Tropical Journal of Pharmaceutical Research November 2022; 21 (11): 2479-2485
ISSN: 1596-5996 (print); 1596-9827 (electronic)
© Pharmacotherapy Group, Faculty of Pharmacy, University of Benin, Benin City, 300001 Nigeria.

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i11.30

Original Research Article

Effect of combined use of orthokeratology and atropine eye drops on correction of myopia in young children, and its influencing factors

Yimeng Ruan*, Lu Qian, Siming Chen
Department of Ophthalmology, Ningbo First Hospital, Ningbo 315000, Zhejiang, China

For correspondence:* ***Email:* *yimdvxabg47137@163.com*

Sent for review: 25 May 2022 *Revised accepted: 10 October 2022*

Abstract

Purpose: *To investigate the corrective effect of combined use of orthokeratology and atropine eye drops on myopia of young children, as well as the factors involved.*
Methods: *84 young children with adolescent myopia who were admitted to Ningbo First Hospital from March 2019 to January 2021, were enrolled in this study. Forty (40) of the patients were treated with orthokeratology (control group, CG); while 44 patients were treated with a combination of orthokeratology and 0.01 % atropine (study group, EG). Clinical efficacy, pupil diameter, vision recovery, and incidence of adverse reactions were determined in both groups before and after treatment. Based on post-treatment clinical efficacy, patients in markedly effective and effective categories were regarded as improved status, while those whose treatments were ineffective were categorized in unimproved status. Logistic regression analysis was used to identify the influencing factors.*
Results: *There was no significant difference in total treatment effectiveness between the two groups. However, post-treatment diameter of eye axis and axial growth of RG were lower in EG than in CG ($p < 0.05$). There were no marked differences in naked eye vision and incidence of adverse reactions between the two groups. Logistic regression analysis revealed that age and course of disease were the risk factors that significantly affected treatment effectiveness ($p < 0.05$).*
Conclusion: *Combined treatment with orthokeratology and atropine eye drops relieves myopia in young children, and early treatment improves treatment effectiveness. However, further clinical trials are required prior to application in clinical practice.*

Keywords: *Orthokeratology, Atropine eye drops, Juvenile myopia, Logistic regression, Adverse reactions*

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Myopia is a very familiar eye disease in China at present. When the eyes of myopia patients are in a relaxed state, parallel light rays converge on the retina, but when observing distant objects, it is difficult for the light rays to focus on the retina, thereby producing blurred vision [1]. Moreover, myopia may lead to many complications such as glaucoma, retinal detachment, macular

© 2022 The authors. This work is licensed under the Creative Commons Attribution 4.0 International License

degeneration, and cataracts [2]. Teenagers are most at risk for myopia. As social habits develop, and as learning tasks increase, the number of teenagers with myopia has continued to increase year by year [3]. An analysis of the overall myopia diagnosis in adolescents aged 7-18 in 31 provinces of China from 2005 to 2014, revealed an increase from 47.4 to 55.6 % [4]. Thus, there is need to develop strategies for myopia correction in teenagers.

Surgery is a familiar treatment for myopia, but it has certain requirements for patients' conditions. Some patients may have sequelae such as dry eye, keratitis or vision regression after operation [5]. Orthokeratology is an effective way of delaying the development of myopia [6]. However, many clinical studies have shown that orthokeratology has very little effect on myopia prevention and control, especially as a non-surgical control method [7].

Drug therapy is also a way to control myopia, among which atropine is one of the best medications [8]. Atropine is a non-selective M receptor antagonist which is frequently used in the treatment and control of myopia[9]. At the present, there are some criticisms regarding the use of atropine. For example, the short-term rapid development of myopia in patients taking atropine makes it difficult to effectively control myopia, and patients experience rebound after they stop taking the drug for a period of time. In the present study, the corrective effect of combined treatment with orthokeratology and atropine eye drops on myopia in young and children was determined.

METHODS

Clinical profile of patients

A total of 84 young children with adolescent myopia who were admitted to our hospital from March 2019 to January 2021 were enrolled as research subjects. Forty of the patients comprising 23 males and 17 females (mean age, 12.8 ± 2.6 years) were assigned to control group (CG) and were treated with orthokeratology, while 44 patients (22 males and 22 females; mean age, 12.5 ± 2.5 years) were assigned to the study group (EG) which received combined treatment with orthokeratology and 0.01 % atropine. This research was conducted after it received approval from the Ningbo First Hospital Medical Ethics Committee, and it complied with international guidelines for human studies. All enrolled children and their families were informed about the purpose of the study, and necessary explanations were made to them regarding details of the study, prior to their signing of informed consent forms.

Inclusion and exclusion criteria

Inclusion criteria

All children diagnosed with myopia, with equivalent spherical diopter ranging from -6.00 to -8.00D, were included in the study. Moreover, patients within the age range of 6 to 18 years, and those who wore orthokeratology, used atropine, and had good treatment compliance, were included.

Exclusion criteria

Patients who reacted to orthokeratology, as well as those who were allergic to medications used, were excluded from the study. Moreover, myopia patients who also had glaucoma, conjunctivitis, cataracts, strabismus, amblyopia and other eye diseases, and those who had eye surgery, were not included.

Treatments

Before treatment, all patients were tested for eye axial and naked eye vision. For each patient, visual acuity, intraocular pressure, corneal topography and corneal curvature were used to assess Ortho-K lenses. The lenses were worn at night for at least 8 h daily. In addition to the treatment given to CG, patients in EG were given 0.01% atropine eye drops 30 min before wearing orthokeratology lenses every night, and the axial and naked eye vision were tested after one year of continuous treatment.

Determination of outcome indices/parameters

The clinical baseline data of both groups were recorded. Treatment effectiveness was compared between the two groups of patients after one year. Efficacy of treatment was classified as *markedly effective, effective* or *ineffective*. If the naked eye vision was greater than 1.0 and the degree of improvement was greater than 2 lines post-treatment, the treatment was *markedly effective*. Treatment was regarded as *effective* if the degree of improvement of naked eye vision was greater than 1 line. However, treatments that resulted in effects different from these two were regarded as *ineffective.* Total treatment effectiveness was calculated as the sum of *markedly effective* and *effective* cases.

Adverse reactions in children during the treatment were recorded. A comparison was

made with respect to naked eye vision and eye distance, before treatment and one year after treatment. Based on efficacy after one year, patients who were in the *markedly effective* and *effective* categories were put in the *improved group*, while those in *ineffective* treatment category were put in the *unimproved* group. The independent risk factors for poor efficacy were determined using multivariate logistic regression analysis.

Statistical analysis

All data were statistically analyzed using SPSS 20.0 software (SPSS Co. Inc, Chicago, USA). Continuous variables are expressed as number of cases, and mean ± standard deviation (SD). Independent *t*-test was employed for statistical comparison between two groups, while paired *t*-test was conducted for intra-group comparison. For classification variables, the data are presented as numbers and percentages [n (%)], and they were analyzed using chi-square (λ^2) test. Values of $p < 0.05$ were regarded as indicative of statistically significant differences.

RESULTS

Patients' baseline data

There were marked differences in age, gender, course of disease, family history of myopia, highest educational level, average duration of use of electronic devices, and place of residence, between the two groups of patients ($p > 0.05$; Table 1).

Treatment effectiveness after one year

There was no marked difference in total treatment effectiveness between the two groups of children after one year of treatment ($p > 0.05$). These results are shown in Table 2.

Table 1: Clinical baseline data of patients in the two groups

Variable		CG (n=40)	EG (n=44)	t/λ^2	*P*-variable
Age (years)		12.8±2.6	12.5±2.5	0.539	0.591
Gender					
	Boys	23 (57.50)	22 (50.00)		
	Girls	17 (42.50)	22 (50.00)	0.474	0.491
Course of disease (months)		5.8±2.5	5.4±3.0	0.660	0.511
Family history of myopia				1.005	0.316
	Yes	15 (37.50)	12 (27.27)		
	No	25 (62.50)	32 (73.73)		
Highest educational level				0.548	0.761
	Primary school	10 (25.00)	14 (31.82)		
	Junior high school	19 (47.50)	18 (40.91)		
	Senior high school	11 (27.50)	12 (27.27)		
Mean duration of usage of electronic devices > 1 h/day					
	Yes	31 (77.50)	30 (68.18)	0.915	0.339
	No	9 (22.50)	14 (31.82)		
Place of residence					
	Cities	29 (72.50)	32 (72.73)	0.001	0.981
	Villages	11 (27.50)	12 (27.27)		

Table 2: Comparison of treatment effectiveness between the two groups {n (%)}

Variable	CG (n=40)	EG (n=44)	λ^2	*P*-value
Markedly effective	16 (40.00)	22 (50.00)		
Effective	17 (42.50)	18 (40.91)		
Ineffective	7 (17.50)	4 (9.09)	1.302	0.254
Total effectiveness	33 (82.50%)	40 (90.91)		

Changes in naked eye vision after one year of treatment

A comparison of uncorrected visual acuity of the two groups of children before treatment, and after one year of treatment showed that there was no marked difference before treatment, and also there was no marked difference after one year of treatment ($p > 0.05$; Figure 1).

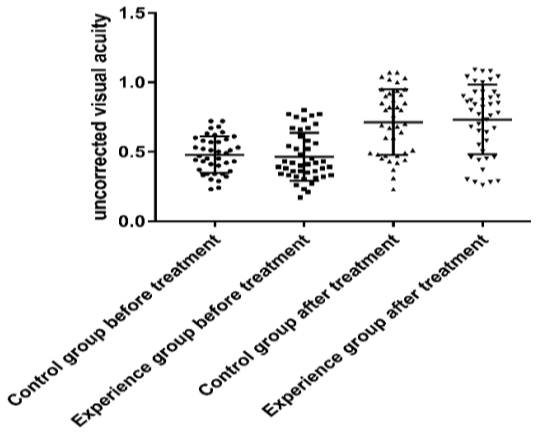

Figure 1: Changes in naked eye vision after one year of treatment

There was no marked difference between both groups before treatment (t =0.601, p = 0.549), and there was also no marked difference after one year of treatment (t = 0.373, p = 0.710).

Changes in eye axis in patients treated for one year

There was no marked difference between the two groups before treatment ($p > 0.05$). However, after one year of treatment, eye axial growth in EG was significantly lower than that in CG ($p < 0.05$). Moreover, after one year of treatment, eye axis growth was markedly lower in EG than in CG ($p < 0.05$; Figure 2).

Incidence of adverse reactions during treatment

It was found that although corneal infection, conjunctivitis, eye pain, tears and ocular hypertension occurred in both groups, there was no marked difference in incidence of adverse reactions between the two groups ($p < 0.05$; Table 3).

Results of univariate analysis of poor efficacy

The patients were categorized based on treatment effectiveness. There were 73 children in the *improved category* with remarkable and effective efficacy, while there were 11 children in the *unimproved category* with ineffective efficacy. The clinical data of the children were subjected to univariate analysis. It was found that there were differences in age, course of disease, family history of myopia, and naked eye vision and eye distance at admission ($p < 0.05$), but there were no differences in other indices ($p > 0.05$). These data are presented in Table 4.

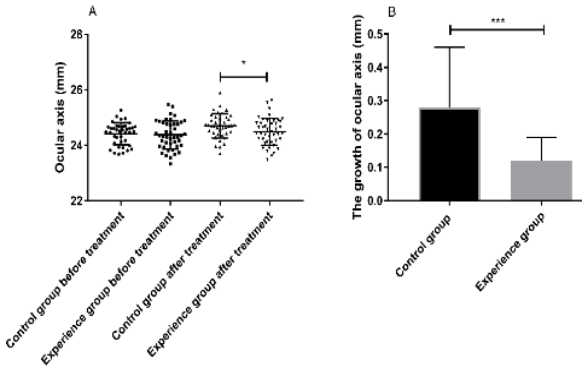

Figure 2: Changes in eye axis of patients in both groups after one year of treatment. A: There was no difference between the two groups before treatment (t = 0.617, p = 0.503), but one year post-treatment, eye axis of EG was lower than that of CG (t = 2.049, p = 0.043). B: Axial growth in EG in one year was lower than that in CG (t =5.096, $p < 0.001$). *$P < 0.05$; ***$p < 0.001$

Table 3: Comparison of incidence of adverse reactions between the two groups

Variable	CG (n=40)	EG (n=44)	λ^2	*P*-value
Corneal infection	2 (5.00)	1 (2.27)	0.199	0.656
Conjunctivitis	1 (2.50)	1 (2.27)		
Eye pain and tears	1 (2.50)	3 (6.82)		
Ocular hypertension	1 (2.50)	2 (4.54)		
Total adverse reactions	5 (12.50)	7 (15.91)		

Multi-factor analysis of poor efficacy

In univariate analysis, values were assigned to the indicators which differed significantly between the two groups (Table 6). These parameters were subjected to multi-factor logistic regression analysis. The results revealed that blood glucose was not independently associated with poor prognosis in 14 days. However, age (OR: 2.802, 95% CI: 1.064-7.941) and course of disease (OR: 2.369, 95 % CI: 1.078-5.206) were independently tied to poor prognosis (Table 7).

Table 4: Results of univariate logistic analysis

Variable		Improved status (n=73)	Unimproved status (n=11)	t/λ^2	*P*-value
Age (years)		12.3±2.5	15.0±1.7	3.454	<0.001
Gender					
	Boys	40 (54.79)	5 (45.45)		
	Girls	33 (45.21)	6 (54.55)	0.335	0.563
Course of disease (months)		5.2±2.6	8.1±2.9	3.398	0.001
Family history of myopia					
	Yes	19 (26.03)	8 (72.73)	9.558	0.002
	No	54 (73.97)	3 (27.27)		
Highest education					
	Primary school	22 (30.14)	2 (18.18)		
	Junior high school	33 (45.20)	4 (36.36)		
	Senior high school	18 (24.66)	5 (45.46)	2.158	0.340
Mean duration of usage of electronic devices > 1 h/day					
	Yes	53 (72.60)	9 (81.82)		
	No	20 (27.40)	2 (18.18)	0.420	0.517
Place of residence					
	Cities	46 (63.01)	8 (72.73)		
	Villages	27 (36.99)	3 (27.27)	0.393	0.531
Treatment mode					
	Individual therapy	33 (45.21)	7 (63.64)	1.302	0.254
	Combined therapy	40 (54.79)	4 (36.36)		

Table 5: Relationship between eye axis and visual acuity and efficacy

Parameter	Improved status (n=73)	Unimproved status (n=11)	t	*P*-value
Naked eye vision at admission	0.50±0.14	0.29±0.07	4.866	<0.001
Eye distance at admission (mm)	24.31±0.41	24.99±0.29	5.292	<0.001

Table 6: Assignment of indicators

Factor	Assignment
Age	Continuous variable; raw data analysis was used
Course of disease	Continuous variable; raw data analysis was used
Family history of myopia	Yes = 1, none = 0
Naked eye vision at admission	Continuous variable; raw data analysis was used
Eye distance at admission	Continuous variable; raw data analysis was used.
Efficacy	Ineffective = 1; markedly effective + effective = 0

Table 7: Multi-factor logistic regression analysis

Factor	B	SE	Wals	Sig.	Exp (B)	EXP (B) of 95 % C.I.	
						Lower limit	*Upper limit*
Age	1.067	0.513	4.328	0.037	2.906	1.064	7.941
Course of disease	0.862	0.402	4.607	0.032	2.369	1.078	5.206

DISCUSSION

Myopia in children not only affects their daily lives, but also seriously impairs their physical and mental health. If myopia is not controlled, it may lead to blindness [10]. An increase in degree of myopia leads to gradual increase in axial length of the eye in the patients. Thus, the current clinical strategy for the control of myopia in young children involves changing the refractive condition of the eye and reducing the axial length.

Orthokeratology, a physical therapy used for controlling myopia, limits the elastopathy of the cornea by causing mechanical compression.

Moreover, the highly permeable materials and structures used in orthokeratology may result in slight depression, since these materials are not consistent with corneal morphology. As a result, the corneal epithelial cells are compressed and redistributed to flatten the central optical area of the cornea, so as to limit myopia and correct vision [11].

Most adolescents have pseudomyopia at the early stage. Several teenagers are still in the developmental stage of myopia, but because of daily overuse of the eye, they are unable to effect rapid removal of metabolic products of the ciliary muscle, leading to the stage of constant visual fatigue. The ciliary muscle is also prone to persistent spasm and pathological changes [12]. Studies have demonstrated that atropine drugs used for treating myopia effectively relieve tension in ciliary muscles, resulting in complete muscle relaxation, thereby eliminating the problem of pseudomyopia due to eye fatigue [13].

The present study showed that after three months of treatment, although the naked eye vision of young children in EG was slightly better than that of CG, there was no statistically significant difference between them. However, it was found that there was a significant difference between the two groups, with respect to one-year axial growth, with lower growth in EG than in CG. This indicates that combined treatment with orthokeratology and atropine eye drops was more effective in preventing myopia of young children and controlling axial growth. Although the use of orthokeratology produces certain beneficial effects on myopia patients, it has been reported that some teenagers had uncontrollable increase in myopia, even when orthokeratology was used, indicating that orthokeratology alone was ineffective in these patients [14]. In the present study, the combination of orthokeratology and atropine eye drops produced a synergistic effect, thereby effectively controlling and treating myopia. Comparison of the two groups revealed that there was no marked difference in incidence of adverse reactions. Some studies have shown that although orthokeratology makes use of materials with enhanced oxygen permeability, the procedure does not result in complete elimination of hypoxia and corneal edema [15]. The use of atropine may result in adverse reactions such as photophobia and pupil dilation [16]. However, none of the patients in this study showed these adverse reactions, indicating that the combined treatment is safe. Finally, logistic regression analysis showed that age and course of disease are risk factors that affect efficacy [17].

Limitations of the study

There are some shortcomings in the present investigation. First of all, since this research focused on the protection of young people from myopia, the subjects used were teenagers. It is still not clear as to how the different treatments will affect the development of adolescents. Thus, there is need to increase the duration of follow-up in subsequent research. Secondly, since adults were not included in the study population, the effect of this treatment scheme on adults is not certain. This defect will be remedied in future research.

CONCLUSION

This study has shown that combined treatment with orthokeratology and atropine eye drops mitigates myopia in teenagers and children. Moreover, early use of the combination treatment enhances treatment effectiveness in these patients. However, further clinical trials are required prior to application in clinical practice.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. *Zhu Z, Chen Y, Tan Z, Xiong R, McGuinness MB and Muller A. Interventions recommended for myopia prevention and control among children and adolescents in China: a systematic review. Br J Ophthalmol 2021.*
2. *Tang M, Fu Y, Fan Y, Fu MS and Xu X. In-silico design of novel myocilin inhibitors for glaucoma therapy. TJPR 2017; 16: 2527-2533.*
3. *Qu Y, Yu J, Xia W and Cai H. Correlation of Myopia with Physical Exercise and Sleep Habits among Suburban Adolescents. J Ophthalmol 2020; 2020: 2670153.*
4. *Dong YH, Liu HB, Wang ZH, Xu RB, Yang ZP and Ma J. [The epidemic status and secular trends of myopia prevalence for Chinese children and adolescents aged 7-18 years from 2005 to 2014]. Zhonghua Yu Fang Yi Xue Za Zhi 2017; 51: 285-289.*
5. *Alhibshi N, Kamal Y, Aljohany L, Alsaeedi H, Ezzat S and Mandora N. Attitude toward refractive error surgery and other correction methods: A cross-sectional study. Ann Med Surg (Lond) 2021; 72: 103104.*
6. *Cheung ATW, Chen PCY, Wong KY, Banerjee A, Tracy BD and To WJ. Microvascular complications in orthokeratology (Ortho-K): A real-time study on the microvasculature of the bulbar conjunctiva in Ortho-K treatment. Clin Hemorheol Microcirc 2019; 72: 119-128.*
7. *Azmat A, Ahmed M. Pharmacological evidence of hypotensive activity of Somina (herbal drug) in normotensive rats. TJPR 2014; 13: 1863-1866.*
8. *Jethani J. Efficacy of low-concentration atropine (0.01%) eye drops for prevention of axial myopic progression in premyopes. Indian J Ophthalmol 2022; 70: 238-240.*
9. *Li FF and Yam JC. Low-Concentration Atropine Eye Drops for Myopia Progression. Asia Pac J Ophthalmol (Phila) 2019; 8: 360-365.*
10. *Huang Q, Yang Y, Huang H, Zheng Y, Wang W, Liao T, Xiao X, Wang J, Zou W and Wang J. Clinical study on acupuncture acupoints around the eyes in treating myopia in children and adolescents: A study protocol. Medicine (Baltimore) 2020; 99: e22659.*
11. *Kang P and Swarbrick H. The Influence of Different OK Lens Designs on Peripheral Refraction. Optom Vis Sci 2016; 93: 1112-1119.*
12. *Khalid K, Padda J, Pokhriyal S, Hitawala G, Khan MS, Upadhyay P, Cooper AC and Jean-Charles G. Pseudomyopia and Its Association With Anxiety. Cureus 2021; 13: e17411.*
13. *Zhou Y, Huang XB, Cai Q, Li JJ, Xiong YJ, Gong YX, Lin LW, Zhu Y and Sun ZM. Comparative Study of the Effects of 1% Atropine on the Anterior Segment. J Ophthalmol 2020; 2020: 5125243.*
14. *Tan Q, Ng AL, Cheng GP, Woo VC and Cho P. Combined Atropine with Orthokeratology for Myopia Control: Study Design and Preliminary Results. Curr Eye Res 2019; 44: 671-678.*
15. *Papas EB and Sweeney DF. Interpreting the corneal response to oxygen: Is there a basis for re-evaluating data from gas-goggle studies? Exp Eye Res 2016; 151: 222-226.*
16. *Cooper J, Eisenberg N, Schulman E and Wang FM. Maximum atropine dose without clinical signs or symptoms. Optom Vis Sci 2013; 90: 1467-1472.*
17. *Hao MH, Zhang F, Liu XX, Zhang F, Wang LJ, Xu SJ, Zhang JH, Ji HL and Xu P. Qualitative and quantitative analysis of catechin and quercetin in flavonoids extracted from Rosa roxburghii Tratt. Trop J Pharm Res 2018; 17: 71-76.*