mean STT value was determined as 12.90±2.21 without atropine and 9.23±2.17 with atropine. The effect of atropine, which is frequently used in veterinary medicine and human medicine, on ophthalmic parameters STT and PD was revealed with measurable values. It was determined that atropine use had an effect on eye parameters STT and PD with the first use, and its effect on IOP appeared after the fifth day.

Limitations of the study

There were some limitations in this study. The Schiötz tonometer and the Schimer tear test are accepted as the gold standard in eye studies. Nowadays, although tonopen studies have not become the gold standard for IOP measurements, they have become widespread. For IOP measurement, comparative studies with tonopen and the Schiötz tonometer and new studies to update the information can provide scientific contribution. Although STT measurement is considered to be the gold standard in pets, including humans, the routine reference parameters of the Schimer tear test in

experimental animals have not been fully established. It is understood that there is a need for studies to obtain both test paper and reference parameters for experimental animals.

Table 3. Comparison of IOP (mmHg) values of eyes with and without atropine administration*

			Mean±Standart Deviation	Minimum-Maximum	Z	P
1st day	Left eye	Atropine	16.95±2.22	14.6-20.6	-2.041	0.041**
		Non-atropine	12.60±0.98	12.2-14.6		
	Right eye	Atropine	20.82±7.08	14.6-34.5	-2.214	0.027**
		Non-atropine	13.40±1.31	12.2-14.6		
2nd day	Left eye	Atropine	17.95±2.30	14.6-20.6	-1.826	0.068
		Non-atropine	15.15±2.51	12.2-17.3		
	Right eye	Atropine	17.30±0.00	17.3-17.3	-2.041	0.041**
		Non-atropine	14.47±2.02	12.2-17.3		
3rd day	Left eye	Atropine	16.82±2.29	14.6-20.6	-0.756	0.450
		Non-atropine	16.10±1.64	14.6-17.6		
	Right eye	Atropine	17.32±1.43	14.6-18.9	-2.264	0.024**
		Non-atropine	12.60±0.98	12.2-14.6		
4th day	Left eye	Atropine	17.50±2.69	14.6-20.6	-1826	0.068
		Non-atropine	13.80±1.24	12.2-14.6		
	Right eye	Atropine	18.00±2.29	14.6-20.6	-2.214	0.027**
		Non-atropine	12.82±1.51	12.2-15.9		
5th day	Left eye	Atropine	17.05±2.25	14.6-20.6	-1.084	0.279
		Non-atropine	15.65±2.21	12.2-17.6		
	Right eye	Atropine	17.05±2.25	14.6-20.6	-2.214	0.027**
		Non-atropine	12.82±1.51	12.2-15.9		
6th day	Left eye	Atropine	17.72±2.45	14.6-20.6	-2.032	0.042**
		Non-atropine	14.30±2.00	12.2-17.6		
	Right eye	Atropine	18.15±1.24	17.3-20.6	-2.207	0.027**
		Non-atropine	13.40±1.31	12.2-14.6		
7th day	Left eye	Atropine	16.50±2.40	14.6-20.6	-2.041	0.041**
		Non-atropine	13.45±2.12	12.2-17.3		
	Right eye	Atropine	17.40±1.90	14.6-20.6	-1.992	0.046**
		Non-atropine	14.52±2.11	12.2-17.6		

*Wilcoxon Signed Ranks Test. **p<0.05

Table 4. Comparison of the difference between days in STT, PD and IOP values*

		P value		
		Schirmer tear test	Pupil diameter	Intraocular pressure
Left eye	Atropine	0.901	0.441	0.876
	Non-atropine	0.059	0437	0.017**
Right eye	Atropine	0.848	0.121	0.463
	Non-atropine	0.130	0.147	0.299

*Friedman's Two-Way Analysis of Variance. **p<0.05

CONCLUSION

In conclusion, it was determined that atropine decreased the STT value and increased the PD value in the eye, and increased the IOP value in long-term use. It is thought that longer-term studies are needed to fully reveal the effect of atropine on IOP.

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Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

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Authorship Contributions

Concept: MSÇ, CTİ, Design: MSÇ, CTİ, Supervising: MSÇ, CTİ, Financing and equipment: MSÇ, CTİ, Data collection and entry: MSÇ, CTİ, Analysis and interpretation: MSÇ, CTİ, Literature search: MSÇ, CTİ, Writing: MSÇ, CTİ, Critical review: MSÇ

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