RESEARCH PAPER

Comparative Short term Efficacy and Tolerability of Methylphenidate and Atomoxetine in Attention Deficit Hyperactivity Disorder

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Objective: To compare the short term efficacy and tolerability of methylphenidate and atomoxetine in children with Attention deficit hyperactivity disorder (ADHD).

Design: Open label randomized parallel group clinical trial.

Setting: Child Guidance Clinic of a tertiary care hospital of Northern India from October 2010 to June 2012.

Participants: 69 patients (age 6-14 y) with a diagnosis of ADHD receiving methylphenidate or atomoxetine.

Intervention: Methylphenidate (0.2-1 mg/kg/d) or atomoxetine (0.5-1.2 mg/kg/d) for eight weeks.

Main outcome measures: Treatment response (>25% change in baseline Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS); Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS); Clinical Global Impression Severity Scale (CGI-S) at eight weeks and adverse effects.

Results: Treatment response was observed in 90.7% patients from methylphenidate group and 86.2% patients of atomoxetine group at an average dose of 0.45 mg/kg/d and 0.61 mg/kg/d, respectively. The patients showed comparable improvement on VADPRS (P=0.500), VADTRS (P=0.264) and CGI-S (P=0.997). Weight loss was significantly higher in methylphenidate group (-0.57±0.78 kg; P=0.001), and heart rate increase was observed at higher rate in atomoxetine group (7± 9 bpm; P=0.021).

Conclusion: Methylphenidate and atomoxetine are efficacious in Indian children with ADHD at lesser doses than previously used. Their efficacy and tolerability are comparable.

Trial Registration No.: CTRI/2011/08/001981

Keywords: *ADHD, Adverse events, Efficacy, Treatment dose.*

Attention Deficit Hyperactivity Disorder (ADHD) is one of the common chronic problems affecting school-age children [1], and have poor family and peer relations [2]. Without effective treatment, such children may develop long-term handicaps [3]. According to current clinical guidelines, psycho-stimulants, especially methylphenidate, are considered the first line treatment of ADHD [4,5]. However, methylphenidate is associated with risk of variation in mood state, motor tics, and abuse potential [6]. Atomoxetine is a nonstimulant that is approved for use in ADHD as the second line treatment [4,5]. The studies comparing therapeutic responses to stimulants and atomoxetine in ADHD have been conducted in Western countries, and have produced conflicting results [7-13]. The present study was carried out to compare the efficacy and tolerability of methylphenidate and atomoxetine in Indian children with ADHD.

METHODS

Patients were recruited from those attending the Child Guidance Clinic of a tertiary care hospital in Northern India from October 2010 to May 2012. Children (age 6 to 14 years) diagnosed as ADHD, according to Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision [14], and having moderate to severe illness as assessed by Clinical Global Impressions Severity Scale (CGI-S) [15] were eligible for inclusion. Patients with history of non-response or adverse drug reactions to methylphenidate or atomoxetine in the past, those who had taken any medication for ADHD in past one month, or those with history of heart disease, seizures, pervasive developmental disorder, substance abuse, mental retardation or tic disorder were excluded.

Parents brought the patients to the child guidance clinic themselves or when referred by school. Before initiating treatment, electrocardiogram (ECG) was performed for each patient to rule out any cardiac abnormality.

Written informed consent was obtained from both parents/guardians and the children. The principles enunciated in the Declaration of Helsinki [16] and Indian Council of Medical Research [17] were complied with. Clearance was obtained from the Ethics committee of the Government Medical College and Hospital, Chandigarh.

The patients were allotted to Group A or Group B by

simple randomization as per computer generated table of random numbers. Patients in Group A received immediate release tablet Methylphenidate (once or twice daily) while those in Group B received tablet Atomoxetine (once or twice daily). The drugs prescribed were from standard pharmaceutical companies, approved by the drug committee of the institute. Patients were started on tablet Methylphenidate (immediate release) 5 mg once a day, or tablet Atomoxetine 10 mg once a day, on their first visit as per Clinical Practice Guidelines of Indian Psychiatric Society [18]. Efforts were made to increase the dose of Methylphenidate up to 1mg/kg/day and of atomoxetine up to 1.2 mg/kg/d once or twice daily depending upon the response and tolerability. Weekly increments of 5 mg were tried for both methylphenidate and atomoxetine. Patients were assessed at baseline and once weekly or fortnightly till 8 weeks. On each visit, improvement in symptoms was assessed by Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) [19]. Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS) Proforma [20] was sent through the parents to be filled up by teachers at baseline and at 8 week. Teachers were contacted telephonically to obtain information about patients' classroom behavior and for clarifying VADTRS. CGI-S was also used to assess the severity of illness at baseline and last follow up visit.

The various side effects were noted on each assessment on the Adverse Events Checklist prepared for the study. It was a semi-structured check list enlisting all the common side effects of methylphenidate and atomoxetine. The parents were asked to rate the severity of each side effects produced in their children as mild, moderate and severe. Those who reported mild side effects were continued on the same dose. For those who developed moderate severity of side effects, dose was reduced. Those who rated any adverse effect to be severe were taken out of the study after stopping the medication. They were then managed as per standard treatment protocol of the department. Heart rate and blood pressure were also recorded at each visit. Laboratory investigations including complete blood counts, renal function tests and liver function tests were done at baseline, four weeks and eight weeks. Primary outcome measures were: improvement in symptoms as assessed by VADPRS, and percentage of patients who developed various adverse effects for estimation of tolerability. Secondary outcome measures were: improvement in symptoms as assessed by VADTRS and CGI-S; and change in patients' heart rate, blood pressure, weight and laboratory investigations for assessment of tolerability.

The sample size was calculated based on data from previous studies that 70% of patients receiving methylphenidate show improvement of 25% or more in ADHD rating scale [18]. It was planned to conclude equivalence of atomoxetine with methylphenidate if 25% or more improvement is seen in 70 ± 30 % of patients. With a power of 70% and an alpha of 5%, a sample size of 37 per group was calculated. Keeping in mind a dropout rate of about 5-10%, it was decided to enroll 40 patients in each group.

Statistical analysis: Data were analyzed using SPSS version 16.. Significance level was $P < 0.05$ (two tailed). Fisher's exact test and *Chi* square test were used to compare categorical variables. Independent sample t-test and paired t-test were administered for analysis of parametric data. Mann Whitney test and Wilcoxon signed rank test were used for analysis of CGI-S score as this parameter was not normally distributed.

RESULTS

Out of 84 children randomized to receive either drug, 17 refused after baseline assessment, and were excluded from analysis. Of remaining, 33 were in methylphenidate group and 36 were in atomoxetine group (***Fig.* 1**). In both methylphenidate and atomoxetine groups, combined type of ADHD was the commonest, followed by inattention

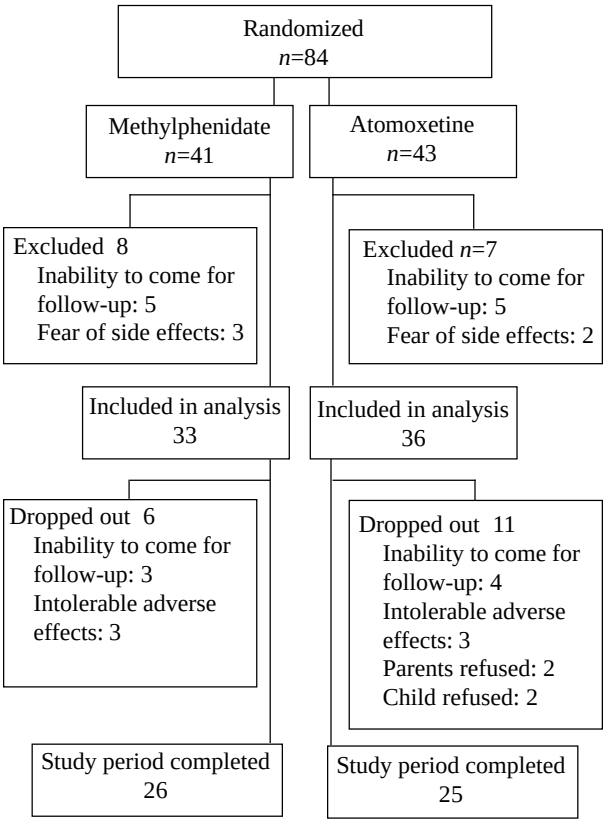

FIG. 1 *Patient flowchart.*

type and hyperactive/impulsive type. The baseline parameters, including VADPRS total score, VADPRS subscale scores, VADTRS score and CGI-S score were comparable between the two groups (***Table* I**).

Out of the total 69 recruited patients, 51 (74%) could be followed up for the eight weeks. Seventeen patients (6 from methylphenidate group and 11 from atomoxetine group) discontinued the treatment at some point. There was no significant difference between mean (SD) baseline VADPRS total score of retained [52.14 (11.99)] and dropped out [57.29 (14.87)] patients ($P = 0.153$).

There was significant improvement over 8 weeks in both methylphenidate and atomoxetine groups when measured on VADPRS total score, inattention subscale score and hyperactivity subscale score. The comparative change in VADPRS (total and subscales) scores from baseline to 8 weeks was not significant (***Table* II**).

With the criteria of 25% reduction in baseline scores of VADPRS, 90.7% patients from methylphenidate group and 86.2% patients from atomoxetine group showed improvement. Three (11.5%) patients in methylphenidate group and five (20%) in atomoxetine group (P=0.465) showed less than 25% improvement after 2 months in VADPRS scores even when maximum therapeutic dose was administered.

There was more than 25% improvement in baseline VADPRS total score from 3rd week onwards both in methylphenidate and atomoxetine groups when the mean (SD) dose administered were 11.59 (2.83) mg/day and 14.03 (3.85) mg/day, respectively. The mean (SD) dose administered at conclusion of the study when there was maximum efficacy and tolerability was 17.35 (7.52) mg/day (or 0.62mg/kg/day) in the methylphenidate group and 17.46 (7.22) mg/day (or 0.7mg/kg/day) in the atomoxetine group (***Web Fig*. 1**).

TABLE I BASELINE CHARACTERISTICS OF THE TWO GROUPS

Variable	*Methylphenidate (N=33)*	*Atomoxetine (N=36)*
Age (y)*	8.47 ± 2.22	8.66 ± 2.44
Weight (kg)*	28.54 ± 9.45	25.26 ± 8.25
Males, No. (%)	27 (81.8%)	29 (80.6%)
Type of ADHD		
Inattention	9 (27.3%)	6 (16.7%)
Hyperactive/impulsive	2 (6.1%)	4 (11.1%)
Combined	22 (66.7%)	26 (72.2%)
Comorbidity		
ODD	15 (45.5%)	22 (61.1%)
Conduct Disorder	1 (3%)	6 (16.7%)
VADPRS*		
Total	51. 18 ± 10.86	55.03 ± 14.44
Inattention	20.88 ± 3.81	19.42 ± 5.50
Hyperactivity	17.85 ± 6.47	19.72 ± 5.79
CGI-S*	5.03 ± 0.95	5.22 ± 0.79
VADTRS*	41.11 ± 14..22	46.11 ± 14.61

*VADPRS = Vanderbilt ADHD Diagnostic Parent Rating Scale; CGI-S = Clinical Global Impression Severity Scale; VADTRS = Vanderbilt ADHD Diagnostic Teacher Rating Scale; ODD = Oppositional Defiant Disorder; All values in No.(%) except * values in mean (SD).*

According to the adverse effects checklist prepared for the study, 18 (55%) patients from methylphenidate group and 20 (56%) from atomoxetine group developed side effects during the course of the study. The commonest reported adverse effect in both groups was reduced appetite. There was no significant difference between two groups in the occurrence of various adverse effects (***Table* III**). Three patients in each group dropped out due to development of adverse effects rated as severe by the parents. These side effects were irritability, fatigue, drowsiness, headache and reduced appetite.

TABLE II CHANGE IN VADPRS, VADTRS AND CGI-S SCORES FROM BASELINE TO 8 WEEKS

Variable	*Methylphenidate*				*Atomoxetine*				
	Baseline n = 33	*Week 8 n= 26*	*Mean difference*	*Intra-group P value*	*Baseline n = 36*	*Week 8 n = 25*	*Mean difference*	*Intra-group P value*	*Inter-group P value*
VADPRS									
Total	51. 18 (0.86)	24.69 (10.29)	-26.69 (1.99)	<0.001	55.03 (14.44)	23.60 (17.21)	-29.32 (15.49)	<0.001	0.500
Inattention	20.88 (3.81)	10.375 (5.39)	-10.00 (4.38)	<0.001	19.42 (5.50)	7.961 (5.82)	-11.23 (4.93)	<0.001	0.690
Hyperactivity	17.85 (6.47)	9.46 (5.11)	-9.23 (6.14)	<0.001	19.72 (5.79)	9.00 (6.92)	-10.20 (7.30)	<0.001	0.610
CGI-S	5.03 (0.95)	2.92 (0.84)	-2.04 (1.15)	<0.001	5.22 (0.79)	3.08 (1.55)	-2.04 (1.37)	<0.001	0.997
VADTRS	41.11 (14.22)	25.29 (9.20)	-17.2619(10.12)	<0.001	46.11 (14.61)	30.42 (14.51)	-14.10 (9.41)	<0.001	0.264

VADPRS: Vanderbilt ADHD Diagnostic Parent Rating Scale; All values in mean (SD).

TABLE III ADVERSE EFFECTS IN METHYLPHENIDATE AND ATOMOXETINE GROUPS

Adverse effects	*Methylphenidate n=32 No. (%)*	*Atomoxetine n=36 No. (%)*	*P value*
Headache	4 (12.5)	2 (5.6)	0.410
Nausea	1 (3.1)	1 (2.8)	1.000
Vomiting	1 (3.1)	1 (2.8)	1.000
Decreased appetite	14 (43.8)	12 (33.3)	0.378
Pain abdomen	3 (9.4)	0 (0)	0.099
Irritability	2 (6.3)	7 (19.4)	0.157
Fatigue	2 (6.3)	1 (2.8)	0.598
Drowsiness	1 (3.1)	6 (16.7)	0.110
Urinary incontinence	1 (3.1)	2 (5.6)	1.000
Sadness	0 (0)	1 (2.8)	1.000
Rash	1 (3.1)	0 (0)	0.471
Hypersalivation	1 (3.1)	0 (0)	0.471
Insomnia	1 (3.1)	0 (0)	0.471

When assessed on VADTRS and CGI-S, there was significant improvement over 8 weeks in both methylphenidate and atomoxetine groups. Teacher's report was available for 78% of patients. The change in VADTRS score and CGI-S score from baseline to 8 weeks were comparable in methylphenidate and atomoxetine groups (***Table* II**). There was no significant change in the mean (SD) heart rate from baseline 87 (9)/min to 90 (8)/min at week 8 in methylphenidate group (P=0.312). However, in atomoxetine group, there was significant increase in heart rate from baseline 84 (6) to week 8, 92(8)/min with mean difference 7 (9)/min and P =0.021. There was no significant decrease in weight (in kg) in methylphenidate group from baseline to week 4 [Mean difference (SD), -0.166 (0.747); P=0.286], but there was significant decrease at week 8 [-0.576 (0.783); P=0.001]. In the atomoxetine group, there was no significant weight differences.

There were no significant differences in hematological and biochemical parameters from baseline to week 4 and week 8 in either of the groups.

DISCUSSION

The present trial documented that both methylphenidate and atomoxetine produced statistically significant and comparable improvements in the symptoms of ADHD, as reported by parents and teachers. The average dose of both methylphenidate and atomoxetine which produced significant clinically improvement in the patients of present study was much lesser than in earlier studies.

Improvements produced by both atomoxetine and methylphenidate in this study were comparable to that reported in earlier clinical trials [21]. Absence of teacher's assessment had been a potential shortcoming in majority of earlier studies comparing relative efficacy of the two drugs [7-12]. In our study, the rate of occurrence of adverse events was comparable to that reported in earlier studies [7,11,12]. Decreased appetite was the commonest adverse event in both the groups and methylphenidate led to a little more weight loss than atomoxetine. The present study had limitations of being an open labelled study without allocation concealment. Placebo arm was not included due to ethical considerations. Moreover, lesser number of patients could be included in the analysis of the study due to the high dropout rate. A high dropout rate has also been reported in an earlier study from India [22].

Nonetheless, the present study has important clinical implications. Equivalent therapeutic efficacy and response rate was found with lesser doses administered for both the drugs than study populations in other countries. Atomoxetine was found to be comparable in efficacy and tolerability methylphenidate in short term. Future studies with larger sample sizes may be taken up in each subtype of ADHD with longer duration of follow up in order to document long term effects of treatment.

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WHAT IS ALREADY KNOWN?

- Methylphenidate is the first line and atomoxetine is the second line treatment of ADHD.

WHAT THIS STUDY ADDS?

- Methylphenidate and atomoxetine have comparable efficacy in Indian Children with ADHD.
- Dose of methylphenidate and atomoxetine for therapeutic response seems to be much lower in Indian population than documented from other settings.

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