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Original Article

Evaluation of the Efficacy and Safety of Atropine Eye Drops 0.01% in Slowing Myopia Progression in Children and Adolescents with High and Low Myopia: A Quasi experimental study

Hannan Masud, Fizzah Batool, Samra Nasir, Sarah Hannan

Department of Ophthalmology, Combined Military Hospital Kharian/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To evaluate the efficacy and safety of Atropine eye drops 0.01% in slowing myopia progression in children and adolescents with high and low myopia.

Study Design: Quasi experimental study.

Place and Duration of Study: Combined Military Hospital, Kharian Pakistan, from Sep 2021 to Jul 2024

Methodology: Seventy-two patients (144 eyes) aged 5-18 years (8.47±3.04 years) with myopia progression (≥0.25mm AL or ≥0.75D SE over 3 months). Participants were stratified by high myopia (HM, AL>26.5mm, SE> -6D) and low myopia (LM, AL<26.5mm, SE< -6D) and randomly assigned to Atropine 0.01% or Control Groups. Double-blinding ensured neither participants nor investigators were aware of Group assignment. Both Groups received treatment for 24 months, with quarterly follow-ups recording AL and SE. The Control Group received placebo eye drops, identical in appearance and administration to the Atropine eye drops. Primary outcome measures included changes in AL and SE from baseline to 24 months, while secondary outcome measures included adverse events and quality of life questionnaires.

Results: In this study, total 144 eyes of 72 patients were included, with 72 eyes in intervention Group (Atropine eye drops 0.01%) and 72 eyes in Control Group (placebo eye drops). Atropine 0.01% eye drops significantly reduced myopia progression in children, with the Atropine Group showing smaller increases in axial length (25.32±1.53 mm vs. 25.80±1.77 mm) and spherical equivalent (-6.29±2.55 D vs. -7.98±3.12 D) compared to the Control Group after 24 months. In contrast, High Myopia and Low Myopia Groups exhibited similar rates of myopia progression, with no significant changes in axial length or spherical equivalent measurements over the same period.

Conclusion: The 0.01% Atropine eye drops effectively slowed myopia progression in both HM and LM Groups, with similar efficacy across different severity ranges.

Keywords: Atropine, Axial length, Myopia progression.

How to Cite This Article: *Masud H, Batool F, Nasir S, Hannan S. Evaluation of the Efficacy and Safety of Atropine Eye Drops 0.01% in Slowing Myopia Progression in Children and Adolescents with High and Low Myopia: A Quasi experimental study. Pak Armed Forces Med J 2025; 75(Suppl-5): S773-S779.DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-5.12439*

INTRODUCTION

Myopia is a significant public health concern, affecting approximately 2.5 billion people worldwide.[1] The prevalence of myopia varies across regions, with high rates found in Asians (21.6%),[2] Americans (25-42%),[3] Europeans (up to 30-40%),[4] and Pakistanis (36.5%).[5] A more recent study in Pakistani university students reported a prevalence of 53.8% for low myopia and 6.0% for high myopia.[6] The prevalence of pathologic myopia ranges from 0.2% to 1.4% in Asian populations and 0.1% to 0.5% in European populations.[7]

Myopia is classified into three categories based on refractive error and axial length: low myopia, high myopia, and pathologic myopia. Low myopia is defined as a refractive error less than 6.00 diopters and an axial length less than 26.5mm. High myopia is characterized by a refractive error greater than 6.00 diopters and an axial length exceeding 26.5mm. Pathologic myopia, the most severe form, is marked by the presence of myopic maculopathy, posterior staphyloma, retinal detachment, myopic choroidal neovascularization, and glaucoma, in addition to the features of high myopia. This classification system helps determine the severity and potential complications of myopia, guiding treatment decisions and management strategies. Several strategies have been proposed to reduce myopia progression, including glasses, contact lenses, Atropine eye drops, increased outdoor activities, reduced near work, and limited screen time. Among these, Atropine is the only medication currently used in clinical practice to slow myopia progression.[8] The typical regimen involves one drop of 0.01% Atropine in both eyes at night for one to two years, typically in children between 5 and 15 years old.[8] Studies such as CHAMPS,4 LAMP 2,8

Correspondence: Dr Hannan Masud, Department of Ophthalmology, Combined Military Hospital, Kharian Pakistan

Received: 09 Jul 2024; revision received: 23 Jul 2024; accepted: 02 Jan 2025

and ATOM,[2,9] have consistently demonstrated the dose-dependent efficacy of Atropine in slowing myopia progression. Research suggests that Atropine's mechanism of action involves inhibiting the growth of scleral or retinal tissue, rather than alleviating accommodative spasm.

Our research team has conducted a two-phase study to investigate the efficacy and safety of 0.01% Atropine eye drops in slowing myopia progression. In Phase 1 (March 2017 to July 2018), we conducted a quasi-experimental study and found that Atropine equally slowed myopia progression in both high and low myopes (p<0.05).[10] Building on these findings, we designed a Phase 2 to further evaluate the treatment's efficacy and safety in intervention and Control Groups, as well as in high and low myopia subGroups.

METHODOLOGY

The Quasi experimental study was conducted at Combined Military Hospital Kharian, Pakistan from September 2021 to July 2024. This study was started after taking approval from the Institutional Ethics Committee (A/24/101). Patients were informed about the study and written informed consent was recorded. Based on the results of our phase 1 trial, research question was refined as; "Does Atropine eye drop 0.01% slow myopia progression in high and low myopes compared to a Control Group?"10 Sample size was calculated using WHO sample size calculator, taking the significance at 0.05, and mean value of Spherical Equivalent in High myopia Group 12.40±3.55 and in low myopia Group 4.99±0.68 from the reference study. Our calculated sample size was much low, however we took 72 patients in each study Group for better generalizability of our results.[10]

Inclusion Criteria: Both genders, with age 5 to 18 years, showing progression of 0.25mm in axial length or 0.75 diopter increase in refractive error over a period of 3 months were included.

Exclusion Criteria: Patients with corneal opacity, keratoconus, lenticular opacity, macular disease, trauma or previous surgery were excluded from the study.

Patient's complete ophthalmic examination included uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), pinhole, cycloplegic refraction with Auto Ref-keratometery and slit lamp examination. Case Report Forms were created to record patients data, demographic information, outcome measures like spherical equivalent (SE) and axial length (AL), using PACSCAN 300A. Quality of life questionnaires were used to assess the impact of myopia and treatment on patients' daily lives, visual functioning, adverse events and overall well-being.

Patients were randomly assigned to either Atropine eye drops 0.01% Group or Control Group (placebo eye drops). Groups were assigned to ensured by equal distribution of high and low myopes in both Groups (Figure).

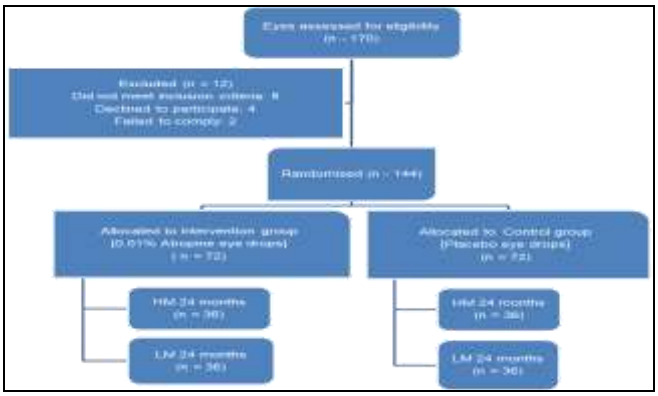

Figure: Consolidated Standards of Reporting Trials, CONSORT) of the Study

Abbreviations: 0.01% Atropine eye drops, Intervention Group that received 0.01% Atropine eye drops for 24 months; Placebo eye drops, Control Group that received placebo for 24 months; HM, High myope subGroup; LM, Low myope subGroup)

Double-blinding technique was used and neither participants nor investigators were aware of Group assignments. Placebo eye drops were identical in appearance and administration to the Atropine eye drops. Both Groups were treated simultaneously for 24 months. Primary outcome measures included changes in AL and SE from baseline to 24 months and secondary outcome measures included adverse events and quality of life questionnaires.

Atropine eye drops 0.01% were prepared by adding 0.1ml of 1% Atropine eye drops in 10ml of blink fresh eye drop by a single researcher to exclude bias. Method of instillation was explained to all patients and their parents, to instill one drop of 0.01% Atropine eye drop at bed time and then occlude the punctum for 2 minutes. Quarterly follow-ups were carried out and UCVA, BCVA, AL, SE, adverse events and quality of life questionnaires were recorded. The results compared AL, SE, adverse events and quality of life questionnaires, at presentation and 24 months of

treatment, in intervention and Control Groups and in high and low myopes,

Statistical analysis was carried out with the help of Statistical Program for Social Sciences (SPSS 20.0). Outcome analysis compared mean changes in AL and SE between the intervention and Control Groups and subGroup analysis explored outcomes in low and high myopes to identify potential differences by using independent sample t-test. We took the significance level at $p \leq 0.05$. Safety analysis evaluated adverse events and assessed the safety of the intervention.

RESULTS

In this study, total 144 eyes of 72 patients were included, with 72 eyes in intervention Group (Atropine eye drops 0.01%) and 72 eyes in Control Group (placebo eye drops). Children between 5 to 18 years of age were included in both Groups with equal distribution of high and low myopes. Normality of data was analysed and found satisfactory. Mean age was 8.47±3.04 years in intervention Group and 8.41±2.43 years in Control Group. Gender distribution was 50(69.44%) males and 22(30.55%) females in intervention Group while 42(58.33%) males and 30(41.66%) females in Control Group. Statistical analysis of SE and AL at baseline and 24 months of treatment in Control and Intervention Groups is given in Table-I.

Table-I: Comparison of Axial Length and Spherical Equivalent at Baseline and 24 Months of Treatment in Atropine versus Control Groups (n=144)

Parameters	Study Groups		*p*-value
	Atropine Group (n=72)	Control Group (n=72)	
Axial Length at Baseline (Mean±SD)	25.24±1.45	25.24±1.69	0.989
Axial Length at 24 months (Mean±SD)	25.32±1.53	25.89±1.77	0.087
Spherical Equivalent at Baseline(Mean±SD)	-5.84±1.53	-6.30±1.07	0.328
Spherical Equivalent at 24 Months	-6.29±2.55	-7.98 ±3.12	0.001

The results of this study showed that there were no significant differences in axial length (AL) and spherical equivalent (SE) measurements between the Atropine and Control Groups at baseline as shown in the Table-I. However, significant differences emerged after 24 months. The Control Group demonstrated a significant increase in AL (25.80±1.77 mm) compared to the Atropine Group (25.32±1.53 mm; $p<0.05$), with a corresponding change in AL from baseline to 24 months of 0.56±0.24 mm in the Control Group versus 0.08±0.24 mm in the Atropine Group ($p<0.05$).

Similarly, SE measurements revealed a significant increase in myopia in the Control Group (7.98±3.12 D) compared to the Atropine Group (-6.29±2.55 D; $p<0.05$) at 24 months. The change in SE from baseline to 24 months was also significantly greater in the Control Group (-1.68±3.09 D) than in the Atropine Group (-0.45±0.71 D; $p<0.05$). These findings suggest that Atropine 0.01% eye drops effectively slow down myopia progression in children. Another comparative analysis of axial length (AL) and spherical equivalent (SE) measurements was conducted between the High Myopia (HM) and Low Myopia (LM) Groups. At baseline, significant differences were observed between the two Groups, with the HM Group exhibiting longer AL (26.67±0.56 mm) and more severe myopia (-8.34±2.18D) compared to the LM Group (AL: 23.81±0.90 mm; SE: -3.80±0.92D). After 24 months, the AL measurements remained relatively stable in both Groups, with no significant changes observed ($p>0.05$). The HM Group demonstrated a minimal increase in AL (0.32±0.29 mm), while the LM Group showed a similar increase (0.31±0.96 mm). Similarly, SE measurements revealed no significant changes in either Group ($p>0.05$), with the HM Group exhibiting a modest increase in myopia (-1.12±0.29 D) and the LM Group showing a comparable change (-1.01±0.96 D). At 24 months, the mean AL measurements were 26.99±0.70 mm for the HM Group and 24.12±0.96 mm for the LM Group. Correspondingly, the mean SE measurements were -9.46±2.41 D for the HM Group and -4.81±1.00 D for the LM Group. These findings suggest that both Groups experienced similar rates of myopia progression over the 24-month period, with no significant differences observed between the HM and LM Groups (Table-II).

Table-II: Comparison of Axial Length and Spherical Equivalent at Baseline and 24 Months of Treatment in High versus Low Myopia Study Groups (n=144)

Parameters	Groups based upon Myopia		*p*-value
	High Myopia Group (n=72)	Low Myopia Group (n=72)	
Axial Length at Baseline (Mean±SD)	26.67±0.56	23.81±0.30	<0.001
Axial Length at 24 months (Mean±SD)	26.99±0.70	24.12±0.96	<0.001
Spherical Equivalent at Baseline(mean±SD)	-8.34±2.18	-3.80±0.92	<0.001
Spherical Equivalent at 24 Months	-9.46±2.41	-4.81 ±1.00	<0.001

Table-III: Comparison of our Findings with International Studies on the Effect of 0.01% Atropine eye Drops on Axial Length and Spherical Equivalent.

Study	Year	Country	Study design	Dose and Intervention period	Age at Baseline, Mean (SD) years	AL at Baseline mm, Mean (SD) atropine Group	AL change in mm compared to Placebo	*p*-value	SE at Baseline, Mean (SD) atropine Group	SE change in D compared to Placebo	Side effect
Repka et al	2023	USA	RCT	0.01% for 24 months	10.1±1.8	24.4±0.8	-0.002 (95% CI: -0.11; 0.10)	Not reported	-2.83±1.17	-0.82 D	87%
Zadnik et al (CHAMP-study)	2023	USA	RCT	0.01% for 36 months	9.0±2.1	24.37±0.81	-0.12 (95% CI: -0.06; -0.18)	<0.01	-2.41±1.17	0.24 D	59.8%
Loughman et al. (MOSAIC-study)	2023	Ireland	RCT	0.01% for 24 months	11.84±2.47	24.85±1.02	-0.072 (95% CI: -0.01;-0.13)	0.007		0.10 D	0%
Lee et al. (WA-ATOM-study)	2022	Australia	RCT	0.01% for 24 months	11.2±2.7	24.60±0.45	-0.05 (95% CI: 0.01; -0.11)	0.1			6%
Hansen et al. (APP-study)	2023	Denmark	RCT	0.01% for 12 months	9.4±1.7	24.60±0.84	-0.07 (95% CI: -0.00;-0.15)	0.16	-2.99±0.27	0.12	16%
Sacchi et al.	2019	Italy	Retrospective	0.01% for 24 months	5-16	N/A	N/A	N/A	-3.0±0.50	-0.54	10%
Kaymak et al.	2021	Germany	Retrospective	0.01% for 12 months	3-15	24.82	Inhibition of 0.08mm/year	<0.00001	-4.21	N/A	17%
Perez-Flores et al.	2021	Spain	Prospective	0.01% for 12 months	6-14	24.57	0.27 mm	<0.00001	-4.00±2.00, progression ≥0.5D/year	-0.44	6%
Myles et al.	2021	Australia	Prospective	0.01% for 60 months	2-18	N/A	0.098 / 0.265	<0.01	-0.25	-0.07 D / -0.25 D	69%
Polling et al.	2016	Netherlands	Prospective	0.5% for 12 months	3-17	25.19	0.35	<0.05	-6.60±3.0, progression ≥1.0 D/year	0.1	83%
Polling et al.	2020	Netherlands	Prospective	0.5% for 36 months	5-16	25.14	0.1	<0.05	-5.03; progression ≥1.0 D/year	-0.3	N/A
Diaz-Llopis et al.	2018	Spain	RCT	0.01% for 60 months	9-12	N/A	N/A	----	-1.1, progression <1.5 D/year	-0.7	5%
Moriche-Carretero et al.	2021	Spain	RCT	0.01% for 24 months	5-11	24.24	0.20	<0.001	-2.15: progression ≤1.5 D/year	-0.51	0
Lee et al.	2022	Australia	RCT	0.01% for 24 months	6-16	24.6	0.34	------	-3.13: progression ≥0.5 D/year	-0.64	-----

DISCUSSION

Although numerous studies have investigated the efficacy of various Atropine eye drop concentrations and treatment durations in slowing myopia progression, a significant knowledge gap remains regarding its outcome in high and low myopia subGroups. Our phase 1 trial aimed to address this gap by evaluating the efficacy of 0.01% Atropine eye drops in treating HM and LM.[10] The results of our phase 2 trial revealed that Atropine 0.01% eye drops significantly reduced myopia progression in children, with the Atropine Group showing smaller increases in axial length (25.32 mm vs. 25.80 mm) and spherical equivalent (-6.29 D vs. -7.98 D) compared to the Control Group after 24 months. In contrast, HM and LM sub-Groups exhibited similar rates of myopia progression, with no significant changes in axial length or spherical equivalent measurements over the

same period. This suggests that Atropine's efficacy is not dependent on the initial severity of myopia, providing a promising therapeutic option for individuals with varying degrees of myopia. The comparable reduction in myopia progression observed in both HM and LM Groups underscores the potential benefits of Atropine treatment in preventing or delaying the onset of high myopia and its associated complications. Overall, these findings support the use of Atropine as an effective and equitable treatment for slowing myopia progression in children, regardless of initial myopia severity. A comparison of our findings with International Studies on the effect of 0.01% Atropine eye drops on AL and SE is presented in Table III, highlighting the consistency of our results with global research.

Recently, two significant studies have corroborated our findings on the efficacy of 0.01% Atropine eye drops in slowing myopia progression. Repka *et al*., (2023) conducted a two-year study in the USA, reporting a significantly reduced AL progression of 0.002 mm in the Atropine Group compared to placebo.[11] Moreover, Zadnik *et al*.,'s phase 3 CHAMP study (2017-2022), spanning the USA and five European countries, demonstrated statistically significant improvements in the low-dose Atropine Group at 36 months. Specifically, they found slower SE progression (mean difference: 0.24 D, $p<0.001$) and slower AL elongation (mean difference: -0.13 mm, $p<0.001$).[12] These studies reinforce our findings, solidifying the evidence for 0.01% Atropine eye drops as an effective treatment for myopia progression. Further supporting our findings, two recent studies have investigated the efficacy of 0.01% Atropine eye drops in slowing myopia progression in pediatric populations. Loughman *et al*., MOSAIC study (2023) in Ireland reported a statistically significant reduction in AL elongation of 0.07 mm at two-year follow-up in White children.[13] Additionally, Lee *et al*., studies (RCT 2020 and WA-ATOM study 2022) in Australia found a modest effect of 0.01% Atropine eye drops on myopia progression in multi-racial Australian children. While a statistically significant difference in SE and AL was observed between the Atropine and placebo Groups at 6, 12, and 18 months, this difference was not sustained at 24 months. These studies reinforce the evidence for 0.01% Atropine eye drops as a viable treatment option for myopia progression in children. After one year of treatment, the Atropine Group showed a significantly smaller increase in SE and AL compared to the placebo Group, with mean changes from baseline of -0.31 D and 0.16 mm versus -0.53 D and 0.25 mm, respectively ($p<0.01$). However, this significant difference was not sustained after two years of treatment, with mean SE and AL changes from baseline of -0.64 D and 0.34 mm in the Atropine Group, and -0.78 D and 0.38 mm in the placebo Group ($p=0.10$). This resulted in a non-significant reduction of 0.05 mm in axial elongation at the two-year follow-up, suggesting that the treatment effect may have diminished over time.[14-16] Three Spanish studies have demonstrated the efficacy of Atropine eye drops in slowing myopia progression. Moriche-Carretero *et al*., 2-year RCT study (2021) found significant differences between the Atropine treatment Group and Control Group, with SE changing by -0.51 D vs. -0.76 D ($p<0.001$) and AL increasing by 0.20 mm vs. 0.37 mm ($p<0.001$) at the 2-year follow-up.[17] Similarly, Diaz-Llopis *et al*., 5-year RCT study (2018) showed a significantly lower annual myopia progression rate in the 0.01% Atropine Group (-0.14 D) compared to the Control Group (-0.65 D). Notably, the study found a three-fold increase in myopia progression (-0.43 D per year) in the 18 children who discontinued Atropine treatment after 2 years, highlighting the importance of continued treatment to maintain efficacy.[18] Perez-Flores *et al*., multicenter GTAM study (2022) in Spain assessed the efficacy of 0.01% Atropine eye drops over one year, reporting a mean SE progression of -0.44 D ($p<0.001$) and a mean AL change of 0.27 mm. While this study lacked a Control Group, the results suggest a significant slowing of myopia progression, consistent with previous findings.[19] A retrospective study by Myles *et al*., (2021) in Australia found a significant decrease in SE progression, ranging from -0.07 D to -0.25 D per year ($p=0.03$), and a significant slowing of AL progression, with a mean reduction of 0.098 mm/year compared to untreated myopes ($p<0.001$).27 Similarly, Sacchi *et al*., analysis (2019) of medical records in Italy showed a significantly lower mean myopia progression rate in the 0.01% Atropine Group (-0.54 D) compared to the Control Group (-1.09 D) after 12 months ($p<0.001$).20 Kaymak *et al*., retrospective analysis (2021) in Germany found a significant reduction in AL growth rate, with a mean decrease of 0.08 mm/year over one year ($p<0.0015$), providing additional evidence for the treatment's effectiveness in slowing myopia progression.[21] The Low-Concentration Atropine for Myopia Progression (LAMP) study, published by Yam *et al*., in 2022, investigated the effects of continued versus stopped 0.01% Atropine treatment on myopia progression in

Chinese children. The results showed that the Group that stopped Atropine treatment had a significantly faster SE progression (0.56 vs 0.38 D, p=0.04) and AL elongation (0.29 vs 0.24 mm, p=0.13) compared to the continued treatment Group.[19] Over three years, the continued Atropine Group had a slower SE progression (1.60 vs 1.81 D, p<0.001) and AL elongation (0.89 vs 0.98 mm, p<0.001), highlighting the importance of sustained treatment to maintain efficacy.[8,22,23] Our findings are consistent with a recent study conducted in Pakistan by Saleem et al. (2022), which also investigated the effect of 0.01% Atropine eye drops on myopia progression in children. In their study, 100 children were treated with 0.01% Atropine eye drops for 12 months, and the results showed a significant change in SE from -3.25±1.37 D at baseline to -3.74±1.34 D at 12 months.[24] Our study demonstrated the safety and tolerability of 0.01% Atropine eye drops over a 24-month treatment period, with no adverse events reported in both HM and LM subGroups, which is comparable to other studies.[25] Additionally, quality of life questionnaires revealed that Atropine treatment had a negligible impact on daily life and vision-related functioning; indicating that the treatment not only effectively slowed myopia progression but also preserved the patients' overall well-being. These findings suggest that 0.01% Atropine eye drops are a safe and effective treatment option for myopia management, without compromising quality of life.

LIMITATIONS OF STUDY

Study limitation include limited number of patients in subGroups and very limited data of myopia progression in wash out period after stopping Atropine eye drops treatment.

CONCLUSION

0.01% Atropine eye drops effectively slowed myopia progression in both HM and LM Groups, with similar efficacy across different severity ranges.

Conflict of Interest: None.

Funding Source:

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HM & FB: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SN & SH: Data acquisition, data analysis, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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