Comparison of low concentration atropine eye drops with different concentrations and administration frequencies in controlling the progression of myopia in children

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Abstract

Objective

To compare the efficacy and side effects of 0.02% atropine eye drops once every other day and 0.01% atropine eye drops once a day in controlling the progression of myopia in children.

Method

231 children with myopic ametropia treated in the First Affiliated Hospital of Zhengzhou University and Henan Provincial eye hospital from June 2016 to June 2017 were included. They were randomly divided into 110 cases in the 0.02% atropine group and 121 cases in the 0.01% atropine group. The 0.02% atropine group was treated with 0.02% atropine eye drops once every other day before going to bed, and the 0.01% atropine group was treated with 0.01% atropine eye drops once a day before going to bed for 1 year. 92 cases in the 0.02% atropine group and 101 cases in the 0.01% atropine group were followed up for 1 year. The right SER,AL, AMP, PD, anterior chamber depth and corneal curvature were measured before and 12 months after treatment. The changes of each parameter 1 year after treatment and the adverse reactions after treatment were observed.

Result

One year after treatment, there was no significant difference in the changes of SER, Al, AMP and PD between 0.02% atropine group and 0.01% atropine group (all P>0.05). Photophobia occurred in 19.1% (21/110) and 20.7% (25/121) eyes in 0.02% atropine group and 0.01% atropine group within 1 month after treatment. Photophobia symptoms disappeared in 12 cases and 13 cases respectively within 1 ~ 6 months. Photophobia symptoms of other subjects gradually relieved but did not disappear. Within one month after treatment, 4.5% (5 / 110) and 5.0% (6 / 121) of the affected eyes in the two groups showed mild near blurred vision, which gradually relieved and disappeared after 2~4 weeks.

Conclusion

The effect of 0.02% atropine eye drops once every other day was consistent with that of 0.01% atropine eye drops once a day, and 0.02% atropine eye drops once every other day did not increase the degree and incidence of adverse reactions.

Introduce

Myopia is a serious public health problem all over the world. It is estimated that the global population with myopia will reach 4.758 billion in 2050 [1]. According to the national myopia survey data in 2018, the overall myopia rate of children and adolescents in China is 53.6%, showing a trend of younger onset, more severe onset and rapid progress [2]. Myopia has been the main cause affecting the eye health of children and adolescents in China, causing heavy economic burden and social problems. Fundus lesions caused by high myopia have increasingly become the main cause of irreversible blindness in China [3,4]. Therefore, effective measures to reduce the incidence rate of myopia, slow down its development speed and prevent complications have become an important part of children's eye care. The main ways to control the progression of myopia in children supported by evidence-based medicine include atropine eye drops of different concentrations, keratoplasty, peripheral defocus frame glasses or corneal contact lenses, double light prisms, etc. [5,6,7,8,9,10,11,12,13]. The research results of atropine eye drops with different concentrations in Singapore, the United States, China and other countries and regions show that the higher the concentration of atropine eye drops, the better the myopia control effect, but at the same time, the adverse reactions such as photophobia and near blurred vision are more obvious [5,6,7,8,9,10,14]. Chia et al. [5] observed the drug withdrawal rebound effect of atropine eye drops of different concentrations after continuous eye drops for 2 years. The results showed that the drug withdrawal rebound rate of 0.01% group was significantly lower than that of 0.1% group and 0.5% group. At present, 0.01% atropine eye drops are mostly used to control the progress of myopia in children [14], but the latest research shows that the degree of discomfort caused by atropine eye drops with a mass fraction lower than 0.05% is within an acceptable range [8]. The previous research of our research group shows that the effect of 0.02% atropine eye drops on controlling the progress of myopia in children is better than 0.01% atropine eye drops, and the adverse reactions of the two concentrations are basically the same [15]. Atropine eye drops need to be used continuously for a long time to control the progress of myopia in children. Medication compliance directly affects the efficacy of drugs. At present, the frequency of once a day is widely used in clinic. Research shows that about 35% of myopia children lack good atropine medication compliance [16]. If we can reduce the frequency of atropine use and maintain its efficacy, it will have a positive significance for clinical medication guidance. This study compared the control effect and adverse reactions of 0.02% atropine eye drops once every other day and 0.01% atropine eye drops once a day on myopia in children, in order to provide reference for its clinical application.

1 Data And Methods

1.1 General information

Using the method of randomized controlled clinical trial, 231 children with myopia ametropia treated in the eye hospital of Tianjin Medical University from June 2016 to June 2017 were included. All subjects wore myopia fully corrected monocular frame glasses. Inclusion criteria: (1) age 6 ~ 14 years; (2) The spherical equivalent refraction (SER) of binocular myopia was -0.75 ~ -6.0 D, and the astigmatism was < 2.00 D; (3) Best corrected visual acuity (LogMAR) 0.1; (4) Binocular ser difference < 1.00 D; (5) The intraocular pressure was 10 ~ 21 mmHg (1 mmHg = 0.133 kPa). Exclusion criteria: (1) allergic reaction or intolerance to atropine eye drops; (2) Long term use of low concentration atropine eye drops, rigid breathable corneal contact lenses or corneal shaping lenses for myopia prevention and control; (3) Unable to ensure regular follow-up; (4) Those with other eye diseases, eye surgery and trauma; (5) Have other systemic diseases. The subjects were randomly divided into 110 cases in 0.02% atropine group and 121 cases in 0.01% atropine group. During the study, 18 cases in

the 0.02% atropine group were abandoned, accounting for 16.4%, of which 6 cases were lost to follow-up, 7 cases stopped the drug due to fear of adverse reactions, 4 cases failed to review on time, 1 case stopped the drug due to photophobia, and finally 92 cases completed one-year follow-up. In the 0.01% atropine group, 20 cases were abandoned, accounting for 16.5%, of which 9 cases were lost to follow-up, 7 cases stopped the drug on their own for fear of side effects, 2 cases failed to review on time, 2 cases stopped the drug on their own due to photophobia, and finally 101 cases completed one-year follow-up. All subjects took right eye data for analysis. There was no significant difference in baseline data between the two groups (all P > 0.05) (Table 1). This study followed the declaration of Helsinki, was approved by the ethics committee of ophthalmic hospital of Tianjin Medical University (approval No.: 2020-35) and registered in the national clinical trial registration center (Registration No.: chictr-ipd-16008844). All subjects and their guardians understood the purpose of the study and signed informed consent.

Table 1

Comparison of baseline data before intervention between 0.02% and 0.01% atropine groups

Groups	cases	Age (mean ± SD, years) [a]	Gender (male/female, n) [b]	BMI(mean±SD，kg/m^2)[a]	Sphericity (mean ± SD, D) [a]	Cylindricity (mean ± SD, D) [a]	SER(mean±SD，D)[a]
0.02% atropine group	92	9.5±1.9	44/48	17.62±2.46	-2.31±1.27	-0.42±0.41	-2.57±1.37
0.01% atropine group	101	9.4±1.8	50/51	17.43±3.54	-2.39±1.60	-0.41±0.38	-2.68±1.59
t/χ2 value		0.986	0.054	1.401	-0.397	-0.046	-0.403
P value		0.191	0.816	0.178	0.702	0.987	0.712

Groups	cases	Intraocular pressure(mean±SD，mmHg)[a]	Corneal curvature(mean±SD，D)[a]	ACD(mean±SD，mm)[a]	PD(mean±SD，mm)[a]	AMP(mean±SD，D)[a]	AL(mean±SD，mm)[a]	Parental myopia(0/1/2，n)[b]
0.02% atropine group	92	16.58±2.80	43.07±1.24	3.65±0.21	6.09±0.53	16.12±6.15	24.32±0.77	30/62
0.01% atropine group	101	16.97±2.82	42.89±1.28	3.69±0.19	6.13±0.69	15.56±4.97	24.51±0.76	28/73
t/χ2 value		0.886	-0.554	1.375	0.021	1.214	1.271	0.547
P value		0.612	0.599	0.186	1.125	0.723	0.446	0.460

Note：(a：Independent sample t test；b： χ2 test)　BMI：body mass index；SER：spherical equivalent refraction；ACD：anterior chamber depth；PD：pupil diameter；AMP：amplitude of accommodation；AL：axial length；1 mmHg：0.133 kPa；corneal curvature was calculated by the mean of the flattest and steepest meridian curvature；myopic parents："0" meant that neither parent was myopic；"1" meant that at least one parent was myopic

1.2 Method

1.2.1 Preparation of test drug

Atropine eye drops with different mass fractions were prepared by professional pharmacists in the drug research room of Henan Provincial eye hospital. Place atropine sulfate powder on the super clean workbench, prepare atropine sulfate into 0.01% and 0.02% atropine eye drops with normal saline, adjust the pH value to 5.4 ~ 5.6, add ethyl paraben preservative, put it into a 3ml eye drop bottle, store it away from light at 15 ~ 25 ℃, and discard it one month after opening the bottle.

1.2.2 Ophthalmic examination of subjects before medication

The axial length (AL), anterior chamber depth (ACD) and corneal curvature were measured by IOL master 500 (Carl Zeiss, Germany). The pupil diameter (PD) was measured by AR-1 computer optometer (Nidek company of Japan). During the measurement, the subjects were completely relaxed, adapted indoors for 5 minutes under the condition of naked eyes, and the illuminance value of the tested eye plane was 300 ~ 310 LX; Intraocular pressure was measured by TX-10 non-contact tonometer (Canon company, Japan); The amplitude of accommodation (AMP) was measured by the approach method. Compound tropicamide eye drops were used once every 10 min for 4 times. After 40 min of paralysis of ciliary muscle, AR-1 automatic computer optometry was used for objective optometry, then retinoscopy and subjective optometry. The spherical and cylindrical degrees were obtained according to the principle of the highest positive

mirror of the best vision, and ser = spherical mirror + cylindrical mirror / 2 was calculated. The above inspections are completed by the corresponding technicians of the same fixed.

1.2.3 Application method of atropine eye drops with different mass fractions

All eye drops shall be kept and distributed by the same pharmacist who does not participate in the auxiliary examination. The subject's Guardian received the eye drops. The 0.02% atropine group used the alternate day eye pricking scheme, and the 0.01% atropine group used the daily eye pricking scheme. Both groups received eye drops once before going to bed at night, 1 drop / time, lasting for 1 year.

1.2.4 Evaluation index and follow-up

The observation indexes included visual acuity, intraocular pressure, PD, amp, Ser and al. The changes of SER, AI, PD and amp were the difference between 1 year after treatment and before treatment. All follow-up examinations were performed in the morning. The newly prepared eye drops for the next stage shall be distributed after each review.

1.2.5 Observation and evaluation of adverse reactions

When signing the informed consent form, explain in detail the possible local or systemic adverse reactions to the tested children and their guardians, and inform the response measures. During each follow-up, the subjects (assisted by the guardian) were asked about the total adverse reactions since the last review in the form of questionnaire and recorded. The ocular adverse reaction questionnaire includes the following three aspects: (1) whether there is photophobia (never, occasionally, often, always), under which circumstances (no, indoor normal light, daily outdoor light, bright sunlight) and duration; (2) There is ambiguity (never, occasionally, often, always) and severity (none, mild, moderate, severe) and duration of near reading; (3) Whether there is eye itching, eye swelling or other discomfort (never, occasionally, often, always) and the severity (no, mild, moderate, severe) and duration. The observation contents of systemic adverse reactions include tachycardia, dry mouth, nose and throat, fever, facial flushing, etc.

1.3 Statistical methods

Statistical software was used for statistical analysis. The normal distribution of measurement data is confirmed by Kolmogorov Smirnov test, expressed as mean ± SD. The differences of SER, Al and other parameters in the two groups at different time points before and after medication were compared by repeated measurement two-way ANOVA, and multiple comparisons between groups were compared by LSD-t test. The counting data were expressed in percentage, and the differences of gender composition and parental myopia rate between the two groups were compared χ 2 inspection. P < 0.05 was statistically significant.

2 Results

2.1 Comparison of ser changes between two groups before and after medication

There was statistically significant difference in ser before and after treatment (f time = 252.125, P < 0.001). Ser in each group was higher than that before treatment for 1 year, and the difference was statistically significant (all P < 0.05). The changes of ser in 0.02% atropine group and 0.01% atropine group were (-0.46 ± 0.49) D and (- 0.48 ± 0.46) d, respectively, with no statistically significant difference (t = -0.875, P = 0.383) (Table 2).

Table 2

Comparison of SER between the 0.02% and 0.01% atropine groups before and one year after treatment (mean±SD，D)

Groups	cases	SER at different time points	
		Before medication	Medication for 1 year
0.02% atropine group	92	-2.57±1.37	-2.90±0.96*
0.01% atropine group	101	-2.68±1.59	-3.16±1.17*
Note：Ftime：252.125，P<0.001；Fgroup：1.137，P：0.358，Finteraction：0.560，P：0.510.Compared with that before treatment within group，*P<0.05(Two-way ANOVA of repeated measurement，LSD-t test)　SER：spherical equivalent refraction			

2.2 Comparison of Al changes between two groups before and after medication

The overall difference of Al before and after treatment was statistically significant (f time = 630.173, P < 0.001). After treatment, Al in the two groups increased compared with that before treatment, and the difference was statistically significant (all P < 0.05). The changes of Al in the 0.02% atropine group and 0.01% atropine group were (0.38 ± 0.21) mm and (0.39 ± 0.19) mm respectively, with no statistically significant difference (t = - 1.472, P = 0.143) (Table 3).

Table 3

Comparison of AL between the 0.02% and 0.01% atropine groups before and one year after treatment (mean±SD，mm)

Groups	cases	AL at different time points	
		Before medication	Medication for 1 year
0.02% atropine group	92	24.32±0.77	24.70±0.91*
0.01% atropine group	101	24.51±0.76	24.90±0.94*
Note：F_{time}：630.173，P<0.001，F_{group}：2.473，P：0.156，$F_{interaction}$：3.016，P：0.572.Compared with that before treatment within group，*P<0.05 (Two-way ANOVA of repeated measurement，LSD-t test)　AL：axial length			

2.3 Comparison of intraocular pressure, ACD, AMP and PD between the two groups before and after treatment

There was no significant difference in intraocular pressure and ACD between 0.02% atropine group and 0.01% atropine group before and after treatment (all P > 0.05) (Table 4). There were significant differences in AMP and PD before and after treatment (AMP: f time = 9.898, P = 0.007; PD: f time = 312.573, P < 0.001). Amp decreased and PD expanded in each group for 1 year (all P < 0.05); There was no significant difference in AMP and PD between groups (AMP: F group = 0.634, P = 0.472; PD: F group = 3.431, P = 0.088) (Table 5 and table 6). The changes of AMP in 0.02% atropine group and 0.01% atropine group were (-1.49 ± 0.29) D and (-1.61 ± 0.26) d, respectively; The changes of PD were (0.72 ± 0.44) mm and (0.70 ± 0.40) mm, respectively, and there was no significant difference (P > 0.05).

Table 4

Comparison of intraocular pressure and ACD between 0.02% and 0.01% atropine groups before and one year after treatment (mean±SD)

Groups	cases	Intraocular pressure (mmHg)		ACD(mm)	
		Before medication	Medication for 1 year	Before medication	Medication for 1 year
0.02% atropine group	92	16.58±2.80	16.80±3.13	3.65±0.21	3.70±0.20
0.01% atropine group	101	16.97±2.82	17.23±2.91	3.69±0.19	3.73±0.20
Note：Intraocular pressure：F_{group}：0.819，P：0.367，F_{time}：1.303，P：0.256，$F_{interaction}$：0.028，P：0.867.ACD：F_{group}：1.721，P：0.192，F_{time}：0.003，P：0.957，$F_{interaction}$：0.006，P：0.941(Two-way ANOVA of repeated measurement)　1 mmHg：0.133 kPa，ACD：anterior chamber depth					

Table 5

Comparison of AMP between the 0.02% and 0.01% atropine groups before and one year after treatment (mean±SD，D)

Groups	cases	AL at different time points	
		Before medication	Medication for 1 year
0.02% atropine group	92	16.12±6.15	14.63±5.84*
0.01% atropine group	101	15.56±4.97	13.95±4.12*
Note：F_{group}：0.634，P：0.472，F_{time}：9.898，P：0.007，$F_{interaction}$：0.453，P：0.573.Compared with that before treatment within group，*P<0.05(Two-way ANOVA of repeated measurement，LSD-t test)　AMP：amplitude of accommodation			

Table 6

Comparison of PD between 0.02% and 0.01% atropine groups before and one year after treatment (mean±SD，mm)

Groups	cases	PD at different time points	
		Before medication	Medication for 1 year
0.02% atropine group	92	6.09±0.53	6.81±0.92*
0.01% atropine group	101	6.13±0.69	6.83±0.51*
Note：F_{group}：3.431，P：0.088，F_{time}：312.573，P<0.001，$F_{interaction}$：6.102，P：0.080.Compared with that before treatment within group，*P<0.05 (Two-way ANOVA of repeated measurement，LSD-t test)　PD：pupil diameter			

2.4 Related adverse reactions after medication in each group

One month after treatment, 19.1% (21 / 110) and 20.7% (25 / 121) of the affected eyes in the 0.02% atropine group and 0.01% atropine group showed fear of strong light, but there was no discomfort under indoor normal light and daily outdoor light. Wearing sunglasses or sunshades during outdoor activities could alleviate it. Photophobia disappeared in 7, 4 and 1 eyes in 0.02% atropine group at 1, 4 and 5 months after treatment; In the 0.01% atropine group, the symptoms of fear of strong light disappeared in 4, 6 and 3 eyes respectively at 1, 4 and 6 months after treatment; The symptoms of fear of strong light in other eyes were slightly relieved during follow-up, but did not completely disappear. During the follow-up of 1 month after medication, no new subjects developed photophobia. In the 0.02% atropine group and 0.01% atropine group, 4.5% (5 / 110) and 5.0% (6 / 121) of the eyes showed mild near vision reading blur within 1 month, respectively, and the symptoms gradually disappeared after 2 ~ 4 weeks. In the 0.01% atropine group, one subject had mild allergic reaction one month after medication, which showed itching and swelling in the morning, and disappeared automatically two days after withdrawal. No other symptoms of eye and general discomfort occurred.

3 Discussion

Atropine is a non selective muscarinic receptor antagonist and an effective drug to control the progression of myopia [12]. It is considered that atropine mainly acts on M1 and M4 receptors on retina and choroid to slow down the growth of eyeball, so as to inhibit the growth of myopia [17]. The efficacy and adverse reactions of atropine eye drops in controlling the progression of myopia are related to its concentration [5,8,18,19]. Chia et al. [20] used atropine eye drops with different mass fractions every day and followed up for 5 years. The results showed that the ser of subjects in 0.5%, 0.1% and 0.01% atropine treatment group had progressed to -1.98, - 1.83 and -1.38 D respectively, while the ser of myopia subjects in placebo control group (atom1 [6]) had progressed to -1.40 D in 2.5 years; The study showed that 0.01% atropine eye drops had the best effect on controlling the progression of myopia, and the rebound effect and adverse reactions after drug withdrawal were the weakest, which laid a clinical foundation for 0.01% atropine eye drops to control the progression of myopia once a day. Yam et al. [8] and Fang et al. [9] showed that 0.025% atropine eye drops once a day could significantly slow down the progression of myopia and the growth of al. Cooper et al. [19] observed the adverse reactions of atropine eye drops of 0.012%, 0.025% and 0.05% in 12 children aged 8 ~ 16 years with ser of + 0.75 ~ + 1.75 D. based on the acceptable comfort criteria of AMP not less than 5 d, pupil dilation less than 3 mm, only slight near vision blur and photophobia, it was found that the appropriate concentration of atropine eye drops was 0.012% ~ 0.025%, It is speculated that 0.02% atropine eye drops is the highest concentration that does not cause obvious regulatory paralysis and pupil dilation. The previous research of our research group found that 0.02% atropine eye drops were applied once a day, the progress rate of ser was -0.44 D / year, and the growth rate of Al was 0.35 mm / year [15]. Based on the research results of various aspects, this study observed the clinical efficacy and adverse reactions of 0.02% atropine eye drops after changing the administration frequency.

The results showed that the average progress of ser in 0.02% atropine group and 0.01% atropine group in one year was -0.46 D and -0.48 D respectively, and Al increased by 0.38 mm and 0.39 mm respectively. The effects of the two groups on controlling the progress of myopia in children were the same; It is close to the results in atom2 [5] that 0.01% atropine eye drops are applied once a day, Ser progresses by -0.43 D and Al increases by 0.24 mm every year; It was significantly lower than the ser progress (- 0.70 D / year) and Al increase (0.62 mm / year) of myopia children wearing only single frame glasses matched with the baseline data of this study in the earlier stage of our research group [10]; At the same time, it was also lower than the SER progression of [21] and Singapore [22] wearing glasses with frame glasses in Taiwan and China (-0.93 D/ and -0.76 D/). Clark et al. [7] studied myopia children aged 6 ~ 15 in the United States and found that the average annual ser progress of myopia children with 0.01% atropine eye drops once a day was -0.10 D, which was quite different from this study. The reason for the great difference may be that it mainly adopts non ciliary paralysis optometry, and there may be errors in diopter measurement; At the same time, the sample size was small, only 28 cases, and 71% (20 / 28) were non Asian people; The ser range of included children is -0.25 ~ -0.75 D. after medication, some children have "hyperopia drift" [9,23]. The results of this study showed that 0.02% atropine eye drops once every other day and 0.01% atropine eye drops once a day had the same effect and adverse reactions in controlling the progression of myopia in children, but the number of medication in 0.02% atropine group was reduced by half.

Administration time and frequency are important factors affecting patient compliance [24]. Li Weina et al. [25] showed that simplifying the medication scheme and reducing the frequency of medication can effectively improve the compliance of patients. On the premise of ensuring the effective treatment effect without causing more adverse reactions, this study tried to explore the medication method of 0.02% atropine eye drops once every other day, which has positive clinical significance.

The ocular adverse reactions of low concentration atropine eye drops are mainly the increase of PD and the decrease of AMP caused by the paralysis of iris sphincter and ciliary muscle, manifested as photophobia, difficulty in seeing near, etc. occasionally, ocular allergy and other irritation symptoms may occur. The incidence and severity of adverse reactions are dose-dependent [5,8,26]. Lamp study showed that there was no significant difference in the incidence of adverse reactions between 0.05% atropine eye drops and 0.01% atropine eye drops, and AMP and PD changed significantly only in the early stage of medication and tended to be stable in the later stage [8]. Zhong Mei et al. [27] applied 0.02% and 0.01% atropine eye drops to myopia children once a day. AMP in the two groups decreased slightly at 4 months, and increased slightly at 8 and 12 months, but still lower than the initial state; PD increased at 4 months, and then remained stable. The incidence of adverse reactions was the same in the two groups. In this study, the reexamination time of the two groups was the morning of the next day after atropine eye drops, so as to understand the maximum degree of adverse reactions. The change trend of AMP and PD in the two groups was basically the same and mild one year after treatment. The symptoms of eye discomfort caused by the changes of AMP and PD showed at the beginning of treatment (within 1 month). The proportion of photophobia symptoms in the two groups was similar. Photophobia could be effectively alleviated only in the bright outdoor sun by wearing sunglasses or sun visors. With the extension of medication time, the photophobia symptoms of some patients disappeared, and the photophobia symptoms of other patients were relieved in varying degrees. It is speculated that PD tends to be stable in the later stage, and the body's tolerance to drugs and its own compensation mechanism [28] show symptom relief. In this study, 4.5% and 5.0% of the subjects in the

two groups had mild near vision reading blur lasting no more than 1 month, which can be relieved naturally, suggesting that the low concentration atropine eye drops used in the study will not have a significant impact on the subjects' life and learning.

The results showed that 0.02% atropine eye drops 1 times daily and 0.01% atropine eye drops 1 times a day were effective in controlling myopia progression in Chinese mainland myopia children. No obvious adverse reactions were observed in long-term use. At present, there is still a lack of evidence-based basis for personalized drug dosage and frequency under the guidance of ocular pharmacological test evidence. This study can provide scientific reference for personalized selection of effective drug concentration and corresponding drug administration frequency according to children and family conditions in clinical practice.

Declarations

Disclosure statement

No potential conflict of interest was reported by the author(s).

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