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Research Article

THE EFFECT OF CHRONIC METHYLPHENIDATE ON EXECUTIVE FUNCTION AND WORKING MEMORY IN DRUG-NAÏVE CHILDREN WITH ATTENTION-DEFICIT DISORDER

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ABSTRACT

Background: The main problem in ADHD patients is disinhibition, while ADD patients mostly suffer from slow cognitive speed. Although studies have shown that children with ADHD have deficits in executive function and working memory, and that acute use of Methylphenidate improves these functions, less study has been done on ADD patients.

Methods: A four weeks, experimental, clinical trial was conducted with MPH 1 mg/kg/dose. Participants were 20 children aged 6-11 years with diagnosis ADD. Neuropsychological performance was assessed with scales taken from the Cambridge Neuropsychological Test Automated Battery.

Results: Methylphenidate improved problems in some aspects of Stocking of Cambridge test including minimum moves, mean subsequent thinking time and in mean moves, between errors, strategy and total error aspects of Spatial Working Memory. It had no effect on Spatial Span and Intra/Extra Dimensional subscales.

Conclusions: Studies show that ADHD patients have defect on all executive and working memory tests. Chronic use of Methylphenidate does not improve their performance. This different effect of chronic Methylphenidate on ADD and ADHD patients is another sign of different brain involvements in these two subgroups.

Keywords: Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, Methylphenidate, Executive Function, Working Memory

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is divided into two subtypes, the ADHD-combined, which includes inattention and hyperactivity/impulsive signs, and ADD (Attention Deficit Disorder). Patients with ADHD are hyperactive and restless. They move their hands and feet frequently and speak frequently. They are also impulsive, cannot wait for their turn to answer questions, and constantly interrupt others. On the other hand, ADD patients cannot pay attention to details. They have difficulty in completing and organizing a process. These patients get distracted by external stimuli, cannot concentrate, and therefore do not involve in thinking processes (1). Several studies have examined to what extent ADHD and ADD patients are different on various cognitive and executive measures (2, 3). Although both groups have attention problems, they have different inattention symptoms.

ADHD patients mostly have inhibition problems and cannot stay focused. But, ADD patients have vigilance and processing speed problems. Day-dreaming, confusion, and staring problems have seen in ADD patients (4). ADD patients show less social initiative and are shy. On the other hand, ADHD patients have difficulty in self-regulation. Despite these differences, both groups have reading and attention problems and are weak on mathematic (5).

Different clinical findings and executive measures in these two groups indicate that ADD is not a sub-group of ADHD. Studies of patients with ADHD indicate that most of them suffer from a variety of cognitive impairments that extend beyond symptoms listed in the DSM-IV diagnostic criteria for ADHD. These include chronic problems in regulating alertness, reading comprehension, and modulating emotion and executive function (EF) (6).

EF is the processes of problem solving, obtaining information about possible choices, and coordinating cognitive functions to make the best action for a given situation (7). These actions are often directed toward achieving long-term goals (8). Frontostriatal region is involved in EF (9). Loss of frontostriatal dopamine and noradrenaline causes executive dysfunction in ADHD patients (10).

Working memory is the brain's ability to hold and manipulate information currently being processed and is tied up with short-term memory. It is clear that many attention impairments associated with ADD and ADHD patients are because of chronic ineffectiveness of working memory and EF. Several cognitive functions, which extend beyond working memory, are apparently impaired in persons with ADD and ADHD (6).

Different studies have identified that children with ADHD have

several deficits in sub-scales and in concerning in executing functions for the Cambridge Neuropsychological Test Automated Battery (CANTAB) (2, 11). These patients have problems in inhibition, working memory (12), attention set shifting (12, 13), and planning (14).

Several authors proposed that different patterns of EF weaknesses could provide key evidence of discriminant validity between the DSM-IV inattentive and combined groups, particularly on measures of response inhibition (15, 16).

Stimulant therapy by Methylphenidate (MPH) is the most commonly proven medication for ADHD. MPH can not only change behavior, activity, and efficacy of the attempts, and the ability to inhibit, but also can improve cognitive function (17). ADHD patients have hypoperfusion in the frontostriatal region. MPH can improve perfusion in these regions, induce inhibition and arousal, and consequently reduce impulsivity (18, 19). In addition, functional neuroimaging suggests that MPH modulates brain activity by increasing frontal and decreasing striatal activation in neurologically normal adults and children. Therefore, MPH can potentially increase both frontal and striatal metabolism in children with ADHD (17) and improve cognitive function in children with ADHD (10). Table 1 shows studies that have been conducted on the acute and chronic effect of MPH on EF (20, 21).

Studies in (22-25) show that MPH can improve the clinical signs of ADHD patients. In addition, studies in (26-29) show that MPH has

Table 1: Results of previous researches on the acute and chronic effects of MPH on Executive Function[i]

Author/date	Use method	Positive effect on tests	Negative effect on tests
Bedard et al.2004	Acute	SWM	SOC
Mehta et al.2004	Acute	SWM, Attention set shifting task	
Turner et al.2005	Acute	SWM, SSP, set shifting	
Mehta et al.2000	Acute	SWM	
Hoare et al.2007	Acute	IED, SWM	
Kempton et al.1999	Acute	SWM, IED, SSP	
Rhodes et al.2006	Acute		SWM, SOC,IED
Rhodes et al.2004	Acute		SWM
Coghill et al.2007	Chronic		SSP, SWM
Rhodes et al.2004	Chronic		SWM

patients. While the effects of chronic and acute using of MPH on the EF for ADHD patients have been studied in literature, these effects have not been fully explored for ADD patients. In this study, we assess the effect of the chronic use of MPH on the executive function of ADD patients.

MATERIALS AND METHODS

This study was approved by research ethics. All participants and parents/guardians completed written informed consent.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The best-available computerized test battery for evaluation of executive functions is Cambridge Automated Neuropsychological Test and Battery (CANTAB) (30). CANTAB has the following sub-scales: Spatial Working Memory (SWM), Spatial Span (SSP), Stocking of Cambridge (SOC), Intra/Extra Dimensional Set Shifting (IED) evaluate executive function.

Intra-Extra Dimensional Set Shift (IED)

Intra-Extra Dimensional Set Shift is a test of rule acquisition and reversal. It evaluates visual discrimination, attentional set formation maintenance, and the flexibility of attention. This test is primarily sensitive to changes in the frontostriatal areas of the brain. Two figures are used in this test: color-filled shapes and white lines. Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both. The participant starts by seeing two simple color-filled shapes, and must learn which one is correct by touching it. Feedback teaches the participant which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g. color filled shapes remain the only relevant dimension), and then become extra-dimensional (white lines become the only relevant dimension). Participants progress through the test by satisfying a set criterion of learning at each stage (6 consecutive correct responses). If at any stage, the participant fails to reach this criterion after 50 trials, the test terminates. This test has eighteen outcome measures, assessing errors, and numbers of trials and stages completed.[ii]

Spatial Span (SSP)

shown to the participant. Some of the squares briefly change color in a variable sequence. The participant must touch the boxes, which changed color, in the same order that they were displayed. The number of boxes increases from 2 at the start of the test to 9 at the final step. The sequence and color also vary through the test. This test has six outcome measures such as covering span length (the longest sequence successfully re-called), errors, number of attempts, and latency.[iii]

Stockings of Cambridge (SOC)

SOC is a spatial planning test to measure the frontal lobe function. The participant is shown two displays containing three colored balls. He/she must use the balls in the lower display to copy the pattern shown in the upper display. The balls can be moved one at a time by touching the required ball and then by touching the position to which it should be moved. The time taken to complete the pattern and the number of moves are considered as the measure of the participant's planning ability. This test has three outcome measures, including the number and percentage of correct trials and latency (speed of participant's response).[iv]

Spatial Working Memory (SWM)

SWM tests the ability to retain spatial information and to manipulate remembered items in the working memory. This test is a sensitive executive dysfunction. The test begins with a number of colored squares (boxes) being shown on the screen. The participant should find a blue token among a number of boxes and use it to fill up an empty column on the right hand side of the screen. The number of boxes is gradually increasing, until it is necessary to reach a total of eight boxes. The color and position of the boxes are changing in different trials. The SWM test has twenty-four outcome measures. The main outcome measures include: errors (touching boxes that have been found to be empty, and revisiting boxes which have already been found to contain a token), a measure of strategy, and latency measures.[v]

Participants

Twenty children were recruited from consecutive outpatient referrals (aged from 6 to 11) to the Neurocognitive Center in Tehran. Exclusion criteria included history of neurological impairment, learning disability, mental retardation (IQ< 80), chronic physical illness, sensory or motor impairment, current or previous exposure to stimulant medication, abuse of any illegal drugs, the presence of commonly comorbid conditions, oppositional defiant disorder,

conduct disorder, and anxiety disorder. Eligible children had DSM-IV criteria for ADD and were interviewed by an experienced adolescent psychiatrist. ADD rating scale, Conners' parent rating scale, and the demographic form were answered by their parents. Then, the IQ of the children was evaluated by the Raven test. The control group was 20 healthy children, interviewed by the psychiatrist. The child behavior checklist (CBCL) form was also completed in order to rule out any potential behavioral problems.

Design

CANTAB and Conners' tests were performed as pre-tests and then MPH 0.5 mg/kg was used by patients twice a day at 8:00 AM and 2:00 PM for 4 weeks. After a month, these tests were taken again as post-tests.

Statistical Analysis

All analyses were conducted using SPSS (SPSS Inc., Chicago, Illinois) and results were produced by paired T-test.

RESULTS

Clinical response to MPH in Conners and ADHD rating scales

After one month of using MPH, ADD children showed significant improvement in inattention (p: 0.03), hyperactivity (p: 0.02), and ADHD (p: 0.008) indexes of Conners' test. However, using Ritalin had no significant improvement in the patients (p: 0.4).

In ADHD rating scale, the patients showed significant improvement in total score (p: 0.02) indexes and inattention (p: 0.02), but did not show significant improvement in hyperactivity index (p: 0.2)

The Results of CANTAB Tests

Stockings of Cambridge (SOC)

Using MPH significant helped ADD patients to improve the following measures: mean moves (3 moves) (0.03), mean sub-sequent thinking (3 moves (0.002) and 5 moves (0.01)), and problems solved in minimum moves (0.003). But, MPH could not help the patients to improve mean initial thinking time (2, 3, 4 and 5 moves), mean moves (2, 4 and 5 moves), and mean sub-sequent thinking time (2 and 4 moves) (p>0.05) (See Table 3).

Intra-Extra Dimensional Set Shift (IED)

Chronic use of MPH helped the patients to perform better in the following measures: stage errors, completed stage trials, EDS errors, errors block 1 to 9, pre-ED errors, stages completed, total errors, total errors adjusted, total trials, and total trials adjusted (p: 0.05) (See Table 4).

Intra-Extra Dimensional Set Shift (IED)

Chronic use of MPH helped the patients to improve the following indexes: completed stage errors, completed stage trials, EDS errors, errors block 1 to 9, pre-ED errors, stages completed, total errors, total errors adjusted, total trials, and total trials adjusted (p: 0.05) (See Table 4).

Spatial Span (SSP)

The patients did not show significant improvement in the following measures: span length, total errors, and total usage errors (p: 0.05) (See Table 4).

Spatial Working Memory (SWM)

Significant improvement was observed for the following measures of SWM: between errors (0.003), between errors (6 boxes) (0.007), strategy (0.04), and total errors (0.003). But no tangible improvement is observed for between errors (4 and 8 boxes), double errors (4, 6 and 8 boxes), and within errors (4, 6 and 8 boxes) (See Table 5).

DISCUSSION

The results of this study show that MPH can improve Conner's and ADHD rating scale in ADD patients. Parents of the ADD patients confirmed that attention and concentration had been improved. The hyperarousal caused by MPH increased the concentration of the ADD patients and helped them to perform better in the exams.

In general, ADD patients suffer from low arousal and willpower. Starting a new task has high arousal for them. They may perform well at first, but as soon as they get involved in the process, everything becomes boring and they lose their interest and consequently their concentration decreases. Therefore, they skip tasks to maintain constant arousal. Using stimulant therapy such as MPH can increase their focus and allow them to complete the tasks.

Table 2: The effect of chronic use of MPH on Conner's-RS and ADHD-RS

	WEEK 0 M (SD)	WEEK 4 M (SD)	P
CPRS			
Oppositionality index	56.80 (9.0)	58.05 (8.6)	0.46
Inattention index	67.45 (9.4)	62.55 (11.0)	0.03*
Hyperactivity index	59.30 (9.4)	55.10 (7.7)	0.02*
ADHD index	64.85 (8.9)	59.80 (9.4)	0.008*
ADHD RS Inattention	86.20 (19.1)	79.30 (21.1)	0.02*
Hyperactivity	76.35 (12.4)	69.40 (22.3)	0.21
Total score	83.95 (16.6)	76.10 (21.2)	0.02*

Table 3: Effect of chronic use of MPH on SOC test

Measures	Week 0 Mean (SD)	Week 4 Mean (SD)	T	P
SOC				
Mean initial thinking time, 2 moves	2123.82 (1890.2)	2215.97 (2001.9)	-0.19	0.84
Mean initial thinking time, 3 moves	7986.47 (19040)	2791.52 (4215.1)	1.53	0.14
Mean initial thinking time, 4 moves	3993.92 (2345.6)	3089.87 (1567.1)	1.44	0.16
Mean initial thinking time, 5 moves	3498.26 (2477.0)	2873.76 (2295.9)	0.92	0.36
Mean moves, 2 moves	2.02 (0.11)	2.00 (0.00)	1.00	0.33
Mean moves, 3 moves	3.60 (0.85)	3.12 (.27)	2.23	0.03*
Mean moves, 4 moves	5.71 (1.2)	5.58 (1.1)	0.31	0.75
Mean moves, 5 moves	7.92 (1.0)	7.58 (1.3)	0.84	0.40
Mean subsequent thinking time, 2 moves	1453.84 (2851.6)	246.25 (568.8)	1.91	0.07

Mean subsequent thinking time, 3 moves	2782.77 (3326.5)	264.32 (498.1)	3.54	0.002*
Mean subsequent thinking time, 4 moves	4460.05 (4416.4)	2515.37 (5416.3)	1.43	0.16
Mean subsequent thinking time, 5 moves	3242.23 (3020.4)	1878.59 (1430.3)	-3.42	0.01*
Problems solved in minimum moves	6.50 (1.8)	8.00 (1.2)	2.77	0.003*

Table 4: Effect of chronic use of MPH on IED & SSP tests

Measures	Week 0 Mean (SD)	Week 4 Mean (SD)	T	P
IED Completed stage errors	15.10 (8.4)	17.15 (10.7)	- 0.65	0.52
Completed stage trials	77.00 (23.9)	83.10 (28.2)	- 0.74	0.46
EDS errors	11.05 (10.7)	7.85 (9.9)	1.22	0.23
Errors, block 1	0.60 (0.82)	0.90 (1.5)	- 0.78	0.44
Errors, block 2	1.60 (0.82)	1.50 (0.82)	0.52	0.60
Errors, block 3	1.95 (4.3)	3.50 (5.7)	- 0.93	0.36
Errors, block 4	0.25 (0.55)	0.35 (0.81)	- 0.49	0.62
Errors, block 5	2.00 (2.4)	2.05 (2.2)	- 0.06	0.94
Errors, block 6	0.60 (0.99)	0.70 (0.86)	- 0.34	0.73
Errors, block 7	1.60 (1.2)	1.70 (1.7)	- 0.23	0.82
Errors, block 8	11.05 (10.7)	7.85 (9.9)	1.22	0.23
Errors, block 9	6.95 (9.1)	5.25 (7.0)	0.59	0.55
Pre-ED errors	8.60 (5.3)	10.70 (6.9)	- 1.30	0.20
Stages completed	8.00 (1.6)	8.30 (1.6)	- 0.57	0.57
IED total errors	26.30 (10.8)	23.80 (11.9)	1.00	0.33
Total errors adjusted	40.05 (36.6)	35.05 (38.4)	0.43	0.66
Total trials	99.50 (22.1)	95.60 (24.0)	0.63	0.53
Total trials adjusted	127.00 (65.9)	118.10 (68.5)	0.43	0.66
SSP Span length	4.42 (1.1)	4.53 (1.0)	- 0.41	0.68
Total errors	12.10 (5.0)	11.45 (5.7)	0.35	0.72
Total usage errors	1.90 (1.9)	2.00 (2.1)	- 0.24	0.81

Table 5: Effect of chronic use of MPH on SWM test

Measures	Week 0 Mean (SD)	Week 4 Mean (SD)	T	P
SWM				
Between errors	56.90 (17.3)	45.85 (21.6)	3.37	0.003*
Between errors (4 boxes)	3.00 (2.5)	2.10 (2.5)	1.70	0.10
Between errors (6 boxes)	19.75 (8.4)	14.05 (8.8)	3.00	0.007*
Between errors (8 boxes)	34.10 (9.9)	29.70 (12.4)	1.78	0.09
Double errors	1.60 (2.2)	1.65 (2.8)	- 0.06	0.95
Double errors (4 boxes)	0.00 (0.00)	0.05 (0.2)	- 1.00	0.33
Double errors (6 boxes)	0.75 (1.8)	0.55 (1.6)	0.34	0.73
Double errors (8 boxes)	0.85 (1.2)	1.05 (1.8)	- 0.45	0.65
Strategy	39.00 (4.2)	37.15 (6.0)	2.13	0.04*
Total errors	57.90 (17.8)	46.70 (21.9)	3.40	0.003*
Within errors	2.65 (3.4)	2.50 (3.6)	0.14	0.88
Within errors (4 boxes)	0.05 (0.22)	0.15 (0.4)	- 0.80	0.42
Within errors (6 boxes)	1.35 (3.2)	0.55 (1.6)	- 1.02	0.34
Within errors (8 boxes)	1.25 (1.6)	1.80 (2.7)	0.96	0.31

Note that, short time tests are not appropriate to study the behavior of ADD patients because the patients do not have executive dysfunction in short time processes. But, when it comes to long time processes, they have difficulties. If high arousal is produced in their brain, they can concentrate. That is why they seem to have executive dysfunction in clinic, but when short time tests are taken, they perform well.

ADHD patients like ADD patients have low arousal state and are hyperactive. When they use stimulants like MPH, their brain can maintain constant arousal. Thus, the disinhibition and hyperactivity decrease and their concentration increases (31).

Chronic use of MPH can improve the performance of ADD patients in IED and SSP and can improve their scores in the SOC and SWM tests. It can also improve planning ability and reaction time of the SOC test, even though ADD patients have problems in time related measures of the SOC test. ADD patients do not have problem in the SWM test, but MPH can still improve their performance in this test.

the first attempt, but when it is used again, it may cause hyperarousal (32-36). Previous studies claim that ADHD patients

In addition, chronic use of MPH can improve the mean moves in the SOC test (3 moves), mean sub-sequent thinking (3 and 5 moves), and problems solved in minimum moves. MPH can also help the patients to improve the following indexes: between errors, between errors (6 boxes), strategy, and total errors in the SWM test. These tests evaluate the ability of the patients in using spatial information in working memory.

The results of this study show that MPH has no tangible effect on IED and SSP for ADD patients. Thus, flexibility of attention and spatial information are the psychological functions that may not be changed by the chronic prescription of MPH.

Studies on healthy individuals show that acute use of MPH and stimulants can improve their working memory (SWM) and planning (SOC), but has no effect on the IED and fluency tests. When MPH is used for the second time on healthy individuals, it may decrease response latency and worsen their performance. A possible explanation is that MPH induces arousal in healthy individuals for

have problem in the tests related to executive function (SOC, IED, SSP, SWM) (12-14, 37).

Chronic use of MPH has no effect in the SOC, IED, SSP, and SWM tests for ADHD patients (14, 38), but acute use of MPH can improve their performance on SWM, IED, and SOC (12, 39). However, some studies claim that acute use of MPH does not have any effect on the IED, SOC, and SWM tests (10, 14).

MPH has a short half-life. Its acute use can raise arousal and improve inhibition in ADHD patients. The chronic use of MPH does not show the same results. This may be related to the tolerance developed in the patients (12, 39). If disinhibition is controlled in ADHD patients, they can executive function and use their working memory. If the impulsive behavior of these patients is controlled, they can also answer the tests correctly.

When MPH is used chronically and after its half-life ends, it cannot raise arousal to the initial level for the ADHD patients, So, the patients still have problems in completing the tests (14, 38). But, the results of this study show that the chronic use of MPH can have positive effects for the ADD patients.

ADHD patients have defects on frontostriatal areas of their brain and have difficulty in inhibition of attempts, specially for movement (3). On the other hand, ADD patients have problem in prefrontal areas of their brain (40). ADD patients do not have a disinhibition problem, but they are sluggish and therefore they show different reactions to MPH. The chronic and acute use of MPH can improve the sluggish problem of the ADD patients, by increasing stimulating neurotransmitters in their brain.

CONCLUSIONS

More investigation should be conducted on the acute and chronic use of MPH in ADD and ADHD patients. Previous studies show that the acute use of MPH can enhance inhibition and reduce impulsivity of the ADHD patients. But, the chronic use of MPH does not show these improvements. To our best of knowledge, no study has been done on the acute use of MPH for ADD patients. In this paper, we showed that the chronic use of MPH did not worsen the performance of the ADD patients and could even improve their performance in planning, working memory, and reaction time. Our findings approved the theory that ADHD and ADD patients have different brain involvement and therefore have different treatment outcomes. The results of this study get rise to new research questions. For instance, how do ADD patients perform in other cognitive exams after the use of MPH? Addressing this question should be part of the future research endeavors.

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