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The effects of medication on intraocular pressure in children with attention deficit hyperactivity disorder: A prospective study

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions in childhood. Psychopharmacological therapy is an effective treatment for ADHD. In this study, we primarily aim to investigate the effects of psychopharmacological agents on intraocular pressure (IOP) in children with ADHD. The sample included 82 children with ADHD and 36 healthy children aged between 8 and 12 years who were referred to the Department of Child and Adolescent Psychiatry in Hatay State Hospital, Hatay, Turkey. Children with ADHD were divided into two groups according to the medication used: methylphenidate (MPH) group and atomoxetine (ATX) group. Before treatment and after 1- and 6-month treatment period, IOP was measured by Goldmann applanation tonometry. There were no statistical differences in terms of age, gender, and IOP between the three groups ($P > 0.05$). After 1- and 6-month treatment, the IOP did not change significantly between baseline and 1 month or 6 months ($P > 0.05$). Children with ADHD may have an IOP similar to healthy children. Six-month treatment with MPH or ATX may not cause significant changes in IOP.

Keywords: *attention deficit hyperactivity disorder, methylphenidate, atomoxetine, intraocular pressure, glaucoma*

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impairments in attention, hyperactivity, and impulsivity. It is a worldwide common condition and the estimated prevalence in children is 5–10%, and in adults, prevalence is 4%.[1] ADHD is suggested to be caused by disturbances of neurotransmitters such as dopamine and noradrenaline in the prefrontal cortex. Psychopharmacological medication is an effective treatment of ADHD to correct this disturbance.[2]

Methylphenidate (MPH) is a central nervous system (CNS) stimulant and is generally the first option for treating ADHD. MPH inhibits the re-uptake of dopamine and noradrenaline in the synaptic cleft. The side effects of MPH are well known and usually reported as headache, stomachache, insomnia, anorexia, and weight loss.[3]

Atomoxetine (ATX) is a nonstimulant medication for the treatment of ADHD. The mechanism of action of ATX is unclear, but it is thought to be a selective noradrenaline re-uptake inhibitor of the prefrontal cortex.[4] Although ATX is commonly well tolerated in pediatric population, adverse effects include headache, stomachache, anorexia, somnolence, nausea, and vomiting.[5]

In addition, some ocular side effects such as accommodation problems, mydriasis, cataract, increase in intraocular pressure (IOP), and glaucoma have been reported due to these medications.[1,5–8] Owing to its mechanism of action, MPH may cause closure of the angle and increase IOP; hence, precautions of its usage in patients with angle-closure glaucoma are needed. However, these potential ocular side effects are limited as case reports and have not been studied in pediatric age groups. In this study, we aim to compare the IOP in ADHD children with healthy controls and investigate the effects of MPH and ATX usage on IOP. Our hypothesis is that there is no significant difference in IOP in children with ADHD and healthy children. On the other hand, we hypothesize that medications used for ADHD could increase IOP in ADHD children.

METHODS

Sample

A total of 102 drug-naïve children aged between 8 and 12 years, who were referred to the Department of Child and Adolescent Psychiatry in Hatay StateHospital, Hatay, Turkey between January 2019 and June 2019, was included in the study.

The inclusion criteria of the patient group were as follows: (1) An age range of 8–12 years; (2) ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (3) not presenting a psychiatric disorder other than ADHD; (4) not presenting a chronic physical disease; and (5) not using any psychiatric medications before enrolling in the study.

For the control group, the following inclusion criteria were used: (1) An age range of 8–12 years; (2) not presenting a psychiatric disorder according to DSM-5; (3) not presenting a chronic physical disease; (4) not using any psychiatric medications before the study.

The control group included healthy children without any physical and mental illness who were referred to the child and adolescent psychiatry clinic. These children were provided admission for counseling purposes, for example, sibling birth, school preference, and friendship problems.

For both patient and control groups, children with chronic physical illness, ocular abnormality, mental retardation, autism spectrum disorders, motor or visual problems were excluded from the study. Eighty-two children with ADHD and 36 healthy children fulfilled the study conditions and participated in the study.

Procedure

At the child and adolescent psychiatry clinic, a detailed psychiatric examination was performed on all children by an experienced child and

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adolescent psychiatry specialist. Duration of the psychiatric examination was 45 min. After psychiatric evaluation, the children were referred to the ophthalmology clinic of World Eye Hospital, Adana, Turkey. IOP was measured twice by an experienced ophthalmologist using Goldmann applanation tonometry at 9.00 am, and a mean value was considered for both eyes.

Children with ADHD were divided into two groups according to the medication used: MPH group and ATX group. The dosage of MPH titrated up to 1 mg/kg/day and that of ATX up to 1.2 mg/kg/day based on clinical response and tolerability. The total daily dose of MPH was not to exceed 60 mg/day and that of ATX 80 mg/day. MPH and ATX were administered as a single morning dose.

After 1- and 6-month treatment period, ADHD children were referred to the ophthalmology clinic of World Eye Hospital. IOP of children was again measured and noted by the same ophthalmologist.

This research was carried out in accordance with the Declaration of Helsinki; the nature and purpose of the study were explained to all children and parents, and informant consent was obtained in all cases. The Ethics Committee of Adana City Hospital approved the study protocol. The approval number was 2018/451.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences, SPSS for IBM, 21.0 program. Demographic variables and general characteristics of the patients were presented by using descriptive statistics. The distribution of variables was assessed using the Kolmogorov–Smirnov test. Analysis of variance (ANOVA) and paired sample t-test were used to compare normally distributed parametric variables. Chi-square test was used for the comparison of normally distributed categorical variables. The $P < 0.05$ was accepted to be statistically significant.

RESULTS

The data were obtained from the measurements of 164 eyes of 82 children with ADHD and 72 eyes of 36 healthy controls. The mean age was 10.1 ± 1.8 years in the MPH group, 10.0 ± 1.8 years in the ATX group, and 10.2 ± 1.6 years in the control group. In the MPH group, proportion of boys was 66.7% ($N = 28$) and that of girls was 33.3% ($N = 14$). In the ATX group, proportion of boys was 62.5% ($N = 25$) and that of girls was 37.5% ($N = 15$). In the control group, proportion of boys was 63.8% ($N = 23$) and that of girls was 36.2% ($N = 23$). When the groups were examined in terms of IOP, mean values of IOP were 14.2 ± 1.6 mmHg (right eye) and 14.6 ± 1.6 mmHg (left eye) in the MPH group; 14.0 ± 1.6 mmHg (right eye) and 14.1 ± 1.7 mmHg (left eye) in the ATX group; and 15.0 ± 2.0 mmHg (right eye) and 14.9 ± 2.0 mmHg (left eye) in the control group. There were no statistical differences in terms of age, gender, and IOP between the three groups ($P > 0.05$) (Table 1).

Table 2 shows IOP in ADHD children before and after the treatment. After 1- and 6-month treatment, the mean IOP was 14.5 ± 1.6 mmHg in the right eye and 14.7 ± 1.6 mmHg in the left eye; 15.0 ± 1.7 mmHg in the right eye and 15.0 ± 1.6 mmHg in the left eye, respectively, in the MPH group. After 1- and 6-month treatment, the mean IOP was 14.1 ± 1.6 mmHg in the right eye and 14.2 ± 1.7 mmHg in the left eye; 14.3 ± 1.6 mmHg in the right eye and 14.3 ± 1.7 mmHg in the left eye , respectively, in ATX group. IOP did not change significantly between baseline and 1 month or 6 months ($P > 0.05$).

DISCUSSION

Findings and Comparisons with Similar Studies

We found one study that examined IOP in children and adolescents with ADHD and healthy controls.[9] In this study, 64 children and adolescents diagnosed with ADHD and 60 age-matched

TABLE 1. Demographic Variables and Clinical Characteristics of the Sample

	MPH *N* = 42 Mean ± SD		**ATX *N* = 40 Mean ± SD**		**Control *N* = 36 Mean ± SD**		**P***
Age (years)	10.1 ± 1.8		10.0 ± 1.8		10.2 ± 1.6		0.673
Intraocular pressure (mmHg)	Right	Left	Right	Left	Right	Left	
	14.2 ± 1.6	14.6 ± 1.6	14.0 ± 1.6	14.1 ± 1.7	15.0 ± 2.0	14.9 ± 2.0	0.129-R 0.308-L
	N (%)		**N (%)**		**N (%)**		P**
Gender							
Male	28 (66.7)		25 (62.5)		23 (63.8)		0.095
Female	14 (33.3)		15 (37.5)		13 (36.2)		0.087

MPH, methylphenidate; ATX, atomoxetine.
**ANOVA (Tukey test) was used.*
***Chi-square test was used.*

TABLE 2. Intraocular Pressure in ADHD Children Before and After Treatment

Intraocular Pressure (mmHg)	**MPH *N* = 42 Mean ± SD**		**P***	**ATX *N* = 40 Mean ± SD**		**P***
	Right eye	**Left eye**		**Right eye**	**Left eye**	
Before treatment	14.2 ± 1.6	14.6 ± 1.6		14.0 ± 1.6	14.1 ± 1.7	
After treatment (1st month)	14.5 ± 1.6	14.7 ± 1.6	0.323-R 0.442-L	14.1 ± 1.6	14.2 ± 1.7	0.496-R 0.397-L
After treatment (6th month)	15.0 ± 1.7	15.0 ± 1.6	0.198-R 0.249-L	14.3 ± 1.6	14.3 ± 1.7	0.216-R 0.274-L

MPH, methylphenidate; ATX, atomoxetine; ADHD, attention deficit hyperactivity disorder.
**Paired sample t-test was used.*

controls were included. There was also no statistically significant difference between the groups in terms of IOP in this study.

Previous reports have stated that several medications could increase IOP by either an open-angle or a closed-angle mechanism.[10,11] While alpha-adrenergic and anticholinergic drugs may cause acute angle-closure glaucoma secondary to mydriasis, other drugs may cause acute angle-closure glaucoma by ciliochoroidal effusion.[12] MPH and ATX are classified as adrenergic agonists because of their mechanisms of action and contraindicated theoretically in patients with glaucoma.[2,13] Although the concern that MPH could increase IOP and the risk of glaucoma, there are only a few case reports about this complication in the available literature. Izci et al. have reported increased IOP (32 mmHg) in a 23-year-old girl after 2 months of MPH treatment with a dose of 18 mg/day.[1] In another case, Lu et al. reported a 10-year-old boy who developed bilateral open-angle glaucoma and dense posterior subcapsular opacity of lens after 2 years of MPH treatment with a dose of 60 mg/day.[7] In contrast, safe use of MPH was reported in two patients with glaucoma who did not present with increase in IOP after initiating MPH treatment.[14,15] On the other hand, Soyer et al. reported a 9-year-old boy, presented with a significant decrease in visual acuity secondary to accommodation disorder after being treated with

MPH, 40 mg/day.[8] Two cases of ATX-related mydriasis have also been reported.[5,6] In the first case, a 15-year-old girl developed mydriasis after a 4-week treatment of ADHD with ATX, 60 mg/day.[5] In the second case, an 8-year-old boy presented with dilated pupils on the first month of ATX treatment with a dosage of 25 mg/day and his IOP was in normal range.[6]

Clinical Implications

We found only one study, conducted by Larrañaga-Fragoso et al., that investigated the effects of MPH on refraction and anterior segment parameters in ADHD children.[2] In this study, the mean visual acuity, sphere, spherical equivalent refraction, IOP, and cup:disk ratio did not change significantly between baseline and 3- or 9-month MPH treatment. However, the anterior chamber depth after cycloplegia decreased significantly between baseline and 9-month MPH treatment.[2] In the present study, at 1- and 6-month follow-up, there were no significant differences in IOP in both MPH and ATX groups. Our study results were consistent with the results of previous research. In the light of these results, it could be concluded that short-term MPH and ATX medications may not increase IOP significantly and could be used in children with ADHD and glaucoma with close follow-up.

Strengths, Limitations, and the Future Directions

In the present study, we primarily examined the effects of MPH and ATX usage on IOP in children with ADHD. Additionally, we investigated whether IOP differs between children with ADHD and healthy controls. According to the results of this study, IOP did not change significantly between baseline and 1- or 6-month MPH or ATX treatment. In addition, there was no significant difference in terms of IOP between ADHD children and controls. The literature is very limited on this subject, and in this regard, the present study could make a significant contribution to literature.

There are some limitations to the current study. The study focused only on IOP. Addition of other measurements, such as visual acuity, could have improved the quality of the study. Other limitations include the relatively small sample size and short follow-up period. The long-term effects of ADHD medication were not determined in this study. Further studies with larger sample size are needed to clarify the findings.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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DATA AVAILABILITY STATEMENT

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

COMPLIANCE WITH ETHICAL STANDARDS

This research was carried out in accordance with the Declaration of Helsinki; the nature and purpose of the study were explained to all children and parents, and informant consent was obtained in all cases. The Ethics Committee of Adana City Hospital approved the study protocol.

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