ORIGINAL RESEARCH

A Study of Safety and Efficacy of Methylphenidate in Children and Adolescents: An Observational Clinical Study

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Abstract

Background: Attention deficit and hyperactivity disorder (ADHD) leads to various problems like academic underachievement, interpersonal relationship problems, and low self-esteem. Medications like methylphenidate (MPH) used for its treatment have decreased appetite and weight loss as the main side effects. There is scarce literature that throws light on the prevalence or severity of these particular side effects in patients with ADHD.

Aims and objectives: So this study was conducted to assess the safety and efficacy of MPH in children and adolescents diagnosed with ADHD.

Materials and methods: Patients of age-group 5–17 years who were diagnosed with ADHD were included in the study after taking informed consent of their parents. Semistructured pro forma was used to collect demographic and phenomenological details. Conners rating scale was used to assess ADHD severity. Methylphenidate was started for treating ADHD and patients were followed up at 1 and 3 months and change in Conners scale and side effects including appetite changes were asked for on follow-ups. Also, height and weight were measured on all visits.

Results: One-hundred and seven patients with a mean age of 9.61 years were enrolled; of which, 79% of them were males. Seventy-three percent of them had a combined type of ADHD. The mean dose of MPH increased on subsequent follow-ups. Forty percent of them experience a decrease in their appetite at 1 month but only 18% of them had appetite issues at 3 months. There were no statistically significant changes in the height and weight of the patients on follow-ups.

Conclusion: MPH is a very well-tolerated treatment for ADHD and not many side effects are observed in children taking it. Appetite reduction is seen for the initial treatment period which can be managed by giving MPH after heavy breakfast and meals.

Keywords: Appetite, Attention deficit hyperactivity disorder, Methylphenidate, Weight.

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Introduction

Attention deficit and hyperactivity disorder is a condition characterized by difficulty in maintaining attention, cognitive and behavioral impulsiveness, and overactivity in children.[1] Patient can either present with predominantly hyperactive/impulsive or inattentive symptoms or a combination of both symptoms. Predominant hyperactive symptoms are seen commonly in children mostly boys which may dissipate as they get older. Inattentive symptoms are seen more commonly in girls which may be underdiagnosed.[1]

The common problems associated with ADHD are academic underachievement, problems with interpersonal relationships with family members and peers, low self-esteem. The usual comorbidities of ADHD are emotional problems, language disorders, and learning disorders.[2,3]

Usually, these problems persist through school years and even into adult life, but many individuals show a gradual improvement in attention and activity. These disorders may be associated with several other abnormalities. Hyperkinetic children are prone to accidents, reckless and impulsive behavior and get into disciplinary trouble because of acting without thinking. They are often socially disinhibited in their relationships with adults. With a lack of reserve and normal caution; they are unpopular with other children and may become isolated. Secondary complications include low self-esteem and dissocial behavior.[4,5]

Stimulant medications like MPH and amphetamines are the most widely used medical agents for the treatment of ADHD and have been shown in many studies to significantly reduce the symptoms of inattention, hyperactivity, and impulsivity that characterize this disorder.[6]

MPH inhibits the reuptake of dopamine and norepinephrine thereby increasing dopaminergic and noradrenergic activity in the prefrontal cortex which explains its efficacy in ADHD.[7] Initially the dose is titrated from 5 mg twice a day to the optimal level of up to 1.2–1.5 mg/kg/day achieves therapeutic benefits and has minimal side effects.[8]

MPH is now a preferred choice over stimulants as it has less abuse potential. It has been especially useful in patients who are unable to tolerate other stimulants or those who have a comorbid substance abuse history.[9]

The adverse event of loss of appetite is one of the most commonly reported with this medication. This may be of much

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concern to parents of growing children, especially when there is a substantial decrease in appetite. In many patients, this decreased appetite may cause a consequent weight loss. In growing children, weight loss can lead to growth disturbances. The weight loss can in turn also cause an increase in the "medication to weight ratio" which may further lead to a rise in other side effects including psychosis, mood disorders, depression, abnormal thought patterns, suicidal thoughts/tendencies, and self-injury.[10]

Not many randomized studies have been done to identify phenotypically, e.g., age, gender, or medication-related, e.g., type of stimulant, dosing schedule, and treatment duration moderators for increased susceptibility to stimulant-induced anorexia and weight loss. Thus little information is available regarding children who are susceptible to persistent anorexia and weight loss during treatment with stimulants like MPH. Also, there is scarce literature that throws light on the prevalence or severity of these particular side effects in patients with ADHD. Even after extensive searching, we were unable to find research, especially Indian, which could give us the frequency and severity of appetite and weight loss in patients, information that the parents of most of our ADHD patients most of whom, were growing children were asking for.

So this study was conducted to assess the safety and efficacy of MPH in children and adolescents diagnosed with ADHD.

Materials and Methods

This was an observational, prospective study undertaken in a tertiary care hospital in Mumbai after approval from the institutional ethics committee. Patients of age-group 5–17 years, fulfilling the inclusion and exclusion criteria visiting the Child Guidance Clinic were recruited from October 2017 to March 2018. Inclusion criteria were children with adequate and reliable objective data, diagnosed as having ADHD as per DSM-5 criteria, no other comorbidities, and parents willing to give consent. Those having medical comorbidities and already taking MPH were excluded. The assessment was done by two psychiatrists (one resident doctor and the other by a faculty member). In all 380 children were screened during the study period of which 290 fitted into inclusion criteria. Ninety-three of them did not consent to the study and 90 of them did not follow up on said visits. So finally 107 children were included for analysis as they had followed up as required till 3 months. Semistructured pro forma was used to collect socio-demographic aspects, clinical profile of patient, height, weight, and appetite was recorded. Conners parent rating scale was used to measure the severity of ADHD.[11] Patients were started on MPH 0.5–1 mg/kg and parents were asked to watch for the emergence of any side effects; the dose was titrated as per response. After regular medication for 1 and 3 months, patients were reassessed, weight, height, and appetite were re-recorded and parents were asked if they noticed any change in the appetite of their children or any emergence of any side effect. Their report for appetite was recorded.

The Conners rating scale was designed by C Keith Conners. It consists of 27 questions, 6 for oppositional, 6 to measure hyperactivity, 6 for cognitive problems, and 12 for ADHD Index. It can be used for the age-group of 3–17. It can be used with parents/guardians of children who may show symptoms of ADHD, oppositional problems, inattention/cognitive problems, and hyperactivity.

It has gender and age norms. The internal reliability was tested by gender and age-groups and the reliability coefficients ranged from 0.857 to 0.938. Test-retest was conducted at an interval of 6–8 weeks. The coefficients ranged from 0.62 to 0.85. Exploratory and confirmatory factor analysis and subscale inter-correlations were calculated. Correlations between short and long-form ranged between 0.97 and 0.98 for males and 0.96 to 0.97 for females.[11]

The data obtained were entered into an MS Excel sheet and analysis was done using computerized software. The tests used were the Chi-square test, Student "*t*" test, and correlation was analyzed using Pearson's correlation coefficient. A two-tailed "*p*" value was obtained for all statistical analyses and a score of $p \leq 0.05$ was considered as statistically significant.

Results

Table 1 describes the various demographic details of the study sample ($N = 107$). Table 2 describes the phenomenological details of the sample. Almost 73% of children had a combined type of ADHD and learning disability (11.21%) was common comorbidity seen in them. The dose of MPH was gradually increased over 3 months as per response (0.20 mg/kg body weight to 0.44 mg/kg body weight). Table 3 describes changes in body weight, height, BMI over 3 months, and also the response of MPH over 3 months. It was observed that there was no statistically significant change in height, weight, and BMI in 3 months but weight has increased at end of 3 months. The ADHD symptoms improved significantly over 3 months and there was a statistically significant improvement in the Conner scale in all domains. Table 4 describes the side effects experienced with MPH, reduction in appetite being commonest. With treatment over a period of time appetite complaints resolved in almost 50% of cases. (39% at 1 month to 18% at 3 months).

Table 1: Demographic details of the study population

Parameter (N = 107)	*Mean ± SD/frequency (%)*
Age in years	9.61 ± 3.44 (5–17)
Education in years	6.50 ± 3.70 (0–17)
Sex	
Male	84 (79%)
Female	23 (21%)
Religion	
Hindu	74 (69.15%)
Others	33 (30.85%)
Family structure	
Nuclear	58 (54%)
Joint	49 (46%)

Table 2: Phenomenological details of the study population

Parameters (N = 107)	*No. of cases (%)/Mean ± SD*
ADHD subtype	
Hyperactive	15 (14%)
Inattentive	14 (13.08%)
Combined	78 (72.92%)
Comorbid condition	
Learning disability	12 (11.21%)
Intellectual disability	9 (8.41%)
Oppositional defiant disorder	9 (8.41%)
Methylphenidate dosage in mg/kg body weight	
Baseline	0.20 ± 0.76
1 month	0.39 ± 0.15
3 months	0.44 ± 0.16

Table 3: Changes in height, weight, BMI, and ADHD score over 3 months

Parameter	*Baseline*	*After 1 month*	*After 3 months*	*F-value, p-value*
Height in meters	1.12 ± 0.22	1.12 ± 0.22	1.12 ± 0.22	0.00, 1.00
Weight in kgs	29.32 ± 13.09	29.37 ± 13.14	29.91 ± 13.20	0.06, 0.94
BMI	23.70 ± 10.30	23.83 ± 10.42	24.03 ± 10.46	0.02, 0.97
Conners oppositional	49.32 ± 7.59	47.93 ± 6.08	46.77 ± 5.70	4.12, 0.01*
Conners inattention	69.53 ± 5.97	65.82 ± 5.22	60.42 ± 4.72	79.09, <0.01*
Conners hyperactivity	73.57 ± 7.12	68.37 ± 6.18	62.17 ± 5.42	88.41, <0.01*
Conners ADHD index	75.6 ± 8.80	69.94 ± 8.32	62.90 ± 7.97	61.82, <0.01*

*p-values were 0.000 so written as <0.01

Table 4: Side effects observed with methylphenidate

Side effects (overlapping data)	*After 1 month*	*After 3 months*
None	62 (57.94%)	86 (80.37%)
Reduced appetite	42 (39.25%)	19 (17.75%)
Vomiting	3 (2.8%)	0 (0%)
Insomnia	3 (2.8%)	3 (2.8%)
Headache	2 (1.86%)	2 (1.86%)
Abdominal pain	1 (0.93%)	0 (0%)

Discussion

The mean age of our study population was 9.61 ± 3.442 years, ranging from 5 to 17 years which corresponds to most of the studies done to understand the prevalence of ADHD in children and adolescents. Some studies like that conducted by Visser et al. found the mean age to be 7 years.[12] The variation in results could be because of the inclusion of preschool children in the above-mentioned study, resulting in the reduction of mean age. It was also noted in our study that parents took an average time of 1–2 years to seek medical attention for the child.

Most of the children diagnosed with ADHD were males (79%) compared to females (21%). The ratio of prevalence of ADHD among males: females was 4:1 approximately. This indicates that the disorder is much more prevalent in males compared to females. The ratio obtained here was on the higher side compared to some studies like the one done by Dr Ujjwal Ramtekkar et al. to study sex and age differences in attention-deficit/hyperactivity disorder symptoms and diagnoses in which the prevalence ratio of male to female was found to be 2.28:1. However, the results of the current study were closer with worldwide estimates for childhood ADHD ranging between 3 and 7% with a male-to-female ratio of approximately 3:1 in population-based studies and between 5:1 and 9:1 in clinical samples.[13–16]

As suggested through various clinical studies, the slightly higher prevalence among males in our study can be explained by differences in the expression of the disorder itself among boys and girls.[17–19] The reason that females with ADHD are reported to have more inattentive and fewer hyperactive/impulsive symptoms when compared with males with ADHD.[20,21] Also, females with ADHD present more commonly with the inattentive subtype than boys.[22] This lack of disruptive behavior among females with ADHD may become contributory to bias in the referral leading to under-identification and lack or delay of treatment for females with ADHD.[23] Explaining similar findings by a study by Sciutto et al., they found that boys were more often referred by teachers than girls for treatment of ADHD even when they may be showing equal levels of impairment. So by overall comparison, more overt acting out behavior seems to drive attention for referral for ADHD assessment in boys.[15,24]

The study also showed that 11.21% of the sample had specific learning disability, 8.41% had intellectual disabilities and 8.41% had oppositional defiant disorder along with ADHD. Previous studies found that the prevalence for oppositional defiant disorder with ADHD was 5–10%, ranging from 25% to as high as 75% of patients showing impairment. It was suggested, in such patients, effective treatments might reduce the risk of complications such as depression, conduct disorder, or substance abuse later on. The comorbidity such as oppositional defiant disorder may predispose children to bullying involvement in early elementary school as mentioned by Verlinden et al.[25–28] The study done by Dupaul GJ and others found a high percentage comorbidity of ADHD and specific learning disorder (SLD), i.e., between 31 and 45% and both disorders presenting with similar complains. The study found that children with SLD faced difficulties in staying attentive on tasks similar to children with ADHD. Deficits in executive functioning and decline in academic performances were also observed and suggested evaluation of specific learning disabilities to optimize treatment so that the academic skill deficits can be accommodated in a school setting and patients can be treated for both disorders with interventions at home and in a school setting.[28,29]

The difference between mean medication dosages per kilogram given at baseline was 0.20 mg after 1 month was 0.39 mg and after 3 months was 0.44 mg. The value showed an increase in the mean dosage by 0.19 mg/kg at the end of the first month and by 0.24 mg/kg by the end of 3 months as compared to the dose given on the first day. The statistical values show that the obtained difference was significant. The dose, hence noted, by the end of 3 months, corresponds to the dose recommended and data obtained through various studies. The study also showed that the difference increase in the mean dosage between 1 and 3 months 0.05 mg/kg was much less than the difference increases between baseline and 1 month 0.19 mg/kg. The dose-response relationship of MPH has been reflected upon in various studies done on children. Supposedly, a dose-response relationship has been observed with osmotic-controlled release oral delivery system methylphenidate OROS-MPH in children with combined-type ADHD. Such a relationship was not observed in children with the ADHD-inattention subtype. A study conducted by Douglas et al. a suggested a linear dose-response relationship between dose 0.15, 0.30, and 0.60 mg/kg and improvements in performance.[30,31] The obtained results in our study were on the higher side as significant improvement at the mean dose of 0.44 mg/kg by the end of 3 months was noted. However, there could be a variation in the results due to the short-term follow-up of 3 months and the lack of further follow-up.

In our study, the difference between mean weight at baseline was 29.32 ± 13.09, after 1 month of medication 29.37 ± 13.14 and after 3 months was 29.91 ± 13.20 The obtained values indicate that the difference of mean weight between baseline and at the end of 1 month was not significant however compared to baseline there was a statistically significant weight gain at the end of 3 months of therapy which corresponds to the pattern of loss of appetite in this study. The differences in the percentage of various side effects were noted after 1 and 3 months of medications. After 1 month, 57.94% had no side effects whereas 80.37% faced no side effects after 3 months. The percentage of samples that had reduced appetite decreased from 39.25 to 17.75% in 3 months. The percentage of samples that had vomiting decreased from 2.80 to 0% and complaints of occasional pain in the abdomen decreased from 0.93 to 0% from 1st to 3rd month. There was no change in the complaints of insomnia and occasional headaches. This result showed that there was a significant reduction in side effects when the MPH was continued for 3 months, including a reduction in appetite. However, in two patients, the drug had to be stopped because of a perceived severe loss of appetite at the end of the first month and couldn't be followed up later. The study also noted nine patients dropping out of the study and treatment because of unknown reasons that can be attributed to any of the side effects or inability to attend the outpatient department.

Since the most common side effect noted here was a loss in appetite, our study also took the percent reduction in appetite at the end of 1 and 3 months and compared it to appetite before starting the medication. This was done using a Likert scale. On inquiry, 10.28% of patients perceived a 20% reduction in appetite at the end of the month. Similarly, 18.69% perceived 40 and 10.28% perceived a 60% reduction in appetite. However, by the end of 3 months, it reduced to 6.54, 7.47, 4.67% perceiving 20, 40 and 60% reduction in appetite respectively. These data were in line with the study conducted by FatihGurbuz August 2015 to understand the effects of MPH on appetite and growth in children diagnosed with attention deficit and hyperactivity disorder concluding that MPH use in children with ADHD causes lack of appetite through leptin and ghrelin.[32]

The result also matched the study conducted by Sonuga-Barke et al. to understand the adverse reactions to MPH treatment for attention-deficit/hyperactivity disorder which found that different children are affected in different ways and on different dimensions. Sleep and appetite were found to be the most commonly affected areas.[33] The results were also in line with the study done by Leddy et al. which found that lunch consumption decreased as a function of MPH dose. Dopamine-related genotypes associated with greater brain dopamine signaling moderated the influence of drugs on consumption.[34] The number of side effects that were seen in our study was similar to the study performed by Ahmann et al. where the dominant side effects were disturbance in appetite, dizziness, stomach ache, headache, and insomnia.[35]

Limitations

The study was carried out in a tertiary hospital and results cannot be generalized. Also, treatment response and side effects in different age-groups have not been compared in the study. Long-term effects have not been checked. There was no comparison done with those on other treatment medications for ADHD like atomoxetine. The investigators were not blinded to the dose and treatment details.

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