ORIGINAL RESEARCH

A comparative study of different formulations of Methylphenidate in treatment of ADHD: A clinical study

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ABSTRACT

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood. Treatment strategy includes pharmacological and psychosocial approach. Stimulant medication is the first choice among pharmacological management. Various formulations of Methylphenidate are immediate release, extended release and osmotic release oral system. **Aims & Objectives**: To compare the clinical outcome of children with ADHD on different formulations of methylphenidate in terms of improvement in core symptoms, and tolerability and side effects. **Methods:** It was a prospective analytic study**.** Study subjects were90 children with ADHD in the age group between 6 and 16 years, who were prescribed different formulation of Methylphenidate ie. Immediate release (MPH-IR), Extended release (MPH-ER) and Osmotic Release Oral System formulations (MPH-OROS), on 1:1:1 basis randomly to form 3 groups.After 3 months of pharmacological and behavioral therapy, these children were re-assessed on Conner's parent rating scale to compare the outcome on behavioral performance. Tolerability and side effects of drugs were compared on the basis of a pre-designed questionnaire completed by the parents. **Results**: All the three groups of Methylphenidate showed significant reduction in scores of inattention (p value=0.00) and significant reduction in scores of hyperactivity (p value=0.04). On comparing each group, long acting MPH-ER and MPH-OROS showed better outcome than short acting MPH-IR (p value=0.04). Out of 90, only 33 subjects complained of adverse effects which was statistically not significant (p value =0.798). **Conclusion**: In the treatment of ADHD, once-daily MPH-ER and MPH-OROS showed significant improvements in behaviour, better than MPH-IR with a favourable side effect profile and a prolonged duration of effect.

Keywords: ADHD, Methylphenidate, Outcome

INTRODUCTION

ADHD is defined as a condition characterized by persistent symptoms of inattention or hyperactivity-impulsivity, or both, sufficient to cause clinically significant impairment with age appropriate academic, social or occupational functioning.[1] Prevalence rate is 5% in children and 2.5% in adults across all cultures & is the most common neurobehavioral disorder of childhood.[2] A diagnosis of Attention Deficit Hyperactivity Disorder is made primarily in clinical settings after a thorough evaluation, including a careful history and clinical interview, on the basis of Diagnostic & statistical manual of mental disorders, fifth edition (DSM-V) and magnitude of symptoms is assessed by behavior rating scales.[3]An effective treatment strategy includes pharmacological and psychosocial approach, intervening in personal, social and academic or occupational spheres.The choice of medication depends on a child's age. In pre-school children, when pharmacological treatment is indicated, the first choice is a stimulant (Methylphenidate and Amphetamine). For a school-aged child or adolescent, a stimulant is the first-line agent, followed by amphetamines or a monoamine reuptake inhibitor i.e., Atomoxetine. Other medications (e.g., Alpha-2-adrenergic agonists) usually are used when children respond poorly to a trial of stimulants or Atomoxetine, or when children have unacceptable side effects or significant coexisting conditions. [4]Stimulants are preferred to other medications because stimulants have rapid onset of action, and a long record of safety and efficacy. The optimal regimen is determined by changes in core symptoms and occurrence of side effects. [5]Stimulant medications usually are started at the lowest dose that produces an effect and increased gradually (e.g., every

3-7 days) until core symptoms improve by 40% - 50% compared with baseline, or adverse effects become unacceptable. The frequency of dosing is based upon the type of ADHD and the functional domains in which improvement is desired. At a therapeutic dose, the effects of stimulant medications on core symptoms usually are apparent in 30-40 minutes after administration and continue for the expected duration of action. Parents are advised that 2-6weeks of medication may be needed for any therapeutic effect to show and before dose-reduction is considered.Pharmacodynamic effects differ with specific targets. Stimulants work at school to increase on-task behaviour and decrease interrupting and fidgeting. At home, they improve on-task behaviour, parent-child interactions and compliance. They also improve peer perceptions of social standing and increase attention while playing sports. [6] Treatment of adolescent patients with ADHD with stimulants has been associated with a reduction in risk for subsequent drug and alcohol use disorders. [7]Methylphenidate (MPH) increases norepinephrine and dopamine levels by inhibiting their reuptake and facilitating their release especially in the dorsolateral prefrontal cortex that improves attention, concentration, executive function and maintains wakefulness.[8]Various formulations of Methylphenidate that are currently available are:

1. MPH – immediate release (MPH-IR):MPH-IR has a short half-life of approximately 2 to 3 hours. This requires multiple daily doses that pose problems for dosing during school timings and can thus compromise patient compliance. The advantages are their safety, robust efficacy, and rapid onset of action. The dose range for MPH-IR is 0.3-1mg/kg TID up to a maximum of 60 mg per day.

2. MPH – extended release (MPH-ER):MPH-ER provides the benefit of a lasting effect that is maintained even about 12 hours after dosing and is equivalent to twice- or thrice-daily dosing of plain MPH. Advantage with the use of MPH-ER formulation is that it provides benefits throughout the day and early part of the evening. Disadvantage is that even though they can be dosed once daily, most patients will still require twice daily dosing to provide symptom control throughout the school day and after school, at home.[9] The dose range for MPH-ER is 0.3-1mg/kg), once in the morning.

3. MPH – osmotic release oral system (MPH-OROS)**:** This is a preparation of MPH with a novel drug delivery system using the osmotic pump process as a release mechanism. It consists of a 50:50 racemic mixture of D, L-threo MPH. It has a 12-hour coverage period per dose and, the release system being gradual, prevents any form of tachyphylaxis.OROS medicine minimizes the fluctuations between peak and trough concentrations associated with the immediate release tablets taken three times a day. [10]Adverse effects seen with Methylphenidate are, decreased appetite, tics, stuttering, poor growth, dizziness, headache, insomnia or nightmares, mood lability (isolation, irritability, agitation), vertigo, palpitation, constipation, hallucinations and rebound symptoms. [11]

Behavioral Management**:** These therapies focus on reducing ADHD related behaviours, reinforcing desired behaviours and developing positive habits which in turn help to improve social relationship and interpersonal functioning.This modality is preferred in children below 6 years of age and mild symptomatology and uncertain diagnosis. It includes parent training, classroom management and peer intervention. [12]The study is aimed to analyse and compare the clinical outcome of different formulations of Methylphenidate used. This study will help in deciding the choice of formulation of Methylphenidate in the treatment of ADHD.There is paucity of studies conducted on Indian population to compare the formulations of Methylphenidate. Keeping this in mind, this study was conducted to assess and compare the efficacy and side effects of different formulations of Methylphenidate.

METHODS

Study design- A prospective analytic study (clinical based study) was conducted over a period of one year ie. from August 2019 to July 2020, at the child development clinic, Sir Ganga Ram Hospital, New Delhi. Children in the age group between 6 years and 16 years who were diagnosed as having ADHD by DSM-V criteria were enrolled in the study after taking informed consent. Process - Detailed history and physical examination, including vitals and anthropometry was done and the severity of symptoms was recorded by Conner's parent and teacher rating scaleWe prescribed Methylphenidate by discussing with parents the advantages and disadvantages of the medicine and also did a thorough cardiac work up.Study subjects were prescribed different formulation of methylphenidate ie. 1. Immediate release, 2. Extended release and 3.OROS formulations, on 1:1:1 basis randomly.After three months of pharmacological andbehavioral therapy, these children were re-assessed to compare the outcome on behavioral performance based on Conner's parent rating scale. Tolerability and side effects of drugs were compared on the basis of pre-designed questionnaire completed by the parents. Due to pandemic situation, Conner's teacher rating scores could not be completed, hence in this study we included scores from Conner's parent rating scale for measuring the outcome of study subjects.**Tools:** 1. Conner's parent rating scale: It is an assessment tool used to obtain the parent's observations about the child and adolescent's behaviour. [13] This instrument is designed to assess ADHD in children and adolescents aged 6 to 18 years old. When used in combination with other information, results from the Conner's 3–P can provide valuable information for guiding assessment decisions.In this study, we used

short form of Conner's parent rating scale that consists of 43 items. T- Score Classification: 70-90= Very Elevated 65-69= Elevated 60-64= High Average 40-59= Average ScoreT-scores from 57–63 is considered borderline and of special note.For diagnosing ADHD, Conner's parent rating scale has specificity of 84% and sensitivity of 75%. [14]2. Parent questionnaire: a parent questionnaire was designed, keeping in mind the common side effects of Methylphenidate. After 3 months of starting the medication, parents were given this questionnaire to notify any side effects they noted in the child during the course of treatment. It is a non structured questionnaire. The side effects included in the questionnaire were: Headache, stomach ache, change of appetite, disturbed sleep, irritability, remaining aloof; changed behaviour (extreme sadness; dull, tired behaviour); tremors, abnormal movements, jerking, twitching, eye blinking, picking at skin or fingers, nail biting, lip or cheek chewing, sees or hears things that aren't there and others.Statistical analysis- Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0.

RESULTS

Demographic profile: Our study had 90 subjects, 75 (83.33%) male and 15 (16.66%) female subjects (table no. 1).24 subjects (26.67%) in the age group of 6-8 years, 37 (41.11%) in the 9-12 years group and 29 (32.22%) in 13-16 years group (figure no. 1). Average age was 10.9 years.Comparison of average Inattention (IN) scores within 3 groups ie. MPH-IR, MPH-ER and MPH-OROS:In the beginning of study, average score for Inattention (IN) on Conner's parent rating scale among subjects on MPH-IR was 79.63, for MPH-ER was 81.47 and for MPH-OROS was 80.97. After 3 months, it reduced to 75.63, 74.50 and 74.37 respectively.This difference is statistically significant(pvalue=0.00) (table no. 2).Comparison of average Hyperactivity (HY) scores within 3 groups is. MPH-IR, MPH-ER and MPH-OROS: In the beginning of study, average score for Hyperactivity (HY) on Conner's parent rating scale, among subjects on MPH-IR was 78.97, for MPH-ER was 79.37 and for MPH-OROS was 78.90. After 3 months, it reduced to 74.57, 74.30 and 71.77 respectively. This difference was statistically significant (p value=0.04) (table no. 3).Comparison of side effects between 3 groups is. MPH-IR, MPH-ER and MPH-OROS: Among subjects receiving MPH-IR, 3 (10%) subjects had decreased appetite, 2 (6.66%) had disturbed sleep, 1 (3.33%) complained of headache and 1 (3.33%) had stomach ache.

Among subjects receiving MPH-ER, 4 (13.33%) subjects had decreased appetite, 3 (10%) had disturbed sleep, 2 (6.66%) complained of headache and 2 (6.66%) had stomach ache.Whereas, among subjects on MPH-OROS, decreased appetite was reported in 5 (16.66%) subjects, stomach ache and disturbed sleep in 3 (10%), headache in 2 (6.66%), 1 (3.33%) subject reported tremors and 1(3.33%) had an episode of syncope.Frequency of side effects between the three groups was statistically not significant, p value= 0.798 (table no. 4).

Table 1: Demographic profile

6-8 years n (%)	9-12 years n (%)	13-18 years n (%)
24 (26.67%)	37 (41.11%)	29 (32.22)

Table 2: Comparison of average Inattention (IN) scores within 3 groups ie. MPH-IR, MPH-ER and MPH-OROS

	MPH-IR	Std. Deviation	MPH-ER	Std. Deviation	MPH-OROS	Std. Deviation
IN Pre-med	79.63	±5.702	81.47	±5.704	80.97	±5.102
IN Post-med	75.63	±5.524	74.50	±6.096	74.37	±6.620
IN reduced	4		6.97		6.6	
p Value	.00		.00		.00	

Table 3: Comparison of average Hyperactivity (HY) scores within 3 groups is. MPH-IR, MPH-ER and MPH-OROS

	MPH-IR	Std. Deviation	MPH-ER	Std. Deviation	MPH-OROS	Std. Deviation
HY Pre-med	78.97	±8.791	79.37	±7.005	78.90	±6.885
HY Post-med	74.57	±8.665	74.30	±7.764	71.77	±8.504
HY reduced	4.40		5.07		7.13	
p Value	.00		.00		.00	

Table 4: Comparison of side effects between 3 groups is. MPH-IR, MPH-ER and MPH-OROS

	MPH-IR	MPH-ER	MPH-OROS	P Value
Decreased appetite	3 (10.0%)	4 (13.3%)	5 (16.7%)	p value=0.798
Disturbed sleep	2 (6.7%)	3 (10.0%)	3 (10.0%)	
Headache	1 (3.3%)	2 (6.7%)	2 (6.7%)	
Stomachache	1 (3.3%)	2 (6.7%)	3 (10.0%)	

Syncope	0 (0%)	0 (0%)	1 (3.3%)	
Tremors	0 (0%)	0 (0%)	1 (3.3%)	
None	23 (76.7%)	19 (63.3%)	15 (50.0%)	

Figure 1: Demographic Profile

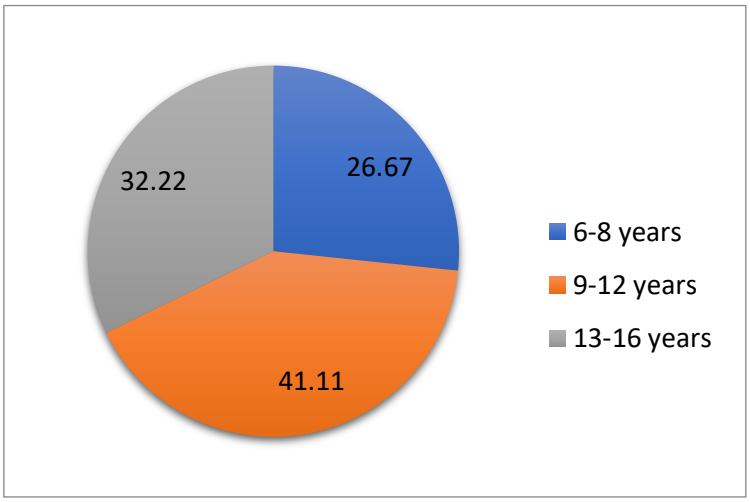


Figure 2: Comparison of average Inattention (IN) scores within 3 groups ie. MPH-IR, MPH-ER andMPH-OROS

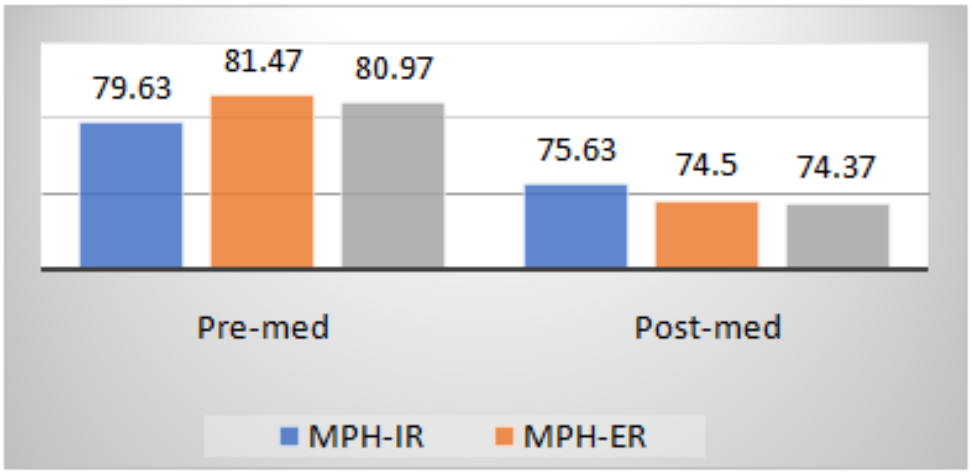


Figure 3: Comparison of average Hyperactivity (HY) scores within 3 groups is. MPH-IR, MPH-ER and MPH-OROS

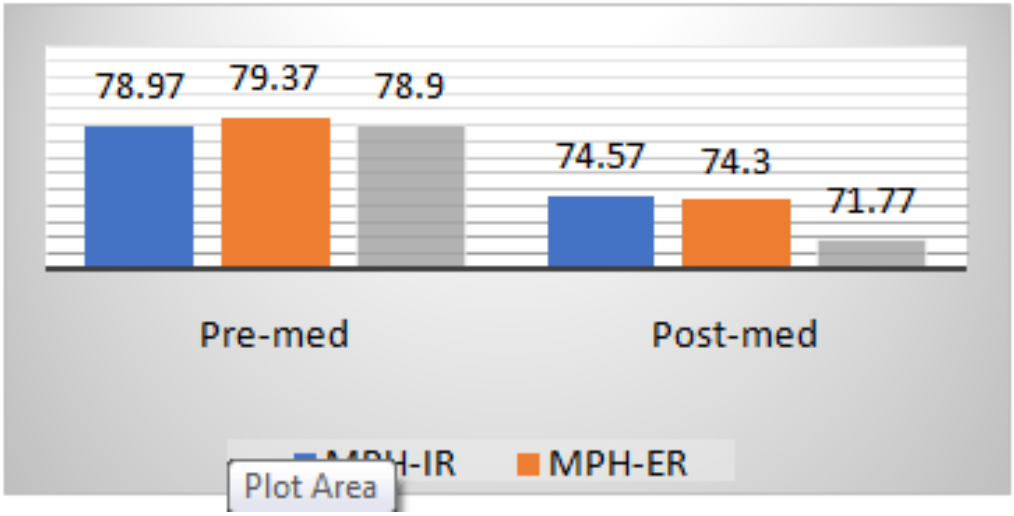
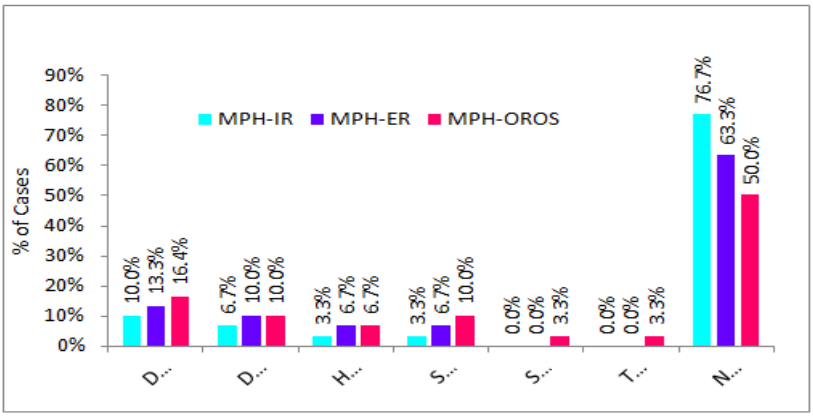


Figure 4: Comparison of side effects between 3 groups is. MPH-IR, MPH-ER and MPH-OROS



DISCUSSION

In the current study, we wanted to see if there were any differences between the effects of MPH immediate release (MPH-IR), MPH extended release (MPH-ER) and MPH-OROS formulations in a short period of time ie. 3 months, with the Conner's parent rating scale and also to compare the tolerability by studying the side effects with each formulation. Improvement in core symptoms of ADHD is an important foundation to educational and social re-integration and improved functioning. We used statistically significant reduction in the average score of inattention and hyperactivity on Conner's parent rating scale as a measure of improvement in core symptoms of ADHD.In this study, after three months of treatment (table 2), there is statistically significant reduction in average scores of inattention on Conner's parent rating scale among all the groups; ie. attention improved after treatment in all children (p value 0.00). Subjects on MPH-ER had more reduction in average scores of inattention (IN) than subjects on MPH-IR and OROS formulation.Similarly, among all the three groups there was statistically significant reduction in the average scores of hyperactivity on Conner's parent rating scale after three months of treatment that suggests, all children showed improvement in behaviour (p value 0.00) (table 3). On post hoc analysis, subjects on MPH-OROS had more reduction in average scores of Hyperactivity (HY) than subjects on MPH-IR and MPH-ER. This difference was statistically significant.The results were consistent with past studies. A metanalysis done by Punja, et al [15]concluded that longer acting formulations have modest effect on severity of inattention and hyperactivity. Similarly these results were consistent with the study done by Sanchez, et al [16] where adherence was better with MPH-OROS and with the analysis done by Faraone, et al. [17] which suggested that long acting formulations had better outcome than short acting ones. These results were also consistent with the study done by Kemner and Lange [18], and Remschmidt et al [19] that conclude, MPH-OROS shows improved outcomes, and the studies by Steele M, et al [20] and Robert, et al [21] where MPH-OROS has proved to have better adherence and thus improved outcomes in patients with ADHD.In treatment of ADHD, once-daily ER and OROSformulation of Methylphenidate showed significant improvements in inattention in almost similar efficacy, whereas, OROS formulation of Methylphenidate showed better control of symptoms of hyperactivity/ impulsivity. Both ER and OROS formulations of Methylphenidate had tolerable side effects profile and better outcome. Methylphenidate, unlike other drugs, has no major side effects. Subjects receiving MPH-IR had least reported side effects, reduced appetite in 3 (10%) subjects, disturbed sleep in 2 (6.66%) subjects and 1(3.33%) subject complained of stomach ache and headache. With MPH-ER, side effects noted were, reduced appetite in 4 (13.33%) subjects, disturbed sleep was reported in 3 (10%) subjects and 2 (6.66%) subjects complained of headache and stomach ache.Although having better outcome, subjects on MPH-OROS experienced maximum side effects. Most frequent side effects were reduced appetite in 5 (16.66%) subjects, stomach ache and disturbed sleep in 3 (10%) subjects, headache in 2 (6.66%) subjets, 1 (3.33%) subject reported tremors and 1(3.33%) subject had an episode of syncope. (Table no.4)Subject who had an episode of syncope was thoroughly examined, and neurological and cardiac check up was done and no abnormality was detected.However, comparison of side effects among the three formulations of Methylphenidate was statistically not significant (p value=0.798).These side effects did not cause the withdrawal of the drug (except in the child reporting an episode of syncope) and the symptoms disappeared later. These results were consistent with the study done by Punja, et al [15]where most common side effects were anorexia, headaches, abdominal pain and insomnia, with both long- and short-acting formulations of Methylphenidate, study by Schachter, et al [22] in which most common side effect was reduced appetite and with study by Khajehpiri et al [11] where reduced appetite was most frequently reported side effect and tremors were noted in a few subjects.The advantages of MPH-IR are its flexibility and management of doses that can be given during the day and have better effect during school hours with

better tolerability. The advantages of long-acting MPH-ER and MPH-OROS reside in better outcome in improving behaviour and, above all, convenience of the single daily dose, resulting in better compliance, less need of other persons like in the school and for doses, and less stigmatization and effect throughout the day both in school and at home. Therefore, each drug has its own indication.

CONCLUSION

The findings of the present study revealed that, in the treatment of ADHD, once-daily MPH-ER and MPH-OROS showed significant improvements in situational behaviour, better than MPH-IR with a favourable side effect profile and a prolonged duration of effect.

KEY MESSAGE

What is already known- Methylphenidate is first drug of choice in treatment of ADHD.

What this study adds- Among different formulations of Methylphenidate, longer acting ones are better as compared to short acting ones, in terms of clinical improvement and tolerability.

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