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Effects of methylphenidate on blood pressure, QT-interval, and cardiac output in ADHD diagnosed children: A three months' follow-up study

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ABSTRACT

Background: Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders of childhood. It's been suggested that both the condition and the medications used to treat it can affect the cardiovascular system. This study aims to determine whether methylphenidate has the significant effects in cardiac indices.

Methods: In this prospective study, 100 newly ADHD-diagnosed children aged 6 to 11 whom all on methylphenidate were included. The demographic, clinical data including the blood pressure and heart rate (HR), echocardiographic, and QT-interval were recorded at baseline and after three months of follow-up.

Results: After the follow-up period, we observed no abnormal systolic, diastolic, or mean arterial pressure in any of the participants based on their age, height, and gender ($p < 0.001$). However, the mean of all these variables was significantly increased ($p \langle 001$). Mean pulse pressure was also higher than baseline but it wasn't statistically significant ($p = 0.059$). No significant change was observed in echocardiographic parameters and QT.

Conclusion: Short-term treatment of ADHD in children with methylphenidate does not have a meaningful relationship with hypertension and increased corrected QT interval. However, an increase in blood pressure and corrected QT interval within a non-pathological range suggests that longer follow-ups may reveal an association.

1. Introduction

ADHD is one of the most common neurodevelopmental disorders, as defined in the DSM, 5th edition, described by symptoms including inattention, hyperactivity, and impulsivity [1,2] The estimated prevalence of ADHD in school-aged children ranges from 3% to 10.2%, with the highest rates in North America and the United States [3–5]. The rate is shown to be 3 times higher in boys than in girls [6]. Studies indicate that between 3 types of ADHD, the hyperactive-impulsive type and the inattentive type are prevalent among boys and girls, respectively [7]. The potential of drugs used to treat this disorder to adversely affect the cardiovascular system has cause concern about their safety, both in the normal population and in those with a history of CVD who may be at higher risk for cardiovascular complications with the use of these medications [8–12]. ADHD symptoms are likely to occur due to impaired brain dopaminergic pathways [13,14], and dopamine itself is shown to be able to cause changes in the cardiovascular system [15,16]. Some previous studies have reported a significant reduction in ADHD patients' systolic and diastolic blood pressures compared with controls and they have also suggested that more severe symptoms of the disease could result in greater blood pressure reductions [17]. On the other hand, some other studies suggest that hypertension and ADHD are positively correlated, in addition, a study on some children and adults revealed that while hypertension in adults is predominantly primary, it often appears to be secondary –usually to medications- in children [18,19]. Interestingly, some older studies have also shown associations between

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increased diastolic blood pressure and the combined form of ADHD [20]. Evidence suggests that there is a large difference between the effects of stimulant and non-stimulant drugs on blood pressure as well as cardiac output. It seems that stimulants (including methylphenidate and doxy-amphetamine medications) used to treat ADHD can lead to a slight elevation in cardiac output as well as systolic and diastolic blood pressures [21–23]. Consequently, among all available ADHD drugs, the CNS stimulants raise the highest concern about cardiovascular complications. Stimulants increase the release of noradrenergic and dopaminergic mediators and mimic the effects of sympathetic stimulation, hence affecting the cardiovascular system [24–26]. Cardiovascular adverse effects of stimulant drugs in children and adolescents are still controversial. The risk for most patients is small but careful evaluation is needed before and during stimulant prescription [16,27–30]. The purpose of our study was to investigate the effects of short-term (three months) medical therapy of children with ADHD in terms of blood pressure, QT interval, and left ventricular velocity time integral (LV-VTI).

2. Methods

2.1. Study description

This study was conducted in 2019 on 100 children aged 6 to 11 years who were referred to the psychiatric clinic of Ziaeian Hospital in Tehran, Iran. The diagnosis of ADHD for all these children was confirmed by a certified psychiatrist using DSM-V criteria. All of the ADHD-diagnosed children were treated with methylphenidate. After being rested for at least 5 min in the stretched legs position, the blood pressure of each patient was measured three times using the Microlife blood pressure monitoring device. The mean of the second and third measured systolic and diastolic blood pressure values stored as baseline information. The pulse pressure was also calculated by subtracting diastolic pressure from systolic pressure. Hypertension in children and adolescents defined based on their age, gender, height, and percentile. BP categories and stages were defined by the 2017 American Academy of Pediatrics High Blood Pressure Guideline [31]. The Seca altimeter (made in Germany) was used to measure the height of the subjects with a precision of one millimeter. To measure their weights, we used the Seca digital scale (made in Germany) with a precision of 0.1 kg. The body mass index (BMI) of the children was calculated individually. Patients who underwent transthoracic echocardiography and left ventricular end-diastolic and systolic diameter, and LV-VTI were recorded. The stroke volume (SV) is procured from the product of the left ventricular outflow tract (LVOT) cross-sectional area (CSA, in cm2) with the LVOT-VTI (known as stroke distance, in cm). The LVOT-CSA is derived from the LVOT diameter (LVOTd) using the formula $\pi r2$ ($3.1416 \times (LVOTd/2)^2$), or its equivalent $(LVOTd)^2 \times 0.785$. The LVOTd is obtained from the parasternal long-axis view, at a mid-systolic frame, measured from the inner edge to the outer edge of the LVOT or eventually between the site of insertion of the right- and non-coronary aortic leaflets [32,33]. The LVOT VTI is acquired by tracing the envelope of the Doppler spectrum of LVOT systolic flow from the apical five- or three-chamber view using pulsed-wave Doppler (PWD), with the sample volume placed within the LVOT, approximately at 1 cm distance to the aortic valve [32]. The product of the SV and heart rate (HR) will yield the cardiac output (CO, in L/min) [33]. QT interval is defined as the interval between Q wave and termination of T wave in surface electrocardiogram (ECG). Patients were then asked to return to the clinic after three months for a re-evaluation of all the previously measured variables. Those who had discontinued their medications or had changed them in this period were excluded from the study.

2.2. Ethics statement

In terms of ethics, the purpose of the study was explained to the families of all children and they were given the right not to participate. Their will to participate in the study was solidified using written consent. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (ethical code: 95–03-30–32906).

2.3. Statistical analysis

Finally, all available data were entered into SPSS 24.0 (Statistical Package for Social Science Inc., Chicago, Illinois, USA) for analysis. Continuous data were described using mean with standard deviation (SD). Number and Frequencies (%) were used for expressing categorical variables. The p-value was calculated using a T-test and the values<0.05 were considered as significant. Pearson Correlation test was used to calculate the correlation between variables.

3. Results

A total of the 100 participants with AHDH disease 26% were girls and %74 were boys. The mean age was 8.48 ± 2.52 years. The mean height, mean weight, and mean BMI of the individuals, were 129.68 ± 15.55 cm, 31.37 ± 11.6 kg, and 18.22 ± 3.95, respectively. After 3 months, none of the children had abnormal blood pressure based on their age, height, and gender. However, the mean of both systolic and diastolic blood pressures significantly increased compared with baseline ($p < 0.001$). Similarly, we saw a statistically significant increase in the MAP, which was within the normal range ($p < 0.001$). The mean of pulse pressure was elevated in patients after three months, but these changes were not significant ($p = 0.059$); heart rate insignificantly elevated as well ($p = 0.101$). Table 1 fully covers the changes in the mean of the measured blood pressure indices, heart rate, QT interval, and LV indices in echocardiography after the follow-up.

4. Discussion

The ADHD effects on the cardiovascular system can be categorized into two major aspects: effects of the disorder itself e.g. through manipulating the sympathetic system and effects of the medications used to treat. The two major key findings of the pre-

Table 1
Comparing baseline and follow-up blood pressure indices, echocardiographic and QT interval.

Variable	Mean(s)		P-value
	Baseline	Follow-up	
Systole pressure	80.9 ± 11.37	85.2 ± 12.85	0.000*
Diastole pressure	45.45 ± 7.35	48.3 ± 9.46	0.000*
MAP	57.49 ± 8.26	60.83 ± 9.87	0.000*
pulse pressure	35.45 ± 8.58	36.9 ± 8.58	0.059
Heart rate	84 ± 9	88 ± 7	0.101
LVED d	3.84 ± 0.47	3.73 ± 0.47	0.052
LVES d	2.58 ± 0.45	2.56 ± 0.30	0.060
VTI	21.1 ± 3.1	21.2 ± 2.9	0.213
QTc	402 ± 36.0	406 ± 24.1	0.367
QT dispersion	57 ± 10.2	55 ± 8.6	0.353

Abbreviations: MAP: mean arterial pressure; VTI: velocity–time integral; QTc: corrected QT; CO: cardiac output; LVEDd: Left Ventricle end-diastolic diameter; LVESd: Left Ventricle end-systolic diameter; P-value < 0.05 is considered significant and is shown with (*) in the table. P-value calculated with Paired Sample T-Test.

sent study were, during a three months therapy with methylphenidate, the blood pressure indices increased significantly however the QT interval did not change significantly.

Psychosocial therapy combined with pharmacotherapy, with methylphenidate is the first-choice medication for ADHD in school-aged children [34,35]. Although first-line drugs for ADHD are considered safe, cardiovascular based personal and familial history alongside with complete physical examination including baseline height, weight, blood pressure, and heart rate should be acquired before the initiation of the treatment [36]. Reports related to sudden deaths of patients, mainly children, treated by these drugs have raised the question of whether these medications increase the risk of cardiovascular events [37]. On the other hand, numerous massive cohort studies have not demonstrated any increased risk of life-threatening cardiovascular events among children treated by stimulants compared with the general population [38]. However, sudden death remains an extremely rare event and not be attributed to methylphenidate as there is no clear evidence supporting this association [39].

Long term use of amphetamines is shown to slightly elevate the patients' HR and BP [40]. A recent review showed ADHD medications cause modest elevations in resting heart rate and blood pressure, in addition, other adverse effects due to ADHD stimulants included arrhythmia, nonischemic cardiomyopathy, Takotsubo cardiomyopathy, and sudden death [41]. Our results indicate that treatment with stimulating agents for 3 months increases the blood pressure and heart rate but these alterations remain within the normal range. However, we assume that this increasing trend may suggest the probability of an amplified risk of developing HTN in the future.

Rapport et al. had investigated the cardiovascular effects of short-term treatment with intermittent release methylphenidate [42]. They Reported elevations of 3 to 10 bpm in heart rate, 3.3 to 8 mm Hg in SBP, and 1.5 to 14 mm Hg in DBP of patients [42]. Another study showed that treatment with stimulants for 4 weeks causes no meaningful alterations in BP and pulse rate. This may be proof of the safety of short-term treatments with these drugs [43]. Our study supports this statement as our results show that alterations in blood pressure indices did not lead to hypertension in a short period (3 months). However, the results should be interpreted with caution since the mentioned indices were still increased.

Several studies showed ADHD medication increase in mean blood pressure, heart rate, and QT interval in children, adolescents, and adults [12,16,44]. Biederman J. et al conducted a study on adults with ADHD in which they used OROS methylphenidate for 6 weeks and reported that methylphenidate was associated with statistically significant increases in systolic and diastolic blood pressure and heart rate but with a statistically significant decrease of QT-interval [45]. In another study, methylphenidate causes an increase in HR as well as increases in both systolic and diastolic BP, but no adverse effect in cardiac depolarization and repolarization duration or homogeneity such as HR-corrected QT and JT intervals or cardiac dispersion values [46]. Ilgenli TF. et al assessed the acute effect (2 h after administration) of methylphenidate on QT-interval duration and dispersion in children with ADHD and showed that methylphenidate reduced QT-dispersion, corrected QT-dispersion, maximum QT-interval but increased minimum QT-interval [47]. The evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with ADHD by Lamberti M. et al demonstrated no significant changes in ECG parameters [48]. In the present study, the QT-interval incremental trend was non-significant.

Given that the LVOT-CSA is constant, any change in the SV and CO is highly dependent on variations in the LVOT VTI; the HR associates to CO as well [33,49,50]. In addition, LVOT-VTI can predict outcomes in selected populations [51]. Kara T. et al demonstrated that methylphenidate usage in children did not damage cardiovascular function at short-term follow-up of echocardiographic parameters [52]. According to our results, there were no significant differences between baseline and 3-month follow-up echocardiographic findings, such as LVEDd, LVESd, and LVOT-VTI.

According to one of the most comprehensive comparative analyses of the efficacy and tolerability of drugs for ADHD in different age groups, first-choice medications for the short-term (12 weeks) treatment of ADHD in children/adolescents and adults are methylphenidate and amphetamines, respectively [53]. This large network analysis could not provide sufficient information for long-term timepoints (26 and 52 weeks). Our findings are consistent with this analysis that methylphenidate is safe in short-time management of ADHD in children and adolescents. The evaluation of long-term effects of ADHD medication should be taken into consideration in the future studies.

Of note, the use of stimulants did not cause any significant changes in adverse cardiovascular events in children and adults [38,44,54]. Despite non-pathological increases in BP, HR, and QT interval, because increased BP, HR, and QT interval are associate with cardiovascular morbidity and mortality during adulthood so pediatric patients treated with ADHD medication need to be monitored for HR and BP, closely and regularly.

5. Limitations

Perhaps the most important limitations of the current study are its small sample size and short follow-up duration. Future studies with longer follow-up durations and larger sample size could be of benefit. evaluating novel ECG indices would be interesting.

6. Conclusions

The results of this study indicate that short-term treatment of ADHD diagnosed children with CNS stimulants does not have a meaningful relationship with altered blood pressure indices, while all indices were increased in a non-pathological range after 3 months of follow up. The QT prolonged after three months but this was nonsignificant. Of note, we recommend studies with larger sample sizes and longer follow-up durations be performed to determine the precise effects of CNS stimulating drugs on blood pressure indices, HR, and ECG parameters.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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