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Research Article

Comparative Evaluation of 0.1% and 0.01% Topical Atropine Eyedrops in Myopic Children

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Abstract

Aim: To compare effects of 0.1% and 0.01% topical atropine eyedrops in myopic children.

Methods : This prospective randomized study was conducted on 80 eyes of 40 myopic children irrespective of age, type of myopia and amount of spherical equivalent correction. 40 eyes were subjected to 0.1% (Group A) and 40 to 0.01% (Group B) topical atropine once at night. Follow-up was done at 3 months,6 months, 1 and 2 years. The effect of atropine on mean change in spherical equivalent, axial length, pupil diameter, keratometry and intra ocular pressure was recorded and compared between two groups. Any adverse effect as well as drop in near vision due to atropine was also noted.

Results: Mean age group studied in two groups was 10.5 years (range 5-13 years). The mean change in spherical equivalent after 2 years of atropine therapy was -0.35 ± 0.93 D in group A and -0.04 ± 0.57 D in group B ($p < 0.05$), the mean change in axial length was 0.27 ± 0.38 mm in group A and 0.05 ± 0.30 mm in group B ($p > 0.05$) and the mean change in pupil diameter was 1.05 ± 0.36 in group A and 0.84 ± 0.14 in group B ($p < 0.05$). 11 (55%) patients of group A and 6 (30%) patients of group B had difficulty while reading. However no statistical significant change was found in intraocular pressure and keratometric readings.

Conclusion: Both 0.1% and 0.01% topical atropine have comparable role in stabilization of myopia over 2 years. However, fewer visual side effects were noted with 0.01% atropine vs 0.1% atropine.

Keywords: Atropine; Children; Myopia; Spherical Equivalent

Introduction

Myopia has been recognized worldwide as one of the most compelling ocular diseases by the World Health Organization's Global Initiative for the Elimination of Avoidable Blindness [1]. Its prevalence has reached its peak of 80-90% among school going children in Asia [2]. The Cochrane database review has assessed and found the role of atropine in control of progression of myopia [3]. Atropine is muscarinic acetylcholine receptor antagonist which has long been used for pupil dilatation and amblyopia therapy as 1% topical solution or ointment. The postulated mechanism is direct effect of atropine on scleral fibroblasts by inhibiting the glycosaminoglycans synthesis and thereby inhibiting stretching of sclera [4]. It causes a potential biochemical change by binding to muscarinic receptors which may be responsible for myopic transformation [5]. However, the exact mechanism of atropine action in myopia progression is still unknown.

Material and Methods

A prospective randomized study was conducted on 40 myopic children (80 eyes) visiting a tertiary care centre in northern India

after taking due approval from Ethics committee (Institutional Review Board) in adherence with Declaration of Helsinki. Patients suffering from any corneal disease like keratoconus, retinal pathology, associated strabismus and known hypersensitivity to atropine were excluded from the study. Best corrected visual acuity was estimated after cycloplegic refraction and corrective concave glasses were prescribed to patients. They were then randomly divided in two groups of 20 each. Group A (40 eyes) was subjected to 0.1% atropine eye drops and Group B (40 eyes) was subjected to 0.01% atropine eye drops once at nighttime daily. Follow up was done at 3months, 6 months, at 1 year and 2 years.

Initial and each visit outcome measurements included visual acuity status, automated refraction (using automated refractor; URK-700, Daejeon, Korea); spherical equivalent, axial length (ultrasonic A-Scan; Appascan AME-01A, Chennai, India); keratometry (Pentacam HR; Oculus, Wetzler, Germany); IOP (Non contact tonometer; Takamatsushi, Kagawa, Japan) and pupil size (Pentacam HR Oculus, Wetzler, Germany).

The data was statistically analysed using SPSS V.17 (SPSS, IBM Corporation, Chicago, Illinois, USA). Paired sample 't' test was used to evaluate change in mean spherical equivalent, mean pupil diameter, mean keratometry, mean IOP and mean axial length as compared to baseline. Wilcoxon Signed rank test was done to evaluate change in near vision as compare to baseline. The values were determined to evaluate the level of significance. p value of>0.05 was considered non-significant; p value of <0.05 was considered significant however p value <0.001 was considered highly significant.

Observations and results

80 eyes of 40 children were enrolled in the study and their data was analysed**.** Of the 40 children, 12 (60%) patients of group A and 9 (45%) of group B were males whereas 8 (40%) of group A and 11 (55%) of group B were females. The mean age of patients in group A was 10.15 ± 1.34 and in group B was 10.6 ± 1.81.

The un-corrected visual acuity (UCVA) in 18 (45%) eyes of group A and 16 (40%) of group B was -1 LogMAR (6/60 Snellen equivalent); 12 (30%) eyes of group A and 13 (32.5%) of group B was -0.78 LogMAR (6/36 Snellen equivalent). Rest all the eyes in both groups had UCVA better than -0.78 LogMAR. 26 (65%) eyes in group A and 29 (72.5%) of group B attained best corrected visual acuity (BCVA)of 0 LogMAR (6/6 Snellen equivalent) whereas 13 (32.5%) eyes of group A and 11 (27.5%) eyes of group B had -0.18 LogMAR (6/9 Snellen equivalent).

In present study, 7 (17.5%) eyes of group A and 7 (17.5%)eyes of group B had spherical equivalent less than -1D; 14 (35%) eyes of group A and 22 (55%) eyes of group B had spherical equivalent between -1 D and -3D; 19 (47.5%) eyes of group A and 11 (27.5%) eyes of group B had spherical equivalent between -3 and -6D. The distribution of spherical equivalent between both the groups was not statistically significant (p > 0.05).

	Group A	Group B	Chi-square value	p value
Males	12(60%)	9 (45%)	0.902	0.342; Not Significant
Females	8 (40%)	11 (55%)		
Mean age at presentation	10.15 ± 1.34years	10.6 ± 1.81years	't' = 1.274	0.207; Not significant
Distribution of UCVA				
-1 LogMAR (6/60 snellen equivalent)	18 (45%)	16 (40%)	6.443	0.265;Not significant
-0.78 LogMAR (6/36)	12 (30%)	13 (32.5%)		
-0.6 LogMAR (6/24)	2 (5%)	6 (15%)		
-0.5 LogMAR (6/18)	1 (2.5%)	3 (7.5%)		
-0.3 LogMAR (6/12)	2 (5%)	0(0%)		
-0.18 LogMAR (6/9)	5 (12.5%)	2 (5%)		
Distribution of BCVA				
0 LogMAR (6/6 snellen equivqlent)	26 (65%)	29 (72.5%)	1.330	0.514; Not significant
-0.18 LogMAR (6/9)	14 (32.5%)	11 (27.5%)		
-0.3 LogMAR (6/12)	1 (2.5%)	0		
Distribution of Spherical equivalent				
Less than-1D	7 (17.5%)	7 (17.50%)	3.911	0.141; Not significant
-1 D and -3D	14 (35%)	22 (55%)		
-3 and -6D	19 (47.5%)	11 (27.5%)		

Table 1: Baseline demographic data and distribution of un-corrected , best –corrected visual acuity and spherical equivalents among two groups.

After the start of 0.1% atropine in group A and 0.01% atropine in group B, the mean change in spherical equivalent at 1 year (-0.20 ± 0.26D in group A and 0.06 ± 0.56D in group B) and at 2 years (-0.35 ± 0.93D in group A and 0.04 ± 0.57D in groupB) was found to be stastically significant ($p < 0.05$).

After 2 years of 0.1% atropine mean change in K1 and K2 was 0.23 ± 0.98D and 0.06 ± 0.59D respectively whereas in group B, the mean change in K1 and K2 was 0.07 ± 0.53D K2 and 0.00 ± 0.32D respectively.The change in mean keratometric readings were compared and found to be stastically non significant ($p > 0.05$).

		Group A		GROUP B		t	p-value	95% Confidence Interval of the Difference	
		Mean	SD	Mean	SD			Lower	Upper
Spherical equivalent	a-b	-0.20	0.26	0.06	0.56	2.656	0.010*	-0.453	-0.065
	a-c	-0.35	0.93	0.04	0.57	2.262	0.027*	-0.734	-0.046
	b-c	-0.14	0.87	-0.01	0.08	0.951	0.345	-0.406	0.143
Keratometry K1	a-b	-0.24	0.89	0.07	0.37	1.968	0.053	-0.603	0.003
	a-c	-0.23	0.98	0.07	0.53	1.713	0.091	-0.654	0.049
	b-c	0.01	0.57	0.01	0.53	0.020	0.984	-0.246	0.241
Keratometry K2	a-b	-0.10	0.44	0.08	0.51	1.594	0.115	-0.382	0.042
	a-c	-0.06	0.59	0.00	0.32	0.539	0.592	-0.270	0.155
	b-c	0.04	0.61	-0.08	0.41	0.968	0.336	-0.119	0.344

Table 2: Intergroup comparison of effect of atropine 0.1% (group A) vs 0.01% atropine (Group B) on spherical equivalent and keratometry.

a = baseline, b= after 1 year, c= after 2 years

Unpaired 't' test: *p < 0.05; Significant; **p < 0.001; Highly significant.

The mean change in axial length after 2 years of atropine therapy was 0.27 ± 0.38 in group A and 0.05 ± 0.30 in group B ($p < 0.05$) which was statistically significant.

The mean change in pupil diameter was 1.05 ± 0.36 in group A and 0.84 ± 0.14 in group B after 2 years of atropine therapy which was highly significant ($p < 0.001$).

		Group A		Group B		t	p-value	95% Confidence Interval of the Difference	
		Mean	SD	Mean	SD			Lower	Upper
Axial length	a-b	0.19	0.28	0.05	0.22	2.630	0.010*	0.036	0.259
	a-c	0.27	0.38	0.05	0.30	2.868	0.005*	0.067	0.372
	b-c	0.07	0.26	-0.01	0.18	1.432	0.156	-0.028	0.172
Pupil diameter	a-b	-1.76	0.36	-1.57	0.20	2.938	0.004*	-0.323	-0.062
	a-c	-1.05	0.19	-0.84	0.14	5.666	<0.001**	-0.293	-0.141
	b-c	0.77	0.31	0.63	0.19	0.426	0.043*	-0.141	0.091
IOP	a-b	0.05	2.62	0.75	2.57	1.206	0.231	-1.855	0.455
	a-c	0.38	2.52	-0.08	2.26	0.851	0.398	-0.609	1.519
	b-c	0.33	2.03	-0.83	2.29	2.387	0.625	0.192	2.118

Table 3: Statistically significant change in axial length ($p < 0.05$) ; highly significant change in mean pupil diameter ($p < 0.001$) and non significant change in IOP ($P > 0.05$) after 1 and 2 years of atropine therapy in both groups.

a = baseline, b= after 1 year, c= after 2 year

Unpaired 't' test : *p < 0.05; Significant; **p < 0.001; Highly significant.

There was no significant change in IOP (0.38 ± 2.52 mmHg in group A and -0.08 ± 2.26 mmHg) after 2 years of atropine therapy.

It was observed that there was significant drop in near vision with 0.1% atropine as compare to 0.01% atropine. 27 eyes in group A and 13 eyes in group B had near vision upto N/8 after 3 months of therapy. One eye in group A had drop in near vision even upto N/10.

11(55%) patients of group A and 6(30%) patients of group B had difficulty while reading. Glare was also reported in 11(55%) patients of group A and 5(25%) patients of group B. However no systemic side effects of atropine were observed in any patient.

Time period	No. of eyes	Near Vision				Z value	p value
		N/6	N/8	N/10	N/12		
At baseline	Group A (n = 40)	40	-	-	-	0.000	1.000
	Group B (n = 40)	40	-	-	-		
At 3 months	Group A (n = 40)	12	27	1		3.385	0.001*
	Group B (n = 40)	27	13	-	-		
At 6 months	Group A (n = 40)	13	26	1	-	3.164	0.002*
	Group B (n = 40)	27	13	-	-		
At 1 year	Group A (n = 40)	13	26	1	-	3.164	0.002*
	Group B (n = 40)	27	13	-	-		
At 2 years	Group A (n = 40)	29	11	-	-	3.549	<0.001**
	Group B (n = 40)	40	-	-	-		

Table 4: Significant drop in near vision in group A as compared to group B after 0.1% and 0.01% atropine respectively.
Mann- Whitney Test : *p < 0.05; Significant; **p < 0.001: Highly significant.

Sr. No.	Adverse-effects	Group A		Group B		chi-square value	p-value
		No. of patients (n = 20)	%age	No. of patients (n = 20)	% age		
1	Glare	11	55.0	5	25.0	3.750	0.053
2	Allergic reaction	-	-	-	-	-	-
3	Difficulty in reading	11	55.0	6	30.0	2.558	0.110
4	Constipation	-	-	-	-	-	-
5	Facial redness	-	-	-	-	-	-
6	Anhydrosis	-	-	-	-	-	-
7	Tachycardia	-	-	-	-	-	-
8	Hot dry skin	-	-	-	-	-	-

Table 5: Adverse effects of atropine seen in patients of group A and group B.
Chi-Square Test : p > 0.05; Not significant.

Discussion

The sight threatening conditions particularly associated with high myopia emphasize the requisite of effective treatment that can stop its progression [6]. Pharmacological intervention, particularly atropine has been touted as having higher efficacy than optical therapy in decreasing eventual level of myopia [7,8]. It has apparent benefits in slowing the myopic shift as well as prevention of onset of myopia in high risk children [9].

In the present study, the mean spherical equivalent before start of atropine therapy, in group A and group B was -2.78 ± 1.29D and -2.42 ± 1.63 D respectively. The mean decrease in spherical equivalent after 1 year of atropine therapy was -0.20 ± 0.26D (p < 0.001) in group A and -0.06 ± 0.56D (p > 0.05) in group B whereas after 2 years, it was -0.35 ± 0.93D (p < 0.05) in group A and -0.04 ± 0.57D (p > 0.05) in group B. The results were compared and found to be stastically significant (p < 0.05). In ATOM 2 study, conducted by Chia A [10] *et al.* in 2012, the safety and efficacy of 0.1% atropine was compared with 0.01% and 0.5%.The mean change in spherical equivalent was –0.14 ± 0.51D (p = 0.05) in 0.1% group and -0.13 ±

0.44D (p=0.05) in 0.5% group, which was significant. Clark., *et al*. [11]. also performed a study on 60 school age children in California and reported slowing of myopia progression rate in 0.01% atropine treated eyes (-0.1D ± 0.6D per year) as compared to control eyes (-0.6 ± 0.4D per year, p = 0.001). Another study was conducted in Spain on 400 eyes of 200 children using 0.01% atropine and found the mean annual myopic progression rate of -0.14 ± 0.35D per year as compared to -0.65 ± 0.54D per year in control group over a 5 year follow-up period [12]. Another clinical trial (LAMP study) has reported mean change in spherical equivalent of -0.59 ± 0.61D in 0.01% group as compared to -0.81 ± 0.53D in placebo group (p < 0.001) [13].

The proposed mechanism of atropine in controlling myopia is its direct effect on scleral fibroblasts by inhibiting stretching of sclera and thus retarding axial length progression. In the present study, the mean axial length before start of atropine therapy, in Group A and Group B was 23.73 ± 1.00mm and 23.90 ± 0.93mm respectively. The mean change in axial length after 1 year therapy of 0.1% atropine in Group A was -0.19 ± 0.28mm (p < 0.001) and after 2 years it was -0.27 ± 0.38mm (p < 0.001). The mean change in axial length after 1 year therapy of 0.01% atropine in Group B was -0.05 ± 0.22mm (p < 0.05) and at 2 years was -0.05 ± 0.30mm (p < 0.05) from baseline. The differential change, therefore, in axial length in two groups was found to be significant (p < 0.05) vs at baseline. In ATOM 2 study [10], the mean change in axial length at 12 months was 0.05 ± 0.16mm in 0.1% group and 0.18 ± 0.15mm in 0.01% group which was highly significant (p < 0.001) The current clinical trial (LAMP study) reported mean increase in axial length of 0.36 ± 0.29mm with 0.01% atropine as compared to 0.41 ± 0.22mm in placebo group (p < 0.001) [13].

Atropine is a muscarinic receptor antagonist which has long been used for pupil dilatation as 1% topical solution. In our study the mean pupil diameter before start of atropine therapy, in Group A and Group B was 3.73 ± 0.0.44mm and 3.34 ± 0.51mm respectively (p > 0.05). The mean increase in pupil diameter after 1 year therapy of 0.1% atropine in Group A was 1.76 ± 0.36mm (p < 0.001) and after 2 years it was 1.05 ± 0.19mm (p < 0.001). The mean change in pupil diameter after 1 year therapy of 0.01% atropine in Group B was 1.57 ± 0.20mm (p < 0.001) and after 2 years it was 0.84 ± 0.14mm (p < 0.001).The difference in mean change of pupil diameter in two groups was found to be significant (p < 0.05) at 1 year and highly significant (p < 0.001) at 2 years. In ATOM2 study [10], the change in pupil diameter was found to be 2.6mm in 0.1% group and 1.13 mm in 0.01% group which was found to be highly significant (p < 0.001).

In Group A the mean keratometry k1 and K2 before starting therapy was 43.93 ± 1.42D and 44.49 ± 1.42D respectively. In group B, the baseline mean keratometry k1 and k2 was 44.05 ± 1.89D and 44.47 ± 1.89D respectively. After instillation of 0.1% atropine mean change in K1 was 0.24 ± 0.89D; p > 0.05 (after 1 year) and 0.23 ± 0.98D; p > 0.05 (after 2 years). In group B, the mean change K1 was 0.07 ± 0.37D; p > 0.05 (after 1 year), 0.07 ± 0.53D; p > 0.05 (after 2 years). After instillation of 0.1% atropine mean change in K2 was 0.10 ± 0.44D; p > 0.05 (after 1 year) and 0.06 ± 0.59D; p > 0.05 (after 2 years). In group B, the mean change K2 was 0.08 ± 0.51D; p > 0.05 (after 1 year), 0.00 ± 0.32D; p > 0.05 (after 2 years). The change in mean keratometric readings were compared and found to be stastically non significant (p > 0.05). These results suggest that topical atropine has no effect on corneal curvatural changes and therefore has no role in curvatural myopia. Chia A., *et al.* [14] also conducted a study on 400 myopic in 2009 after which they concluded that atropine eye drops has no effect on astigmatism and corneal curvature.

In our study the mean intraocular pressure before start of atropine therapy, in Group A and Group B was 14.43 ± 1.96 mm Hg and 15.30 ± 2.57 mm Hg respectively. The mean change in intraocular pressure after start of 0.1% atropine in Group A was 0.05 ± 2.62mm Hg; p > 0.05 (after 1 year) and 0.38 ± 2.52 mm Hg ;p > 0.05 (after 2 years). The difference was compared between two groups and was found to be non significant (p > 0.05%). Chia-Yi Lee., *et al.* [15] also conducted a study in Taiwan on 56 children regarding the effect of low dose atropine on IOP. The mean change in IOP after 6 months of 0.125% and 0.25% atropine was 14.19 ± 2.81 and 14.00 ± 2.09 (p = 0.98) respectively which was also non significant.

Atropine is a acetylcholine receptor antagonist and thus induces cycloplegia by paralyzing the ciliary muscles resulting in blurred vision. In our study the baseline near vision (NV) before start of atropine therapy was N/6 in both groups. After 1 year of 0.1% atropine therapy in group A, 13 eyes had N/6, 26 eyes had N/8 and one eye had N/10 near vision whereas after 2 years, 29 eyes had N/6 and 11 had N/8 near vision. In group B, 27 eyes had N/6 and 13 had N/8 near vision after 1 year of 0.01% atropine therapy whereas all patients had N/6 at the end of two years. There was a ten-

dency of difficulty in reading in 0.1% atropine eye drops group vs 0.01% atropine group though statistical significance could not be reached. In ATOM 2 [10] study also, the group ascribed to 0.1% and 0.01% topical atropine had significant ($p < 0.001$) decrease in accommodation at their first follow-up (after 24 months of therapy) as compared to baseline. A study conducted by Kennedy., *et al.* [16] on 214 residents of Minnesota who received atropine for myopia also reported blurred near vision in 23% of patients as main adverse- effect of atropine.

In our study, glare was encountered by 11(55%) patients of group A and 5 (25%) patients of group B. 11 (55%) patients of group A and 6 (30%) patients of group B had difficulty in reading. However no systemic side effects including constipation, facial redness, anhydrosis, tachycardia, hot dry skin were reported in either group. Kennedy., *et al.* [16] study on 214 residents of Minnesota who received atropine for myopia also reported photophobia in 40.2% and blurred near vision in 23% of patients as main adverse-effects of the atropine. Another study conducted by Polling., *et al.* [12] in 76 children of myopia subjected to 0.5% topical atropine eye drops also reported side effects like photophobia in 78%, reading problems in 38% and headaches in 22% of the patients.

Their were a few limitations in our study including lack of age and refractive error matched control group who didn't receive any pharmacotherapy, a small sample size and lack of long term data on efficacy and safety beyond two years. Another limitation was absence of cases of pathological myopia in both the study groups. Future studies should include a large number of patients and follow them up over a long time frame to fully ascertain therapeutic benefits of atropine eye drops in altering natural history of myopia progression.

Conclusion

Both 0.1% and 0.01% topical atropine have comparable efficacy in stabilization and halting myopia progression over short time period of two years. Lower dose 0.01% atropine eyedrop is associated with fewer side effects as compared to higher dose 0.1% eyedrops.

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