 DOI: 10.18231/2455-8451.2017.0010

Efficacy and tolerability of methyl phenidate and atomoxetine in children with attention deficit hyperactivity disorder –An open label randomized control trial from a tertiary care centre

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Abstract

Attention Deficit Hyperactivity Disorder is a commonly encountered problem in School aged Children. Recent studies have shown a significant improvement of symptoms with pharmacotherapy. We analyzed the effectiveness of Methyl phenidate and Atomoxetine in ADHD patients.

Objective: To compare the efficacy, tolerability and medication adherence of Methyl phenidate and Atomoxetine in Children with ADHD.

Study Design: Randomized controlled open label study in children aged 6-12 years with a diagnosis of ADHD as per DSM IV attending the Paediatric Neurology OPD of a Tertiary Care centre. Children were randomized to receive either Methyl phenidate or Atomoxetine for eight weeks. Baseline and post treatment (eight weeks) Attention Deficit/ Hyper Activity Disorder Rating Scale and the Clinical Global Impression Severity of Illness scales were compared between the two groups.

Results: There was significant improvement in ADHD symptoms with therapy. The mean reduction in the total Pre and post treatment ADHD RS score from baseline following drug therapy was 17.9 and 15.1 respectively in Methyl phenidate and Atomoxetine groups which was not statistically significant. 67.5% of children on Methyl phenidate showed significant improvement CGI scale compared to 60% on Atomoxetine. There was no significant difference between the groups. Both the drugs were well tolerated.

Keywords: Attention Deficit Hyperactivity disorder, Methyl phenidate, Atomoxetine, Attention Deficit Hyperactivity disorder Rating scale, Clinical Global Impression of severity scale

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neuro behavioral in children which can adversely affect their academic achievements, social interaction and well-being.[1,2] The worldwide pooled prevalence of the disease is 5.29%.[3] Pharmacotherapy and behavioral interventions are found useful in managing children with ADHD. Behavior therapy alone has only limited effect on controlling symptoms of ADHD. Drug therapy is effective in controlling the core symptoms of ADHD.[4] Combination of behavior therapy with medication appears to improve the symptoms better.[5] Methyl phenidate, a stimulant drug and Atomoxetine, non-stimulant drug are the two commonly used medications for ADHD. We tried to compare the efficacy, tolerability and treatment adherence of these two drugs.

Objective

We conducted a randomized open label study to compare the efficacy of Methyl phenidate and Atomoxetine in children diagnosed to have ADHD according to DSM IV criteria. Tolerability and medication adherence was also analyzed.

Materials and Method

Children aged 6 - 12 years who met the DSM IV criteria for ADHD attending Pediatric Neurology OPD our institution were recruited to the study over a period of six months. Patients with eating and substance abuse disorder, Tourette syndrome, hyperthyroidism, glaucoma and cardiac arrhythmias were excluded. The study was approved by Institutional ethical committee. A written informed consent of caregivers was obtained prior to enrolling patients.

Patients were allocated to take either Methyl Phenidate or Atomoxetine based on random number method. Demographic details like age, gender and clinical details like symptoms of ADHD, Co morbidities and other relevant data were collected prospectively by interviewing the caregivers using valid questionnaire and from the hospital records. Baseline Intelligence quotient was assessed. Attention Deficit Hyperactivity Rating Scale (ADHD-RS) total scores, Inattention, subscale scores and Hyperactivity-impulsivity subscale sores were obtained at baseline and after two months of therapy. The difference in mean scores following therapy was compared between the two treatment groups. The grades of severity of illness and improvement of symptoms from baseline following therapy were analyzed using Clinical Global Improvement (CGI) scale. Medication adherence was

identified using Morinsky Medication Adherence Scale. Analysis of data was done using SPSS Version 11.0 statistical software. P value of <0.05 was considered statistically significant.

Results

Initially 87 ADHD patients were enrolled in the study. 44 children received Methyl phenidate and 43 received Atomoxetine. Two patients in Methyl phenidate group and one patient in atomoxetine group discontinued treatment due to adverse events. Four patients were lost to follow up. 40 patients each in Methyl Phenidate and Atomoxetine group were finally analyzed for efficacy, tolerability and drug adherence.

Demographic details: Majority of our patients were 8-9 years of age (45%). Majority of the patients were males. The average dose of Methyl phenidate was 10mg (range 5-15mg) /day and that of Atomoxetine was 15mg /day (Range 10-25mg). The duration from onset of symptoms to therapy, the average school performance, Percentile IQ, ADHD subtype and family history were comparable between the groups (Table 1).

Table 1: Demographic Details of patients

Demographic variable	Methyl Phenidate group % (n)	Atomoxetine group % (n)	Total % (n)
Age (years)			
6-7	25 (10)	32.5 (13)	1.7 (23)
8-9	50 (20)	40 (16)	45 .0 (36)
10-12	25 (10)	27.5(11)	26.3 (21)
Gender			
Male	75 (30)	82.5 (33)	78.7 (63)
Female	25 (10)	17.5 (7)	21.3 (17)
Residence			
Rural	60 (24)	60(24)	60 (48)
Urban	40 (16)	40 (16)	40 (32)
Duration of illness (years)			
<1 year	7.5 (3)	5(2)	6.3 (5)
1-2 year	67.5 (27)	55(22)	61.2(49)
3-5 year	25 (10)	40(16)	32.5(26)
Family History of ADHD	5(2)	10(4)	7.5(6)
School Performance			
Average	22.5(9)	10(4)	16.3(13)
Below Average	42.5(17)	45.0 (18)	43.7(35)
Poor	35.0(14)	45.0(18)	40.0 (32)
ADHD Sub type			
Hyperactive- Impulsive	0(0)	7.5(3)	3.7(3)
Inattentive	5.0(2)	5.0(2)	5.0(4)
Combined	95.0 (38)	87.5(35)	91.3 (73)
Percentile IQ			
≤25	50.0(20)	67.5(27)	58.8(47)
26-74	35.0(14)	27.5(11)	31.2(25)
75-94	0.0 (0)	2.5(1)	1.3(1)
≥95	15.0(6)	2.5(1)	8.7(7)

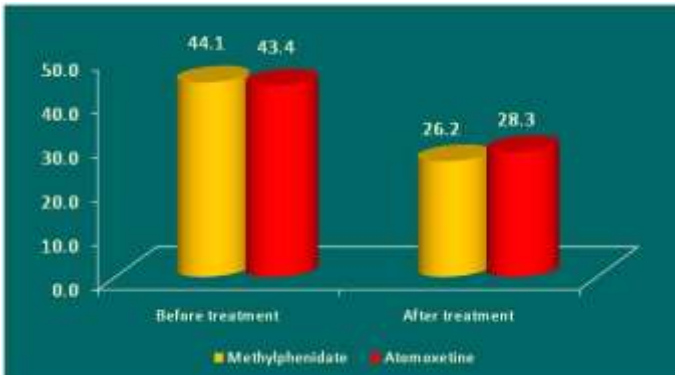

Fig. 1: Change in ADHD RS Total Scores

Improvement following drug therapy: The mean ADHD RS total score improved from 44.1 (sd 5.9) to 26.2 (sd 8.9) in the Methyl phenidate group and 43.4 (sd 8.3) to 28.3 (sd 12.0) in the Atomoxetine group. The mean reduction in the total Pre and post treatment score from baseline following drug therapy was 17.9 (paired t 11.85; p= .000) and 15.1 (paired t 9.66; p= 0.000) respectively. However, between the groups there was no significant difference. (t=1.26; p= 0.21) (Table 2, Fig. 1)

Table 2: Mean scores - Inattentive Scale, Hyperactivity- Impulsivity scale, ADHD – RS total

Scale	Group (n)	Pretreatment Mean (sd)	Post treatment	Mean difference	Paired t (p)
Inattentive Subscale score	Methyl phenidate (40)	22.3 (2.9)	12.9 (5.5)	9.4	13.35 (p= 0.000)
	Atomoxetine (37)	21.8 (3.6)	14.5(6.0)	7.3	8.44 (0.000)
Hyperactivity-Impulsive subscale score	Methyl phenidate (38)	22.9 (2.4)	12.9(5.6)	10.1	11.15 (p=0.000)
	Atomoxetine (39)	23.8 (2.9)	15.5 (6.4)	8.3	9.96 (p=0.000)
ADHD –RS Total Score	Methyl Phenidate (40)	44.1 (5.9)	26.2 (8.9)	17.9	1.85 (p=0.000)
	Atomoxetine	43.4 (8.3)	28.3 (12)	15.1	9.66 (0.000)

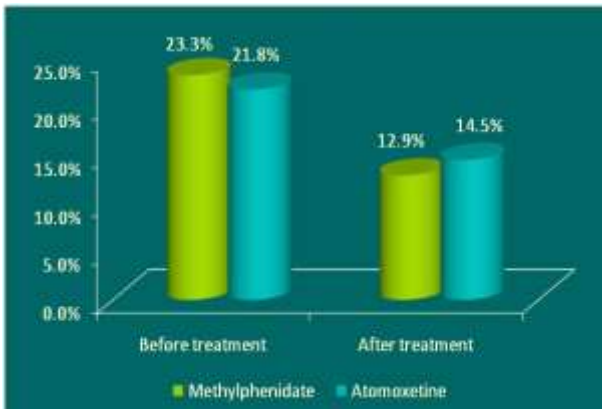

Fig. 2: Comparison based on inattentive subscale score

The mean Inattentive subscale scores at baseline was 22.3 (sd 2.9) in Methyl phenidate group and 21.8 (sd 3.6) in Atomoxetine group. The scores after 2 months of therapy were 12. 9 (sd 5.5) and 14.5 (sd 6) respectively. The mean difference in the pre and post treatment scores was 9.4 (paired t 13.35, p=0.000) and 7.3 (8.44, p=0.000) between the groups. There was statistically significant reduction in the Inattentive score in both groups. Group wise comparison, however, did not show any statistical difference in reduction of score from baseline (t=1.89; p= 0.063) (Table 2, Fig. 2)

The mean baseline Hyperactive- Impulsive subscale score before therapy was 22.9 (sd 2.4) for Methyl phenidate group and 23.8 (sd 2.9) for Atomoxetine group. Post treatment scores at the end of 2 months were 12.9 (sd 5.6) and 23.8 (sd 6.4) respectively. The mean difference from baseline in post treatment scores were 10.1((Paired t = 11.15, p= 0.000) and 8.3 (paired t 9.96, p=0.000) in Methyl phenidate and Atomoxetine group. Comparison of reduction from baseline in Hyperactivity - Impulsivity score- between the two treatment groups did not show any significant difference (t =1.42; p= 0.16). (Table 2, Fig. 3)

Table 3: Severity of Illness before and after treatment

Methyl Phenidate Group			
Severity of Illness	**Before treatment % (n)**	**After treatment % (n)**	**Z (p)**
Border line mentally Ill	0 .0 (0)	17.5 (7)	5.17 (0.000)
Mildly Ill	0.0 (0)	47.5 (19)	
Moderatley Ill	35% (14)	25.0 (10)	
Markedly Ill	47.5%(19)	10.0 (4)	
Severely Ill	17.5%(7)	0.0(0)	
Atomoxetine Group			
Severity of Illness	**Before treatment % (n)**	**After treatment % (n)**	**Z (p)**
Border line mentally Ill	0 .0 (0)	5 (2)	5.12 (0.000)
Mildly Ill	0 .0 (0)		
Moderatley Ill	35.0	30 (12)	
Markedly Ill	37.5 (15)	15 (6)	
Severely Ill	27.5 (11)	7.5 (3)	

Fig. 3: Comparison based on hyperactive GÇôimpulsive subscale score

Clinical Global Impression – severity of Illness Scale: The split up patients based on severity of illness before and after treatment is shown in Table 3. There was statistically significant reduction in severity of ADHD in both treatment groups after two months of therapy, but there was no statistically significant difference between two groups with respect to change in severity of illness following treatment (z =1.82; p=0.07).(Table 4, Fig. 4)

Table 4: Comparison of change in Severity of illness on Drugs

Change in severity of Illness	Methyl phenidate % (n)	Atomoxetine % (n)	Z (p)
No change	15 (6)	20 (8)	1.82 (0.069)
Grade I change	37.5 (15)	52.5 (21)	
Grade II change	25.0 (10)	20 (8)	
Grade III change	22.5 (9)	7.5 (3)	

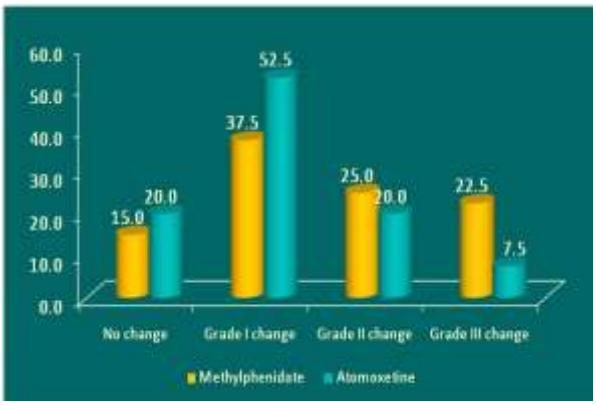

Fig. 4: Comparison of change in severity of illness scale

There was no statistically significant difference between two treatment groups with regard to global improvement in CGI scale (p=0.145). In Methyl phenidate group 17.5% (n=7) patients were reported to be very much improved, 50% (n=20) patients much improved, 27.5% (n=11) minimally improved, and 5% (n=2) reported no improvement. In the atomoxetine group, 7.5 % (n=3) patients had very much improved, 52.5% (n=21) had much improved, 20% (n=8) had minimally improved and 20% (n=8) reported no improvement. (Table 5, Fig. 5).

Table 5: Comparison of Change in Global improvement based on Drugs

Global improvement	Methyl phenidate % (n)	Atomoxetine % (n)	Z (p)
Very much improved	17.5(7)	7.5 (3)	1.46 (0.145)
Much improved	50 (20)	52.5 (21)	
Minimally improved	27.5 (11)	20 (8)	
No change	5.0 (2)	20 (8)	

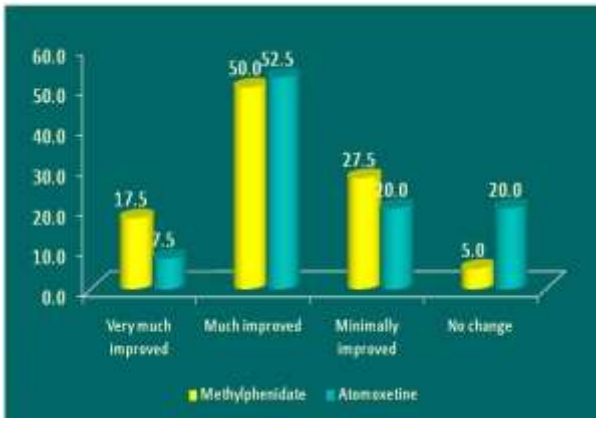

Fig. 5: Comparison of change in global improvement based on drug

Adverse effects: The most common adverse effects were head ache (30%), insomnia(12.5%) and abdominal pain (10%) in those on Methyl phenidate. In Atomoxetine group, head ache was reported by 15%, abdominal pain by 15%, anorexia by 15%, insomnia by 12.5% and somnolence by 15% patients. There was no statistically significant difference between two groups in terms of side effects.

Medication Adherence: In Methyl phenidate group, 42.5% had high adherence, 52.5% had medium adherence and 5% had low adherence. In the Atomoxetine group, there were 37.5% patients with high adherence 42.5% with medium adherence, and 20% with low adherence. There was no significant difference between groups with respect to medication adherence. Variable like age, parental education, Urban or rural, income, associated co- morbidities and the number of drugs used by patients showed no statistically significant correlation with adherence in either treatment group.

Discussion

We studied the efficacy, tolerability and the medication adherence of Children diagnosed to have ADHD based on DSM IV. We randomly assigned patients to receive either Methyl phenidate or Atomoxetine and analyzed them at the end of two months. There were 40 patients each in both groups.

Majority of patients in the study population were aged 8-9 years. Similar findings have been published by Anne F Klassen et al.,[6] Mark A. Stein et al[7] and Soochurl Cho et al.[8] Even though many children with ADHD develop symptoms before eight years, majority remain unrecognized due to lack of awareness of parents about the disease. The mean age of children with ADHD on Methyl phenidate was 8.6 years (sd1.9) and on Atomoxetine was 8.3 (sd `1.8) years in our study.

The incidence of ADHD is reported to be high among male children[9,10] 78.7% patients in our study were males. Male to female ratio was 3.6: 1 in the present study. 30 patients in Methyl phenidate group and 33 patients in Atomoxetine group were boys. Other studies also have reported similar male preponderance of ADHD.[11,12,13] Male predominance may be due to Y chromosome. Disorders with increase in number of y Chromosomes are associated with hyperactivity and violent behavior where as those with increased number of X chromosomes are associated with reduced activity and poor intelligence. Restrictive rearing of female children compared to male children may be another reason for male predominance.

There was significant reduction in total ADHD RS score, Inattentive subscale score and Hyperactive – Impulsive subscale score following therapy with both Methyl phenidate and Atomoxetine. A double blind RCT by Jeffrey H Newcorn[11] demonstrated a similar reduction in inattentive subscale in those treated with Methyl phenidate and Atomoxetine. Our findings are consistent with the findings of Hanwella R et al and Kratochvil CJ et al;[14,15] however, a recent meta analysis showed that Methylphenidate is better in controlling ADHD symptoms and better safety profile compared to Atomoxetine.[16]

Before treatment, majority of patients on Methyl Phenidate and Atomoxetine were markedly ill with regard to CGI- Severity of illness scale. At the of two months, majority became mildly ill in both treatment groups. However, there was no significant difference between two groups with respect to the change in severity of illness. Similar results have been observed in other studies.[14,15] In global improvement scale also, patients on Methyl phenidate and Atomoxetine showed significant improvement. But between groups, both drugs were found to be equally effective in improving ADHD symptoms. Headache was the most common side effects for patients on Methyl phenidate and somnolence for those on Atomoxetine, but this was not statistically significant. The incidence of adverse events were also similar between the two treatment groups.

One important limitation of our study was that it was an open label study. Another limitation was the presence of epilepsy in one third of children. This may be because ours was a tertiary care Paediatric Neurology centre where children with epilepsy are often referred. Epilepsy and anticonvulsant therapy are associated with poor attention and memory span and hyperactivity. However, the patients with epilepsy were equally distributed between the treatment groups. Another draw back was a relatively short term follow up. ADHD is a chronic disease which requires long term therapy and follow up. Absence of a drug naïve control group is another limitation.

In conclusion, there was significant improvement in all symptoms of ADHD following drug therapy. Methyl phenidate and Atomoxetine were equally effective in significantly reducing symptoms. No serious adverse events were reported in our study population. Safety and tolerability were also r comparable between these two drugs. Larger, double blind placebo controlled trials are needed to evaluate the comparative efficacy between the two drugs.

References

1. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011 Nov;128(5):1007-22.
2. Polanczyk G1, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta regression analysis. Am J Psychiatry. 2007 Jun;164(6):942-8.
3. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder.)J Am Acad Child Adolesc Psychiatry. 2007 Jul;46(7):894-921.
4. Brown RT, Amler RW, Freeman WS, Perrin JM, Stein MT, Feldman HM, Pierce K, Wolraich ML; Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005 Jun;115 (6):e749-57.
5. Anne F. Klassen, Anton Miller, et al, Health –Related quality of Life in Children and Adolescents who have a Diagnosis of Attetion Deficit/ Hyperactivity Disorder. Pediatrics 2004;114:541-547.
6. Mark A. Stein, Christopher S Sarampote, Irwin D. Waldman et al, A Dose- Response Study of OROS Methyl Phenidate in Children with Attention- Deficit/ Hyperactivity Disorder. Pediatrics 2003;112:404-412.
7. Soochurl Cho , Soyoung Irene Lee, Hnik Yoo et al, A Randomised Open –Label Assessment of Reponse to various Doses of Atomoxetine in Korean Pediatric Outpatients with Attention Deficit/ Hyperactivity Disorder. Psychiatry Investig 2011;8:141-148.
8. Goldman LS, Genel M, Bezman R J et al, Diagnosis and Treatment of Attention Deficit /hyperactivity Disorder in Children and Adolescencts. JAMA 1998;279:1100-1107.

9. American Academy of Child and Adolescent Psychiatry. Practice Parameters for the assessment and treatment of Children, Adolescents and adults with Attention Deficit / hyperactivity disorder. J Am Acad Child Adolesc Psychiatry.1997;36;85-121.
10. Jeffrey H Newcorn, Albert J Allenet et al, Atomoxetine and Osmotically Released Methyl phenidate for treatment of Attention Deficit Hyperactivity Disorder: Acute Comparison and Differential Response. Am J Psychiatry 2008;165:721-730.
11. Kemner JE, Ciccone PE et al, Outcomes of OROS Methyl Phenidate compared with Atomoxetine in Children with ADHD: A Multicenter, Randomized Prospective Study. Adv Ther 2005;22(5):498-512.
12. Par Svanborg, Gunilla Thernlund, Per A. Gustafsson et al, Efficacy and Safety of atomoxetine as add-on to psychoeducation in the treatment of Attention Deficit/ Hyperactivity Disorder. Eur Child Adolesc Psychiatry 2009;18(4):240-250.
13. Hanwella R Senanayake M, de Silva V, Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry. 2011 10(11):176. J Am Acad Child Adolesc Psychiatry. 2002 Jul;41(7):776-84.
14. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, Newcorn JH, Casat C, Milton D, Michelson D, Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry. 2002;41(7):776-84.
15. Liu Q, Zhang H, Fang Q, Qin L, Comparative efficacy and safety of methylphenidate and atomoxetine for attention-deficit hyperactivity disorder in children and adolescents: Meta-analysis based on head-to-head trials. J Clin Exp Neuropsychol. 2017 Jan 4:1-12.