Original Article

Safety and Efficacy of Low Dose Atropine in Nepalese Children with Progressive Myopia

Srijana Adhikari[1], Namrata Gupta[1], Birendra Mahat[1], Manish Poudel[1], Rojeeta Parajuli[1], Ang Jangmu Lama[1], Richa Poudel[1]

[1]Tilganga Institute of Ophthalmology, Gaushala, Kathmandu, Nepal

ABSTRACT

Introduction: Myopia is emerging as a public health emergency worldwide. Low dose atropine has been proven to be safe and efficacious in halting the progression of myopia.

Objectives: Aim of this study was to evaluate safety and efficacy of low dose atropine in Nepalese children with progressive myopia.

Materials and methods: It is a prospective non randomized interventional study. Children with myopia progression of >0.5D in the last six months with baseline myopia of -1.5 to -8 Diopter and astigmatism of 3 D or less were prescribed 0.01% atropine daily at bedtime for two years. Demography including age, gender, race, and examinations including anterior and posterior segment, axial length, near point of accommodation and near vision were recorded in all the children. Ocular and systemic side effects were documented.

Results: A total of 200 children were enrolled in the study. Mean age was 11.9±2.97 years with 41% female. Baseline mean axial length was 24.47±1 and mean spherical equivalent was 3.69±1.33. Average increase in axial length was 0.18(±0.02), 0.17(±0.02), and 0.19(±0.04) mm in six months, one year, and two years respectively. The increase in spherical equivalence was 0.2 (±0.01), 0.3(±0.02), and 0.3(±0.02)) diopter in six months, one year, and two years respectively. The myopia progression was found more in the Mongolian race compared to the Aryan race. No ocular or systemic side effects were documented.

Conclusion: Topical low dose atropine appears to be safe and efficacious in halting the progression of myopia in a cohort of Nepalese children. Further randomized control trial on various doses of atropine are recommended.

Key words: Childhood blindness, Children, Low dose atropine, Myopia, Nepal.

Financial Interest : Nil
Conflict of Interest : Nil

Received : 27.10.2022
Accepted : 27.12.2022

Corresponding Author
Dr. Srijana Adhikari
Tilganga Institute of Ophthalmology
Gaushala, Kathmandu Nepal.
E-mail: srij_a@yahoo.com

Access this article online
Website: www.nepjol.info/index.php/NEPJOPH
DOI: https://doi.org/10.3126/nepjoph.v15i1.49076

ISSN: 2072-6805, **E-ISSN:** 2091-0320

INTRODUCTION

Myopia is one of the leading causes of childhood visual impairment worldwide. The global prevalence of myopia is 22.95% (Holden et al, 2016). It has been estimated that around 49.8% of people worldwide will develop myopia by year 2050 (Nouraeinejad, 2021). The prevalence in some east Asian countries are very high with prevalence increased up to 80% in young adults. (Ma et al, 2016). In China, the prevalence of myopia reaches 5.2% in children aged six years, nearly 70% in seventh-grade students, and exceeds 80% in university students (Ohno-Matsui and Jonas, 2020; Li et al, 2013). It is a disease of concern as high myopia may lead to complications such as choroidal neovascularization, retinal detachment, glaucoma which ultimately may results into irreversible blindness (Dragoumis et al, 2017; Ohno-Matsuik, 2012). Because of increased near work, urbanization, and less time in outdoor activities, myopia has emerged as a public health problem in both Asia and western countries (Pan et al, 2012). Pathologic myopia is estimated to have a global prevalence of 0.9%-3.1%, and it is the cause of low vision in 5.8%-7.8% of Europeans and 12.2%-31.3% of east Asians (Hayashi et al, 2010). Myopia is, therefore, a significant public health problem due to its increasing prevalence, associated visual morbidity, visual disability with reduction in the quality of life, and its considerable cost for correction. Studies from Nepal have shown myopia as the most common cause of refractive error. Its prevalence ranges from 10-25% in Nepalese population (Pokharel et al, 2000; Adhikari, 2013; Pokharel et al, 2010). Myopia usually commences during primary school and progresses until adolescence {correction of myopia evaluation trial (COMET), 2013}. Therefore, controlling myopia during this growing age of six years to 18 years is essential. There are different modalities of treatment for halting the progression of myopia. Interventional approaches such as bifocal glasses, progressive lenses, orthokeratology, and anticholinergic eye drops are current methods to suppress the progression of myopia (Huang et al, 2016; Cheng et al, 2014; Cho and Cheung, 2012; Gwiazda et al, 2003). Atropine is a non-selective muscarinic antagonist. The mechanism for retarding the progression of myopia with atropine is based on the actions at the choroid or the sclera (Tan et al, 2016; Chua et al, 2006).

Atropine eye drops were first proposed as a treatment of myopia in the 1920s. Since then, there have been numerous studies on this subject. However, evidence from randomized controlled trials has become available only over the last two decades. These trials confirm that atropine eye drops are effective in the control of myopia in a dose-dependent manner (Saxena et al, 2021; Wei et al, 2020; Joachimsen et al, 2019; Moon and Shin, 2018; Clark and Clark, 2015; Chia et al, 2012). Atropine for myopia control is still a very new concept in Nepal with no reported study on its safety and efficacy in Nepalese children. It is important to determine the effects of atropine in different countries and racial groups to confirm whether similar or unique effect exists. It is also important to identify the risk factors associated with myopia progression in children. There is a handful studies on effect of race and ethnicity in the progression of myopia (Loung, 2020; Hyman et al., 2005). In Nepal, there are chiefly two race types, Aryans and Mongols. The Mongols are

the Tibeto-Burman races similar to the Chinese population. Aryans are similar to Caucasian race (Kafle, 2022; Pokharel, 2013). Our study is an ongoing five-year long prospective study being conducted in three phases. In this paper we analyze the initial two years result of the effect of low dose atropine in myopia progression in Nepalese children including two racial groups.

MATERIALS AND METHODS

It is a prospective non randomized interventional study. The study was approved by the institutional review committee of Tilganga Institute of Ophthalmology (Reference number 23/2018). The study adheres to the tenets of declaration of Helsinki. Nepal Atropine Myopia study is an ongoing five-year study December 2018 to December 2023) being conducted in three phases. Phase I is the treatment phase in which children were treated with low dose atropine 0.01% for two years. The phase II is the washout phase in which the treatment will be stopped and children will be followed up for 12 months. The phase III is the follow-up study in which children with myopia progression more than 0.5D SE will be restarted with the atropine for another 24 months. In this paper we have analyzed the data of phase I of the study. Informed consent was taken from all the parents of children less than 12 years old and informed assent was taken from children 12 years and older.

Children aged 6 years to -16 years presenting in the outpatient department with baseline myopic refractive error of -1.5 D to -8 D, the astigmatism of 3D or less and progression of myopia of more than -0.5D prior to the start of atropine were included in the study. The prior myopia progression was determined by Electronic medical record data, patient's previous prescription. Children with any other associated ocular diseases causing a decreased in vision were excluded. Children with severe developmental delay or systemic diseases were excluded from the study.

Information on demography including age, sex, racial group were collected from each child. Children were divided into two racial groups, Aryans and Mongols.

All the children underwent following clinical examinations:

Distance visual acuity examination was done by using Snellen's E chart, and near acuity was examined by Rosenbaum near vision acuity card.

Cycloplegic refraction using 1% cyclopentolate drop instilled three times in 10 minutes apart and wet retinoscopy after 45 minutes by using Heines retinoscope.

Post mydriatic test for subjective refraction after three days of wet refraction.

Anterior segment examinations using slit lamp biomicroscope Haag Streit Germany.

Posterior segment examination using slit lamp biomicroscope and 90D condensing lens.

Axial length measurement was done by Nidek inc A Scan device.

Near point of accommodation and convergence were measured using Royal Air Force (RAF) ruler. All these parameters were taken as baseline value. Refractive error was documented as

spherical equivalence. Children were treated with commercially available 0.01% atropine eye drop every day at bedtime for two years. The drop was Atrop PD prepared by Aurolab in Aravind Eye Hospital Madurai India. The medicine was made available by the authorized distributor of Aurolab in Nepal. The first follow-up was done in three months. Parents were asked about any ocular or systemic side effects of drug. The subsequent follow-up examinations were done at six months one year, and two years. Findings from six months, 12 months, and 24 months follow-up were taken for analysis. Data collection, data coding, and cleaning were done in Microsoft Excel. The cleaned data were transported to IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. For continuous variables, normality was checked using Kolomogorov Smirnov test and independent t-test was used for statistical difference. P value <0.05 was considered as statistically significant.

RESULTS

A total of 200 children who fulfilled inclusion criteria were enrolled in the study. There were 106 (53%) male and 94 (47%) female. The mean age of children at the time of presentation was 11.9±2.97 years. There were 31% of children between the age of six years and 10 years and 69% of children between 11 years to 16 years. The mean age of onset of myopia was 8.9±2.75 years (Table 1).

Results were analyzed at six months, one year, and two years. Among children enrolled in the study, 70% completed six months follow-up, 67% completed one year, and 50% completed two years follow-up. The mean spherical equivalence at six months, one year, and two years were 3.96±1.4, 4.22±1.5, and 4.56±1.6) respectively. Similarly, mean axial length at six months, one year, and two years were 24.65±0.98, 24.82±1.02, and 25.01±1.06

Table 1: Baseline characteristics of children.

Variables	Mean±SD	Range
Age in years	11.9±2.97	6-16
Mean SE of refractive error in Diopter	3.69±1.38	2-8
Mean axial length in mm	24.47±1.00	22.29-26.63
Mean age of onset of myopia (years)	8.9±2.75	2-15
Variables	**Categories**	**Number (Percent)**
Spherical equivalence of refractive error	Mild (<2D)	24 (12)
	Moderate (2-8D)	176 (88)
Race	Aryans	110 (55)
	Mongols	90 (45)

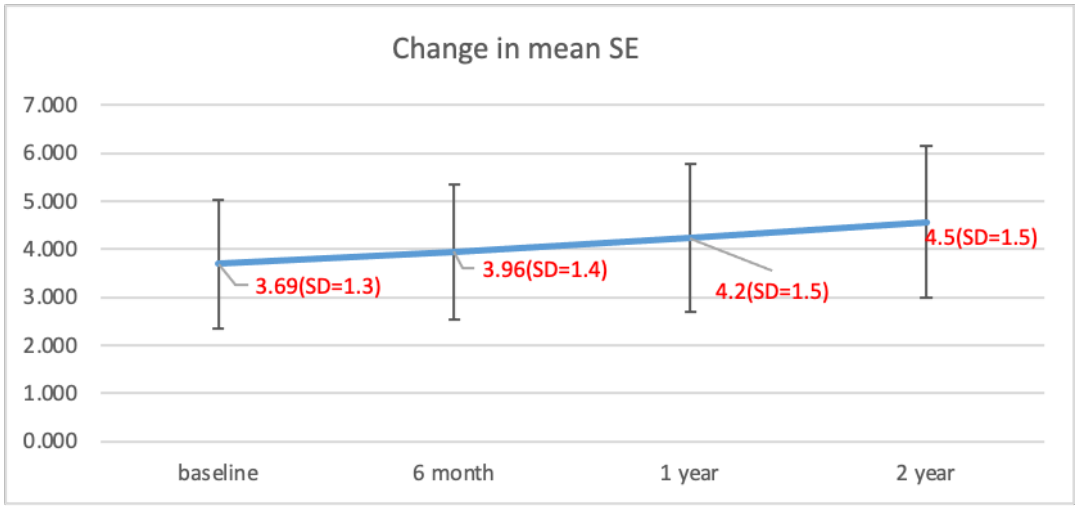

Figure 1: Rate of progression of spherical equivalence from baseline at six months, one year, and two years.

respectively. On analyzing the increase in axial length and spherical equivalence, we found that there was mean increase in the spherical equivalence of 0.18, 0.17, and 0.19 in six months, one year, and two years respectively (P <0.01). Similarly mean increase in the axial length was 0.2, 0.3, and 0. 3 in six months, one year, and two years respectively (P <0.01).

Figure 1 shows the rate of progression of myopia (Spherical equivalence) from baseline at six months, one year, and two years.

Similarly, Figure 2 shows the rate of change in axial length from baseline in six months, one year and two years.

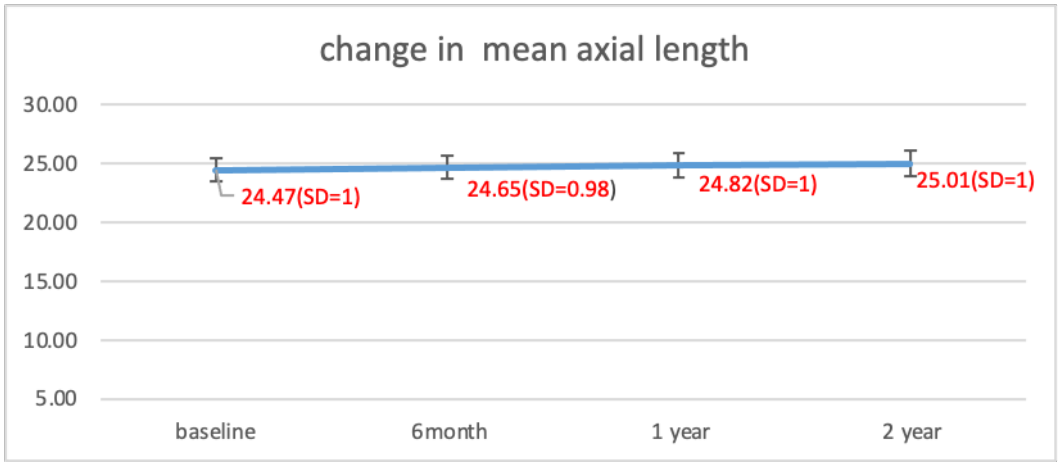

Figure 2: Rate of progression of axial length from baseline at six months, one year and two years.

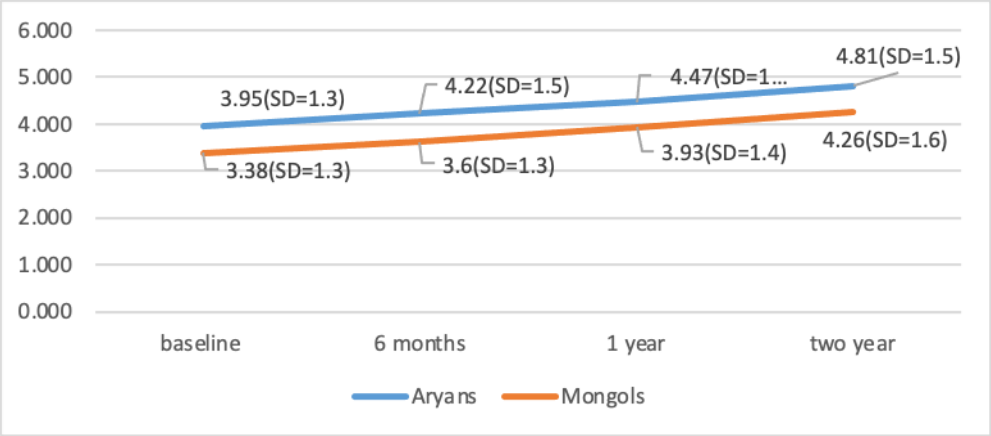

Figure 3: Mean spherical equivalence comparison in Aryans and Mongols races.

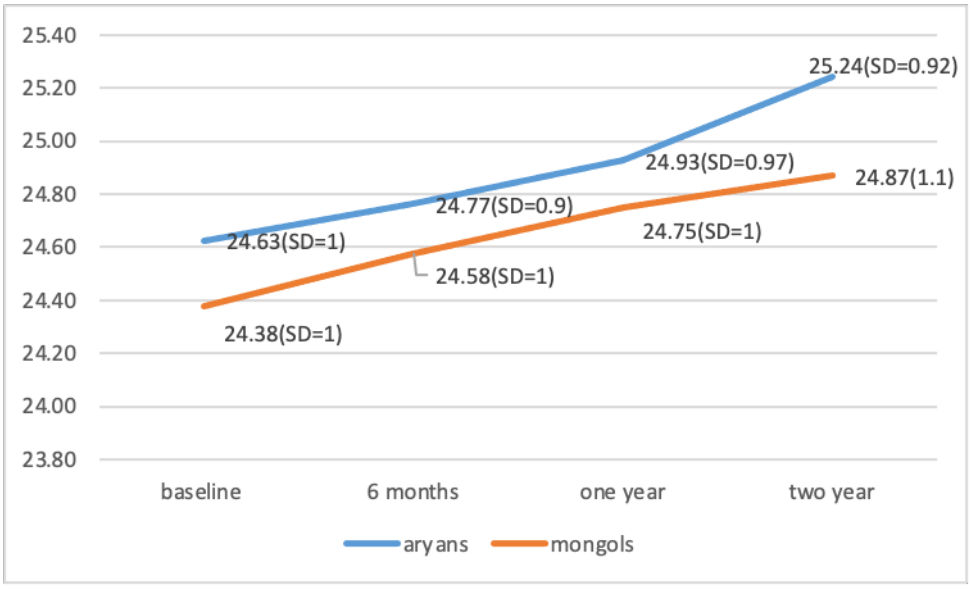

Figure 4: Mean axial length comparison in Aryans and Mongols races.

We compared the rate of progression of myopia in terms of spherical equivalence in two races.

The mean baseline spherical equivalence and the subsequent increase was more in Aryan race than the Mongolian races (P <0.01) (Figure 3).

Similarly, the baseline axial length and the subsequent rate of progression was more in Aryan races than the Mongolian race (P <0.01) (Figure 4).

DISCUSSION

Atropine 0.01% has been used widely in different countries, races and ethnic groups with proven safety and efficacy. However, this is the first time it has been used in Nepal. Our data show a significant effect of low dose atropine in myopia progression. Findings of this study concur with the findings from other similar studies (Vidhya et al, 2020; Loughman and

Flitcroft, 2016; Nishiyama et al, 2015;Wu et al, 2011). Atropine for the Treatment of Myopia (ATOM) is the milestone study of the use of atropine for myopia progression. We did not find any ocular and systemic side effects. Similarly, we did not document any change in the near vision and near point of accommodation in our population. Table 2 shows the results of our findings compared with some landmark studies in south east Asia, Europe as well as studies from India the population of which is similar to our study population.

Along with axial length in our study, we measured near vision and near point of accommodation in all children in every follow up. However, in contrary to some other studies, we did not find any change in the near point of accommodation and near vision in our children. We did not find any ocular and systemic side effects in our population except for one child who developed diarrhea after atropine use and presumed to be the side effect of drops. Only two children complained of mild photophobia for few days after the use of drops. One important aspect of our study was the comparison of progression of myopia in different ethnic groups. Few studies compared the rate of myopia in children using atropine in different races and ethnic groups (Donovan et al., 2012; Luong et al., 2020). We found that the children belonging to Tibeto-Burman or the Mongolian race had higher axial length, spherical equivalence and rate of progression of myopia compared to those belonging to Aryan race. The Nepalese population has relatively darker pupils the color of which is similar to the east Asian population. Hence there can be a dose response effect in our population. The study done by Yam et al. (2019) has shown dose related response on the use of atropine in myopia (Yam et al., 2019).

Further study in different doses of atropine may be helpful in exploring the dose response effect in our population as well.

There are few limitations in our study. First this is not a randomized clinical trial. Second limitation was smaller sample size. Third limitation was short follow-up and missing follow-up visits by these children. The main reason for missing follow-up was ongoing pandemic which

Table 2: Comparison of our findings with ATOM 2 and other similar studies.

Study	Atropine concentration (%)	Ocular side effects	Systemic side effects	Mean change in SE in one year	Mean change in AL in one year
ATOM2	0.01	Photophobia	nil	0.43±0.52	0.24±0.19
	0.1	Allergic		0.31±0.5	0.13±0.18
	0.5	Conjunctivitis		0.17±0.47	0.11±0.17
Vidya et al.	0.01	nil	nil	0.32±0.29	0.2±0.29
Lutz et al.	0.01	nil	nil	0.22±0.48	NA
Wei et al.	0.01	nil	nil	0.49±0.42	0.32±0.19
Saxena et al.	0.01	nil	nil	0.16±0.4	0.22±0.2

prevented many children traveling to base hospital. There was unavailability of low dose atropine drops in other parts of Nepal. There are factors which have an effect on progression of myopia such as near activity and time spent outdoor. We did not address these issues in our study. Further studies on addressing these issues may be helpful for myopia treatment protocols in Nepalese children.

CONCLUSION

In conclusion we can say that low dose atropine is safe to use and effective in controlling myopia in the Nepalese population. A double blind randomized controlled trial with long term follow-up would be a further addition to this current finding. We hope that the results from this study will contribute to the wide use of atropine therapy in progressive myopia in Nepalese children by eye-care professionals in Nepal. We recommend the concerned authorities to make the drug easily available across the country.

ACKNOWLEDGMENT

We would like to acknowledge Ms. Radhika Uprety and Mr. Pradeep Banjara for their help and support in conducting this study.

REFERENCES

Adhikari S (2013). Myopia in school children from high mountain region of Nepal. Nepalese Journal of Ophthalmology; 25;5(2):246-9. doi: 10.3126/nepjoph.v5i2.8737.

Cheng D, Woo GC, Drobe B, Schmid KL (2014). Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. JAMA ophthalmology;132(3):258-64. doi:10.1001/jamaophthalmol.2013.7623.

Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D (2012). Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). Ophthalmology;119(2):347-54.doi:10.1016/j.ophtha.2011.07.031.

Cho P, Cheung SW (2012). Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Investigative ophthalmology & visual science.1;53(11):7077-85. doi:https://doi.org/10.1167/iovs.12-10565.

Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, Tan D (2006). Atropine for the treatment of childhood myopia. Ophthalmology.;113(12):2285-91. doi:10.1016/j.ophtha.2006.05.062.

Clark TY, Clark RA (2015). Atropine 0.01% eyedrops significantly reduce the progression of childhood myopia. Journal of Ocular Pharmacology and Therapeutics;31(9):541-5. doi:10.1089/jop.2015.0043.

Donovan L, Sankaridurg P, Ho A, Naduvilath T, Smith III EL, Holden BA (2012). Myopia progression rates in urban children wearing single-vision spectacles. Optometry and vision science: official publication of the American Academy of Optometry;89(1):27. doi:10.1097/opx.0b013e3182357f79.

Dragoumis I, Richards A, Alexander P, Poulson A, Snead M. Retinal detachment in severe myopia (2017). The Lancet;390(10090):124. doi:10.1016/s0140-6736(17)31614-8.

Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, Leske MC, Manny R, Marsh-Tootle W, Scheiman M, COMET Group (2003). A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Investigative ophthalmology & visual science;44(4):1492-500. doi:10.1167/iovs.02-0816.

Hayashi K, Ohno-Matsui K, Shimada N, Moriyama M, Kojima A, Hayashi W, Yasuzumi K, Nagaoka N, Saka N, Yoshida T, Tokoro T (2010). Long-term pattern of progression of myopic maculopathy: a natural history study. Ophthalmology;117(8):1595-611. doi:10.1016/j.ophtha.2009.11.003.

Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Naduvilath TJ, Resnikoff S (2016). Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology;123(5):1036-42. doi:10.1016/j.ophtha.2016.01.006.

Huang J, Wen D, Wang Q, McAlinden C, Flitcroft I, Chen H, Saw SM, Chen H, Bao F, Zhao Y, Hu L (2016). Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. Ophthalmology;123(4):697-708. doi:10.1016/j.ophtha.2015.11.010.

Hyman L, Gwiazda J, Hussein M, Norton TT, Wang Y, Marsh-Tootle W, Everett D, COMET Study Group (2005). Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. Archives of ophthalmology;123(7):977-87. doi:10.1001/archopht.123.7.977

Joachimsen L, Böhringer D, Gross NJ, Reich M, Stifter J, Reinhard T, Lagrèze WA (2019). A pilot study on the efficacy and safety of 0.01% atropine in German schoolchildren with progressive myopia. Ophthalmology and therapy;8(3):427-33. doi: 10.1007/s40123-019-0194-6.

Kafle DR (2022). The historical development of settlement by Aryan people in Terai of Nepal. Historical Journal;13(1):1-7. doi:10.3126/hj.v13i1.46211.

Li SM, Liu LR, Li SY, Ji YZ, Fu J, Wang Y, Li H, Zhu BD, Yang Z, Li L, Chen W (2013). Design, methodology and baseline data of a school-based cohort study in Central China: the Anyang Childhood Eye Study. Ophthalmic Epidemiology;20(6):348-59. doi:10.3109/09286586.2013.842596.

Loughman J, Flitcroft DI (2016). The acceptability and visual impact of 0.01% atropine in a Caucasian population. British Journal of Ophthalmology;100(11):1525-9. doi:10.1136/bjophthalmol-2015-307861.

Luong TQ, Shu YH, Modjtahedi BS, Fong DS, Choudry N, Tanaka Y, Nau CL (2020). Racial and ethnic differences in myopia progression in a large, diverse cohort of pediatric patients. Investigative Ophthalmology & Visual Science;61(13):20. doi:10.1167/iovs.61.13.20.

Ma Y, Qu X, Zhu X, Xu X, Zhu J, Sankaridurg P, Lin S, Lu L, Zhao R, Wang L, Shi H (2016). Age-specific prevalence of visual impairment and refractive error in children aged 3–10 years in Shanghai, China. Investigative ophthalmology & visual science;57(14):6188-96. doi:10.1167/iovs.16-20243.

Moon JS, Shin SY (2018). The diluted atropine for inhibition of myopia progression in Korean children. International journal of ophthalmology;11(10):1657. doi: 10.18240/ijo.2018.10.13.

COMET Group (2013). Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). Investigative ophthalmology & visual science;54(13):7871.doi: 10.1167/iovs.13-12403.

Nishiyama Y, Moriyama M, Fukamachi M, Uchida A, Miyaushiro H, Kurata A, Tokoro T, Ohno-Matsui K (2015). Side effects of low dose atropine. Nippon Ganka Gakkai Zasshi;119(11):812-6. PMID: 26685486

Nouraeinejad A (2021). More than fifty percent of the world population will be myopic by 2050. Beyoglu Eye J;6(4):255-6. doi:10.14744/bej.2021.27146.

Morgan IG, Ohno-Matsuik K, Saw SM (2012). Myopia.Lancet;379(9827):60272–60274. doi:10.1016/S0140-6736(12)60272-4

Pan CW, Ramamurthy D, Saw SM (2012). Worldwide prevalence and risk factors for myopia. Ophthalmic and Physiological Optics;32(1):3-16. doi: 10.1111/j.1475-1313.2011.00884.x.

Pokharel A, Pokharel PK, Das H, Adhikari S (2010). The patterns of refractive errors among the school children of rural and urban settings in Nepal. Nepalese Journal of Ophthalmology;2(2):114-20. doi:10.3126/nepjoph.v2i2.3717.

Pokharel GP, Negrel AD, Munoz SR, Ellwein LB (2000). Refractive error study in children: results from Mechi Zone, Nepal. American journal of ophthalmology;129(4):436-44. doi:10.1016/s0002-9394(99)00453-5.

Pokharel R (2011). Politics and problematics of the definition and categorization of ethnicity in Nepal. Bodhi: An Interdisciplinary Journal;5(1):1-5.doi:10.3126/bodhi.v5i1.8042.

Saxena R, Dhiman R, Gupta V, Kumar P, Matalia J, Roy L, Swaminathan M, Phuljhele S, Velpandian T, Sharma N (2021). Atropine for the treatment of childhood myopia in India: multicentric randomized trial. Ophthalmology;128(9):1367-9. doi:10.1016/j.ophtha.2021.01.026.

Vidhya C, Murali K, Sowmya R (2020). Safety and efficacy of reconstituted atropine 0.01% eye drops for Indian children with myopic progression. Asian Journal of Ophthalmology;17(2):209-15. doi: 10.35119/asjoo.v17i2.572.

Wei S, Li SM, An W, Du J, Liang X, Sun Y, Zhang D, Tian J, Wang N (2020). Safety and efficacy of low-dose atropine eyedrops for the treatment of myopia progression in Chinese children: a randomized clinical trial. JAMA ophthalmology;138(11):1178-84. doi:https://doi.org/10.1001/jamaophthalmol.2020.3820.

Wu PC, Yang YH, Fang PC (2011). The long-term results of using low-concentration atropine eye drops for controlling myopia progression in schoolchildren. Journal of ocular pharmacology and therapeutics;27(5):461-6. doi:10.1089/jop.2011.0027

Yam JC, Jiang Y, Tang SM, Law AK, Chan JJ, Wong E, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP (2019). Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Ophthalmology;126(1):113-24. doi:10.1016/j.ophtha.2018.05.029.