ATOMOXETINE THERAPY EFFECTIVENESS IN CHILDREN WITH ADHD AT DAY CARE, DR. SOETOMO HOSPITAL, SURABAYA

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ABSTRAK

Attention Deficit Hyperactivity Disorder (ADHD) adalah gangguan kronis psikiatri, onset pada masa kanak-kanak, dengan kurangnya perhatian, hiperaktif dan impulsif sindrom dalam dua kondisi sosial minimal yang berbeda, dan biasanya didiagnosis sebelum berusia tujuh years. Prevalensi ADHD diperkirakan antara% sekolah 3-7 siswa berusia. Pada Daycare RSU Dr Soetomo, ADHD mengambil tempat kedua yang paling kasus dalam 5 years ini. Obat pilihan yang digunakan untuk ADHD adalah stimulan methylphenidate. Karena efek samping nontolerable dan keterbelakangan pertumbuhan efek, atomoxetine nonstimulant digunakan sebagai farmakoterapi alternatif. Di Indonesia, sejauh penulis tahu, atomoxetine adalah baik jarang digunakan atau diamati. Penelitian ini observasional analitik bertujuan untuk mengetahui efektivitas atomoxetine di Daycare RSU Dr Soetomo Surabaya dengan membandingkan gejala tingkat keparahan sebelum dan setelah terapi. Penelitian ini juga membandingkan kemanjuran atomoxetine antara dua jenis ADHD ditemukan di Daycare. Jumlah tugas pengambilan sampel digunakan untuk pasien ADHD dan orang tua mereka yang membutuhkan kriteria inklusi (N: 42 kurangnya perhatian: 22 gabungan: 20). Data yang digunakan adalah data sekunder dari skor Rating Scale Iowa Conner dinilai oleh orang tua, yang tersedia pada catatan medis pasien, dan data primer melalui wawancara. Analisis data menggunakan uji statistik. Hasil penelitian menunjukkan perbandingan skor sebelum dan setelah terapi memiliki p-value <0,0001. Perbedaan keparahan gejala ADHD pada kurangnya perhatian dan jenis gabungan menunjukkan perbedaan p <0,05. Rata perubahan nilai pada ADHD tipe Combination lebih besar dari jenis kurangnya perhatian. Kesimpulannya, terapi atomoxetine efektif dalam mengurangi tingkat keparahan pada pasien ADHD di Daycare RSU Dr Soetomo, dan lebih efektif untuk pasien jenis gabungan dari tipe kurangnya perhatian. ***(FMI 2012;48:190-197)***

Kata kunci: *ADHD, Atomoxetine, Efficacy, Inattentive Type, Combined Type*

ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is a chronic psychiatry disorder, onset in childhood, with inattention, hyperactivity and impulsive syndrome within minimal two different social conditions, and usually diagnosed before seven years old. ADHD prevalence estimated between 3-7% school aged students. On Daycare RSU Dr. Soetomo, ADHD takes the second place the most case within these 5 years. Drug of choice used for ADHD is stimulant methylphenidate. Since its nontolerable side effects and growth retardation effect, nonstimulant atomoxetine is used as the alternative pharmacotherapy. In Indonesia, as far as writer knows, atomoxetine is either rarely used or observed. This observational analytical research aims to know the efficacy of atomoxetine in Daycare RSU Dr. Soetomo Surabaya by comparing the symptoms severity level before and after therapy. This research also compared the efficacy of atomoxetine between two types of ADHD found at Daycare. Total sampling assignment is used for ADHD patients and their parents who required the inclusion criteria (N: 42 inattention: 22 combined: 20). The data used is secondary data from Iowa Conner's Rating Scale score assessed by parents, available on patient's medical records, and primary data through the interview. Data analysis used statistical test. The results showed comparison of scores before and after therapy had p-value <0.0001. The difference of the severity of ADHD symptoms on the inattention and combined types showed differences p <0.05. Average change in scores on the ADHD combined type is larger than inattention type. In conclusion, atomoxetine therapy is effective in reducing severity level in ADHD patients at Daycare RSU Dr. Soetomo, and more effective for combined type patients than inattention type. ***(FMI 2012;48:190-197)***

Keywords: *ADHD, Atomoxetine, Efficacy, Inattention Type, Combined Type*

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INTRODUCTION

Concentration of Attention Disorders/Hyperactivity (GPPH) or Attention Deficit Hyperactivity Disorder (ADHD) is a chronic psychiatric disorder with onset during childhood with a group of symptoms inability to concentrate, hyperactivity and impulsivity in at least two different social conditions, which is usually diagnosed in the early school years before 7-year-old (American Psychiatric Association 2000). The

prevalence of ADHD is estimated at 3-7% of school-age children (American Psychiatric Association 2000). In Indonesia, according to research results Dwidjo 2001-2004, in 4013 children in 10 elementary schools in Jakarta shows, 25% of students showed indications of ADHD. In detail, 15% difficulty concentrating (inattentive type) and the rest is divided between the hyperactive-impulsive type, and the type of combination.

The study by Weiss and Hechtman (1993) showed that as many as 50-60% of children with behavioral problems, especially symptoms of ADHD continue to show symptoms of these conditions when they grow up. This can cause other psychiatric disorders are antisocial personality traits (Gittelman et al 1985), have a higher risk of suffering from major depressive disorder, interpersonal relationship problems, problems of suicide deaths and accidents, failures in the study, lower occupational status, condition socioeconomic less, frequent sexual intercourse at a younger age, have more sexual partners in their lifetime, resulting in more suffering from sexually transmitted diseases (Barkley 1998).

Figures ADHD visit was ranked second highest in the Day Care in the last five years. In 2007, found as many as 47 cases consisted of 37 boys and 10 girls. In 2008, found an increase in the number of cases to 72 cases in 2009 to 103 cases, and in 2010 as many as 96 cases, and in 2011 it was 80 cases (Mandy 2012). ADHD showed a chronic course of the disease, thus requiring proper containment procedures. The management of this disorder includes behavior management and administration of drugs, which are multimodal management.

The first choice drug (Drug of Choice) used in the treatment of ADHD is methylphenidate. Psycho-stimulant methylphenidate is a substance that improves the attention span of children in the performance of duty, lowering hyperactivity behavior, and reduces impulsive behavior (Brandon et al 2003). This drug action is to inhibit the dopamine transporter function in presynaptic neurons that affect the growing number of dopamine in the synaptic cleft (McCracken, 2000, Courvoisie et al 2004). However, in some studies, it was found that the use of methylphenidate in under 5 years of age may slow growth in children.

Studies conducted by Lisska and Rivkees (2003) showed a significant difference of average height with a standard deviation between children with ADHD who received methylphenidate therapy every day (10-80mg/day) with sibling controls after two years of treatment. Other studies have also found a lack of growth in height and weight of children with ADHD treated with methylphenidate for 14 months is -1.23 cm per year, and -2.48 kg per year. After three years, the difference reached 2 cm and 2.7 kg. The results of the systematic review also showed slower growth of about 1-1.5 cm per year (Anonymous 2011).

Using stimulant medication is effective in 80% of patients with ADHD, but some patients do not respond to or can not tolerate the side effects which include decreased appetite, sleep disturbances, mood instability, and the expansion of its comorbidity (Wilens & Spencer 2000). In addition there is also the possibility of abuse, especially in patients with a history of drug abuse (Ledbetter 2006).

Atomoxetine hydrochloride is a norepinephrine re-uptake inhibitor first non-stimulant indicated by the Federal Drug Administration (FDA) for the management of ADHD in children over the age of six years, adolescents, and adults. The results of various studies show atomoxetine therapy can reduce the severity of symptoms of ADHD (Ledbetter 2006). In the United States in 2002, this drug can be used as an alternative in patients who failed to give a response to the treatment of stimulant (Donnelly et al, 2009). The use of atomoxetine for the treatment of ADHD in Indonesia's own knowledge of the authors have not been studied and used. The side effects of stimulants are less tolerated by most patients and the limited use of atomoxetine as an alternative to pharmacological treatment of ADHD in Indonesia, the underlying writer to do this research. The purpose of this study was to determine the effectiveness of atomoxetine in the treatment of ADHD patients at Day Care, Dr. Soetomo Hospital.

MATERIALS AND METHODS

This type of research is analytic observational prospective. The population in question is a reasonable population, ie all patients with ADHD with sex men and women and the age of 6-12 years in Day Care, Dr. Soetomo Hospital. Samples were male or female children aged 6-12 years with ADHD in Day Care, Dr. Soetomo Hospital, who met the inclusion criteria. Samples also comprised on parents of children with ADHD who meet the inclusion and exclusion criteria. Estimates of the sample of children with ADHD who meet the inclusion and exclusion criteria and the biological parents met the inclusion criteria were 42 children. Large samples were taken from total sampling children with ADHD who met the inclusion criteria and biological parents met the inclusion criteria.

Inclusion criteria for the child is a child with ADHD inattentive type (first sample group) or a combination (both sample groups), sex, men and women with an age range of 6-12 years and receiving atomoxetine treatment over a period of 3 months at a dose of 1.2 mg/kg/day. Criteria for inclusion in the elderly are the biological parents of children with ADHD, willing to participate in research (signed informed consent) and willing to fill out a questionnaire that was given to him (Iowa Conner's Rating Scale).

Exclusion criteria were children with ADHD who received additional therapy includes psychotropic and other drugs that affect the central nervous system significantly, the presence of comorbidities such as autism, psychosis, bipolar disorder, suicidal ideation, and a history of substance abuse. Exclusion criteria in the elderly is when the biological parents suffer from severe mental disorders, when parents suffer from severe physical illness and admitted to the hospital and have more than one child with ADHD

This study uses the Iowa Conner's Rating Scale to determine the severity of the symptoms of ADHD before and after administration of atomoxetine therapy. The instruments used are: collecting data sheet to record the results of observations Iowa Conner's Rating Scale of medical records. Location of the research was Day Care, Dr. Soetomo Hospital between August and December 2012. Data are secondary data taken through Iowa Conner's Rating Scale from the medical records of patients who met the inclusion criteria were assessed by parents, and primary data through interviews. From the data obtained a description of the characteristics and also conducted a comparative analysis.

RESULTS

This research was conducted in Day Care, Dr. Soetomo Hospital in children with ADHD who met the inclusion criteria in the period from August to December 2012. It was found 42 samples with the following details:

Table 1. Number of patients with ADHD based on its type

ADHD Types	N (%)
Inattentive	22 (52.38)
Combination	20 (47.62)

Most ADHD were at the age of 7 years (23.8%). In most inattentive type 9 years old (27.27%), whereas the highest combination type at the age of 7 years (35%). Price P = 0.664, CI = 95%,? = 0.05 on a two-sided test probability (0.664/2 = 0.332) > 0025, the average age of patients with ADHD inattentive types and combinations are the same.

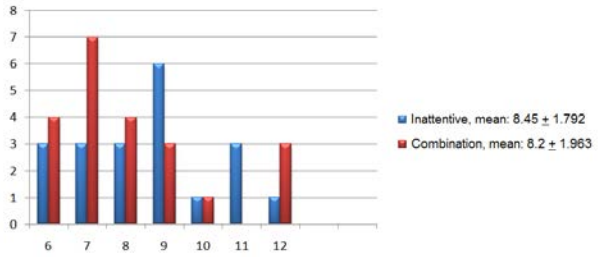

Figure 1. Overview ADHD by age

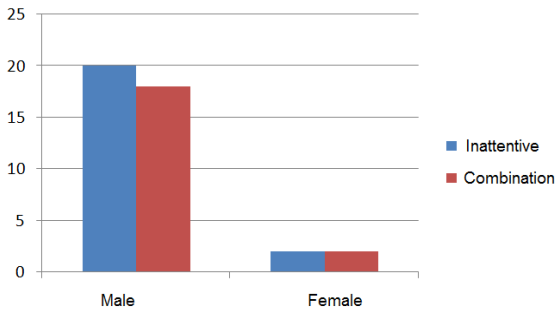

Figure 2. Gender ADHD patients

ADHD patients mostly male sex are a number of 38 children (90.48%). Or a combination of both inattentive type dominated by boys with number 20 (90.91%) and 18 (90%) children. The p value was 0.920, CI = 95%, ? = 0.05, p > 0.05 indicates no relationship between the gender of patients with type ADHD. Patients are mostly first child with number 20 children (47.62%) with inattentive type 12 children (54.55%) are the type of combination of 8 children (40%). Highest number of patients you are one person in 20 children (47.62%), or in other words, there are two children in the family of the patient, the type of inattentive 12 children (54.55%) and the type of combination of 8 children (40%). Price P = 0.346 and 0.937. P> 0.05 then there is no relationship between the child to how and number of siblings with ADHD types. Age dad most patients in the age range 41-45 years is 16 people (38.09%), 9 (40.91%) in inattentive, and 7 (35%) in the combination type. While the majority of education is high school level that is equal to 20 people (47.62%), and the status of the majority of the work is that private sector employees 23 people (54.76%). Price P = 0.411 for the age of the father, 0.715 to 0.129 for the level of education and employment status. All prices P> 0.05 so there is no relationship between the three types of ADHD characteristics of the father with his son.

Table 2. Characteristics of children to how and number of siblings of patients

Data	Inattentive	Combination	Total	P value
Child no.				0.346
1	12 (54.55)	8 (40)	20 (47.62)	
2	5 (22.73)	7 (35)	12 (28.57)	
3	2 (9.09)	4 (20)	7 (16.67)	
4	2 (9.09)	1 (5)	3 (7.14)	
Total sibling				0.937
0	5 (22.73)	5 (25)	10 (23.80)	
1	12 (54.55)	8 (40)	20 (47.62)	
2	2 (9.09)	6 (30)	8 (19.05)	
3	1 (4.55)	3 (15)	4 (9.52)	
>3	1 (4.55)	0 (0)	1 (2.38)	

Table 3. Age, educational level and employment status of the patient's father

Data	Inattentive	Combination	Total	P value
Father's Age	42.05 ± 5.802	40.35 ± 7.325		0.411
< 31 years	1 (4.55)	1 (5)	2 (4.76)	
31-35 years	3 (13.64)	5 (25)	8 (19.05)	
36-40 years	1 (4.55)	4 (20)	5 (11.9)	
41-45 years	9 (40.91)	7 (35)	16 (38.09)	
46-50 years	6 (27.27)	2 (10)	8 (19.05)	
51-55 years	1 (4.55)	3 (15)	4 (9.52)	
Level of Education				0.715
Elementary School	1 (4.55)	0 (0)	1 (2.38)	
Junior High School	3 (13.64)	2 (10)	5 (11.9)	
Senior High School	11 (50)	9 (45)	20 (47.62)	
University Educated	6 (27.27)	10 (50)	16 (38.09)	
Occupation Status				0.129
Civil Servant	5 (22.73)	2 (10)	7 (16.67)	
Private Sector	11 (50)	12 (60)	23 (54.76)	
Entrepreneur	5 (22.73)	5 (25)	10 (23.80)	
Unemployed	0 (0)	2 (10)	2 (4.76)	

Table 4. Age, level of education, and employment status of patients

Data	Inattentive	Combination	Total	P value
Mother's age	39.77 ± 5.529	37.9 ± 7.49		0.367
< 31 years	1 (4.55)	3 (15)	4 (9.52)	
31-35 years	3 (13.64)	7 (35)	10 (23.80)	
36-40 years	7 (31.82)	3 (15)	10 (23.80)	
41-45 years	6 (27.27)	4 (20)	10 (23.80)	
46-50 years	4 (18.18)	3 (15)	7 (16.67)	
51-55 years	0 (0)	1 (5)	1 (2.38)	
Mother's Education				0.563
Elementary School	1 (4.55)	0 (0)	1 (2.38)	
Junior High School	4 (18.18)	5 (25)	9 (21.43)	
Senior High School	12 (54.55)	9 (45)	21 (50)	
University Educated	3 (13.64)	8 (40)	11 (26.19)	
Mother's Occupation				0.694
Civil Servant	2 (9.09)	7 (35)	9 (21.43)	
Private Sector	6 (27.27)	5 (25)	11 (26.19)	
Entrepreneur	4 (18.18)	2 (10)	6 (14.28)	
Unemployed	9 (40.91)	7 (35)	16 (38.09)	

Age mother most patients have the same number in the age range 31-35 years, 36-40 years, and 41-45 years at 10 people (23.8%). In inattentive highest maternal age at the age of 36-40 years with 7 people (31.82%), whereas the type of combination is in the range of 31-35 years with 7 people (35%). The majority of high school education level is the amount of 21 people (50%), and the status of the majority of the work is unemployed that is 16 people (38.09%). Price P = 0.367 for maternal age, education level and 0.563 to 0.694 for the job status. All

prices P> 0.05 so there is no relationship between the three types of ADHD characteristics of mothers with children. From the results of data collection was also found that all children are raised by their parents. The results showed a decrease in the severity of ADHD symptoms in patients demonstrated by a decrease in scores on the IOWA Conner's Rating Scale. A total of 28 children consisting of 11 with inattentive type (50%) and 17 with type combination (85%) decreased by 6-10 pointsts after administration of atomoxetine therapy.
Paired t test between scores IOWA Conner's Rating Scale before and after atomoxetine therapy at a specified time period. Before therapy, the inattentive type have averaged a relatively lower value of this type of combination, namely respectively 23.6 ± 3.2 and 26.8 ± 1.7. Whereas after treatment, ADHD scores of inattentive types and showed relatively not too different combinations that row of 17.1 ± 1.7 and 17.8 ± 1.8. Based on the probability value paired t test, in both types of P <0.0001. This suggests that atomoxetine therapy is effective in reducing the severity of ADHD symptoms as well as a combination of both inattentive type significantly.

From the results obtained differences mean that the average patient inattentive type ADHD scores declined as much as 6.6 ± 2.6 after treatment atomoxetine. Whereas in patients with ADHD combined type, after treatment decreased the average score of 9.0 ± 1.7. Delta value is obtained from the value before deducting the value of the scores after IOWA Conner's Rating Scale, revealed p > 0.05. This shows that there are real differences in the difference between the value of pre and post on ADHD inattentive type than type combination. From the results of the average change in score, type of combination has a decrease in the average score greater than inattentive type. The average difference of delta scores amounted to 2,359 with a range of 1.0 to 3.7. This may indicate that atomoxetine therapy for type combination is more effective than the inattentive type.

DISCUSSION

The study was conducted in the month of August to December 2012 for a total sampling in ADHD patients at Day Care, Dr. Soetomo Hospital. Based on the calculation, the sample size used was 42 children and all of them meet the criteria necessary research. According to the DSM-IV-TR classification of ADHD consists of three types, namely inattentive, hyperactive-impulsive, and combined type. However, the data that was able to find in Day Care, Dr. Soetomo Hospital is inattentive types were 22 children and a combination of 20 children.

Table 5. Impairment Score with IOWA Conner's ADHD Rating Scale

Points	Inattentive	Combination
0-5 points	8 (36.36)	1 (5)
6-10 points	11 (50)	17 (85)
11-15 points	2 (9.09)	2 (10)

Table 6. unpaired t test scores before and after treatment of ADHD

ADHD types	ADHD scores		Delta	P value paired Test
	Before therapy	After therapy		
Inattentive type	23.6 ± 3.2	17.1 ± 1.7	-6.6 ± 2.6	< 0.0001
Combination type	26.8 ± 1.7	17.8 ± 1.8	-9.0 ± 1.7	< 0.0001

Table 7. Statistical tests of the independent t? ADHD scores

ADHD types	Delta Skor	*Mean Differences*	Lower-Upper	P value (2 sides)
Inattentive type	-6.6 ± 2.6	2.4	1.0-3.7	0.001
Combination type	-9.0 ± 1.7			

Studies comparing children with the combined type ADHD hyperactive impulsive type mentioned that the second type has relatively the same functional level. The study also explained that the majority of children with hyperactive-impulsive type some time later diagnosed as a type of combination. This may indicate that the hyperactive-impulsive type is the initial phase of this type of combination (Riley et al 2008).

Data obtained through medical records of patients, the results of charging IOWA Conner's Rating Scale by the mother of the patient, and also interview the patient's mother to ask incomplete data. Data were taken through medical record is the basic data of patients; age, gender, number of children to how brothers, father and mother of data of patients; age, education level, employment status, and also the status of child care.

In IOWA Conner's Rating Scale contained 10 questions posed to patients and answer using interval data. Analysis of data using statistical test that begins with the Kolmogorov-Smirnov normality test. When the data were normally distributed statistical test to determine the effectiveness of atomoxetine therapy is paired t test, while to know the differences between inattentive type delta scores and combinations, independent t test was used.

A total of 42 children who met diagnostic criteria for ADHD are then classified into certain types. Type obtained at the study site is inattentive types and combinations. There are 22 (52.38%) patients were included in the inattentive type, while the other 20 children (47.62%), including the type of combination.

From the analysis using statistical tests, variance age of patients in both groups of samples are not homogeneous but the average age of the patients alike. Patients were predominantly male gender, the eldest son, and two brothers. Gender, child into how, and number of siblings of patients did not show an association with the type of ADHD patients.

From the data of parents, the average age of the father and mother of the two groups of the same sample. Education levels have the same father and mother of the two groups of samples that the majority of high school graduates. As for the employment status of the father majority is a majority of private sector employees, while the mother is a housewife. The data also showed no effect of these factors on the type of ADHD.

The severity of the symptoms of ADHD can be determined using the IOWA Conner's Rating Scale. To determine its effectiveness, used paired t test between the scores before treatment and after treatment. Results of paired t test showed that atomoxetine therapy proved effective in reducing the severity of symptoms of ADHD both on the type of inattentive or in combination with a p-value <0.0001. The results are consistent with the literature indicating that atomoxetine therapy proved effective in reducing the severity of symptoms of ADHD. It has been proved from the various studies conducted by Michelson et al (2001), Michelson et al (2002), Kratochvil et al (2002), Spencer et al (2002), and Waxmonsky et al (2010).

The difference of the severity of the symptoms of ADHD in inattentive types and combinations showed significant differences with independent t-test p <0.05. The average change in ADHD scores on the type of combination of greater value than the inattentive type. It can be said that based on the results of this study, atomoxetine therapy is more effective for patients with type combinations than inattentive. These differences may be based on the effectiveness of some of the things that distinguishes the characteristics of both types. Several studies compared inattentive type with a combination of various aspects. Children with inattentive type usually older age, female sex ratio is greater, and more demonstrate the inability of learning rather than the type of combination. Inattentive type also has speech and language disorders in two to five times greater. Although this type have fewer functional disturbances of the type of combination, but still have difficulty in academic achievement (Weiss et al 2003). Children with ADHD combined type have a higher frequency of comorbidities. In terms of etiology, has conducted research on exposure to maternal stress during pregnancy the child, as well as genotype L/L for 5-HTT-linked polymorphic, type of combination has a frequency greater than the second type of inattentive. Response to stimulant treatment for the type of combination is also higher than the inattentive type (Grizenko et al 2010).

Barkley (1998) explained that there are two types of attentional problems were identified from a factor analysis of the teacher assessment and direct observation, namely inattentive-passive and persistent/distractibility. McBurnett et al (2001) also reported that the tempo slugghish items (like daydreaming) is a good indicator of attention problems in ADHD inattentive type, but not with attentional problems of this type of combination. This raises a presumption that ADHD is a disorder of inattentive type separate. Some scientists also agree with these allegations because of the discovery of some of the differences between the two types of some aspects of the (Hinshaw 2001). The difference in these characteristics may be the cause of differences in the response of both types of atomoxetine treatment, the

same as the difference in the effectiveness of stimulants. However, further research is needed for a deeper understanding.

In this study, there are limitations that by not accounting for therapy and psychosocial interventions given in the home, school and in the Day Care itself. Whereas psychosocial therapy in the management of ADHD, including which, if done properly will help reduce the symptoms of ADHD, and when combined with a stimulant drug that has become the gold standard in the treatment of this disease (Daly et al, 2007). In addition, the number of samples will yield more accurate data more.

CONCLUSION

Atomoxetine is effective for the treatment of children with ADHD. There is a difference between delta scores in ADHD inattentive type and combination. Atomoxetine therapy is more effective in combination than inattentive type.

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