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Original Article

Comparison of Efficacy of Fluoxetine with Nortriptyline in Treatment of Major Depression in Children and Adolescents: a double-blind study

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ABSTRACT

Background: The incidence of depression is 0.9% in preschoolers, 1.9% in school age children, and 4.7% in adolescents. Current antidepressant treatment of mood disorders in children and adolescents is still in the early phases of being validated with double-blind efficacy studies. In this study the efficacy of nortriptyline has been compared with fluoxetine in the treatment of major depression in children and adolescents.

Methods: This was a double–blind clinical trial for 8 weeks, undertaken in the Isfahan Child and Adolescent Guidance outpatient Clinic, Isfahan, Iran. Subjects were 40 outpatients children and adolescents (20 boys and 20 girls) aged 7-16 years of old who met the Diagnostic and Statistical Manual of Mental Disorders, Forth Edition, for Major Depression. To determine the scores of two groups (Baseline and after treatment), we used Children Depression Inventory (CDI). Subjects were randomly assigned to receive nortriptyline 2mg/kg/day for 8 weeks (group A) or fluoxetine 1mg/kg/day for 8 weeks, (group B). Paired t-test was used to compare the mean of CDI score of each group before and after treatment. To compare the reduction in the Children Depression Inventory score, an unpaired t-test was used.

Results: The mean depression score was 28.9 (SD±8.46) before intervention in fluoxetine group while that was 28.4 (SD±8.76) in nortriptyline group. Independent t-test showed a significant difference between after treatment mean depression scores in both groups (t=2.97, df=38, P=0.004). The changes at the endpoint compared with baseline were -10.95±2.61 and –2.6±0.8 for fluoxetine and nortriptyline, respectively. t- Paired test showed a significant decrease in mean depression score in fluoxetine group (P≤0.0001) while that was not significant one in nortriptyline group (P=0.34). At the endpoint (8th week), 10 cases 50% didn't meet the criteria of Major Depression based on DSM-IV in fluoxetine group. Although, it was only 2 cases (10%) for nortriptyline group.

Conclusion: The present study suggest that the treatment with fluoxetine in subsiding depression was significantly preferable compared with nortriptyline. The general conclusion of this study provides evidence in favor of an efficacy advantage of fluoxetine over nortriptyline in the treatment of depression in children and adolescents.

Key words: Major Depressive Disorder, Nortriptyline, Fluoxetine, children and adolescents.

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In the third edition of Diagnostic and Statistics Manual of Mental Disorders (DSM-III), DSM-III-R, and DSM-IV, the diagnostic criteria for depressive disorders for children and adolescents are the same as adults, with small exceptions stated as notations to the criteria [1]. Varying prevalence rates have been reported for depression. Epidemiological studies done in the United States have reported the incidence of depression to be 0.9% in preschoolers, 1.9% in school age children, and 4.7% in adolescents. Lifelong prevalence of depression in

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adolescents is 10-20%, similar to adults. Current antidepressant treatment of mood disorders in children and adolescents is still in the early phases of being validated with double-blind efficacy studies [2].

The selective serotonin reuptake inhibitors (SSRIs) are widely accepted as a first-line pharmacological intervention for moderate to severe depressive disorders in children and adolescents [3].Thus far, few studies have supported the use of tricyclic drugs in children or adolescents [3]. Nevertheless, Nortriptyline is approved by the FDA for the treatment of symptoms of depression in adolescents and adults [4].

Geller and her colleagues have studied pharmacokinetic parameters of nortriptyline and its use in treating children and adolescents diagnosed with MDD. They (1989, 1992) enrolled 72 prepubescent children, aged 6 to 12 years, with diagnosed MDD, in a double-blind, placebo-controlled study of the efficacy of nortriptyline. Of the 72 subjects entering the study, 12 (16.7%) responded during the placebo phase, 10 were discontinued for various reasons during the active treatment phase, and 50 (24 on placebo and 26 on nortriptyline) completed the study. Both the nortriptyline and the placebo groups had a low rate of positive response (30.8% on nortriptyline and 16.7% on placebo), and there was no significant difference between them [5].

At least one published placebo-controlled double–blind study exists comparing fluoxtine`s efficacy for depressive symptoms in adolescent with that of placebo. One controlled study supports the efficacy of fluoxetine in this population. Tricyclic drugs have not been shown to be superior to placebo in double - blind, placebo-controlled studies of children and adolescent with major depressive disorder [3]. Fluoxetine is a selective serotonine reuptake inhibitor (SSRI) that is chemically unrelated to any current antidepressant. Several studies, including some that were placebo controlled, have found fluoxetine`s therapeutic efficacy to be comparable to that of the tricyclic in treating adults with MDD [4].

Emslie et al (1997) reported an 8-weeks, double-blind, randomized (stratified for age, ≤12 years or ≥13 years, and sex), placebo-controlled study of 96 children and adolescents, diagnosed by DSM-III-R criteria with nonpsychotic MDD. Overall effectiveness was rated on the Clinical Global Impressions Improvement Subscale (CGI-I). Fluoxetine was statistically better than placebo on the CGI-I; using the intent-to-treat sample, 27 (56%) of the fluoxetine group versus 16(33%) of the placebo group were rated much or very much improved [6].

The report of Riddle et al describes a randomized double-blind, placebo-controlled, fixed-dose (20mg qd) trial of fluoxetine in 14 children and adolescents with Obsessive compulsive Disorder (OCD), age 8 to 15 years old. During the initial 8 weeks, the magnitude of improvement for the fluoxtine group significantly exceeded than for the placebo group, as measured by the CGI-OCD. The most common drug side effects were generally well tolerated. The results suggest that fluoxetine is a generally safe and effective short-term treatment for children with OCD [7].

Some studies have been undertaken to compare the nortriptyline with fluoxetine in adults depression and their side-effects. Kelly et al compared body weight changes after short-term treatment with fluoxetine and nortriptyline. At pretreatment, the two groups did not differ in terms of demographic, BMI, or clinical characteristics. A greater proportion of patients in the fluoxetine- than the nortriptyline–treated group repotted a weight change of more than 2 kg. Patients treated with fluoxetine demonstrated a significant mean downward change in weight and BMI, compared with those treated with nortriptyline [8].

Akhondzadeh et al compared fluoxetine and nortriptyline in the treatment of major depression. The results suggest that the efficacy of nortriptyline is superior to fluoxetine in this group of major depressed patients [9].

Robinson RG et al. compared the efficacy of fluoxetine and nortriptyline in both depressed and nondepressed poststroke patients for anti-

depressant effect as well as influence on recovery from physical, cognitive, and social impairment. Nortriptyline was significantly more effective than fluoxetine in the treatment of depression and anxiety symptoms and improving recovery in activities of daily living as measured by the functional independence measure. Neither medication has a significant effect on recovery in activities of daily living [10].

The safety and efficacy of nortriptyline and fluoxetine were compared by Fabre et al.. Average total scores on the Hamilton Rating Scale for Depression (HAM-D) for both treatment groups declined from 22-23 at baseline to 11.5 at the conclusion of the 5-week period.

Majority of the studies in field of comparison of fluoxetine and nortriptyline have been undertaken in adults [8-11]. So, there are a few studies in children and adolescents in this area [2]. Also, using SSRIs for treatment of Major Depression in children and adolescents is a new experience and still uncommon in clinical practice in Iran.

Some studies have shown that fluoxetine was associated more frequently with nausea, while nortriptyline was associated more frequently with dry month [11].

The study reported here was undertaken to compare the efficacy of nortriptyline and fluoxetine in the treatment of major depression in children and adolescents.

Subjects and Methods

Trial organization

This was a double – blind clinical trial for 8 weeks, undertaken in the Isfahan Child and Adolescent Guidance outpatient Clinic, Isfahan, Iran in 2001-2002.

Participants

The subjects were 40 outpatient children and adolescents, (20 boys and 20 girls) aged 7-16 years old who met the Diagnostic and Statistical Manual of Mental Disorders, Forth edition (DSM IV), for Major Depression [12].

They were recruited from the of Isfahan Child and Adolescent Guidance outpatient Clinic. The diagnosis of major depression was made by structured clinical interview based on DSM IV. Patients had a baseline Children Depression Inventory (CDI) for score of at least 20. The CDI is a self-report, symptom-oriented scale which requires at least a first grade reading level and was designed for school-aged children and adolescents. This inventory was read for those children who couldn't read it 13. The CDI has 27 items, each of which consists of three choices. The child or adolescent is instructed to select one sentence for each item that best describes him or her for the past two weeks. Scores vary from 0 to 54 indicative of the severity of depression, in which scores 1-8 are as healthy, 9-19 as depression with no disorders, and 20-over as depressive disorder [13, 14]. The reliability of the CDI has been examined among elementary, middle, and high school students in Kuwait. Overall alpha reliability coefficient for the CDI was 0.85 [15]. In the study of Smucker et al the distribution statistics for the combined samples yielded an overall CDI mean of 9.09, a standard deviation of 7.04, and a cutoff score of 19 for the upper 10% of the distribution. Reliability assessed through coefficient alpha, item total score product-moment correlation's, and test-retest coefficients proved acceptable [16].

Participation was precluded for patients with any other primary psychiatric disease, current or past history of bipolar disorder, or mental retardation (IQ<70). In addiction, we excluded patients if they had a significant chronic medical condition, including a past history of cardiovascular problem, organic brain disease, seizures, drug abuse, and patients requiring treatment with psychotropic drugs. Patients were excluded if they posed any significant serious side effects or risk of suicide at any time during participation. Patients taking antidepressant before the beginning time of study were allowed to stop their antidepressants for a 2-weeks washout period before the study (N=5).

After providing a complete description of the study to the patients and their parents, we obtained their parents, written informed consent for participation.

Study design

1- Patients underwent a standard clinical assessment and structured diagnostic interview based on DSM IV. Also a medical history and an electro cardiogram were taken. Patients were assessed by Children Depression Inventory, at baseline and after 8 weeks. Subjects were randomly assigned to receive nortriptyline 2mg/kg/day (titrated-up over 4 weeks and were put in capsules to provide similar appearance with fluoxetine) (Group A) or fluoxetine 1mg/kg/day for 8 weeks (titrated-up over 4 weeks) (group B) [1,4,17]. For the nortriptyline group (A), Patients initially received 1mg/kg/day for one week. After that the dosage of nortriptyline was increased gradually up to 2mg/kg/day during next 3 weeks. For the fluoxetine group (B), patients initially received 0.5mg/kg for two weeks. After that the clinician increased the dosage up 2mg/kg/day gradually during next two weeks.

Throughout the study, the person who administered the mediations, rater, and patients were blind to assignments. The mean decrease in CDI score from baseline was used as the main outcome measure of response of depression to treatment. Successful treatment response was defined as CDI score<20 and no longer fulfilling diagnostic criterion for major depression.

Statistical analysis

The severity of depression, according Children Depression Inventory, has normal distribution [14]. Paired t-test was used to compare the mean of CDI score of each group before and after treatment. Also, to compare the mean of two groups at baseline, independent t-test was used. To compare the reduction in the Children Depression Inventory score at week 8 with baseline, an unpaired two-sided students t-test was used. Results are presented as mean ± SD and were considered significant with P<0.05. To compare the baseline demographic data, the fishers' exact test was performed.

Results

Forty patients were randomized to trial medication (20 patients in each group). No significant differences were identified between patients randomly assigned to groups A and B with regard to basic demographic data including age, gender, and ethnicity (Table 1).

Table 1. Baseline data of groups A and B.

	Nortriptyline group	Fluoxetine group
Girls	9	11
Boys	11	9
Age (mean±SD)	12.5±2.5	13.2±2.3
Mean depression score before intervention	28.4±8.7	28.9±8.4

The mean±SD scores of two groups of patients are shown in Table 1. There were no significant differences between the two groups before intervention (baseline) on the Children Depression Inventory rating scale (F=0.3, DF=38, P=0.85). Most of the patients aged 11-14 years old.

Independent t-test showed a significant difference in after treatment mean depression scores of two groups (t=2.97, df=38, P=0.004). The changes at the endpoint compared with baseline were-10.9±2.6 and –2.6±0.8 for fluoxetine and nortriptyline respectively (Table 2).

Table 2. Comparison of mean depression scores based on CDI before and after treatment in both studied groups.

Group	Before treatment		After treatment		P- value
	Max-	SD	Mean-	SD	
Fluoxetine	28.9	8.4	17.9	8.1	0.0000
Nortriptyline	28.4	8.7	25.8	8.5	0.3422

t- paired test showed a significant decrease in mean depression score in group of fluoxetine (P≤0.0001) while that was not significant in group of nortriptyline (P=0.34).

At the endpoint (8th week), 10 cases (50%) didn't meet the criteria of Major Depression based on DSM-IV in fluoxetine group. Although, it was only 2 cases (10%) for nortriptyline group. The dropout in nortriptyline group and fluoxetine group were 4 and 2, respectively during the study. So, they were replaced by new cases.

Table 3. Frequency of adverse Drug effects.

Side effect	Fluoextine	Nortriptyline	P-value
Nervousness	2	1	NS
Drowsiness	3	3	NS
Diarrhea	1	-	NS
Disinhibition	2	1	NS
Abdominal pain	3	1	NS
Insomnia	1	-	NS
Hypersomnia	2	2	NS
Headache	1	1	NS
Constipation	1	2	NS
Dry mouth	-	1	NS
Tachycardia	-	1	NS
Dizziness	1	1	NS

NS= non significant

Discussion

Depression is a common psychiatric disorder among children and adolescents. Antidepressant effects of medication in this age group are yet at the primary level of validity based on double blind studies being carried out [1]. This study tried to investigate the efficacy of fluoxetine and nortriptyline in treatment of depression in children and adolescents.

The present study suggest that the treatment with fluoxetine in subsiding depression was significantly preferable compared with nortriptyline. The efficacy difference of these two medications was apparently obvious, so, the fluoxetine is more effective than nortriptyline in this group of major depressed patients and it got statistically significant 8 weeks after treatment. The result of the current study was opposed the some previous studies in adults e.g. Akhondzadeh et al, Robinson et al, and Fabre et al [9-11]. The objective of the study of Akhondzadeh was to compare the efficacy and safety of fluoxetine and nortriptyline in adults. The results suggest that the efficacy of nortriptyline is superior to fluoxetine 9. Robinson RG et al suggested that nortriptyline was significantly more effective than fluoxetine 10. Fabre et al conducted a double-blind, multicenter trial involving 205 outpatients with major depression. At week 5, 71% of Nortriptyline group and 65% of Flouxetine group were improved 11. All of these studies only have been undertaken in adults.

Existing no significant difference between depression scores before and after the treatment by nortriptyline is an emphasis on previous studies. For instance, Geller. B et al found no difference in their study on the efficacy of nortriptyline compared with placebo in treatment of depression in adolescents [5].

Fluoextine efficacy in treatment of major depression in children and adolescents, showed no variation in this study with other studies conducted in this field [2, 3, 6].

Similar including and excluding criteria with the same results was carried out in 1997 by Graham Emslie [6].

The general conclusion of this study provides evidence in favor of an efficacy advantage of fluoxetine over nortriptyline in the treatment of depression in children and adolescents. Fluoxetine (SSRIs) can be considered as first choice in pharmacological treatment of this disorder [3]. The tricyclic drugs have shown efficacy in multiple studies of adults mood disorder, but since the advent of antidepressants with safer adverse-effect profiles (i.e. minimal risk of cardiac arrhythmia and considerably lower lethal potential), the tricyclic are usually not among the first–choice antidepressants for children and adolescent 2. Although tricycle antidepressant produce initial remission rates similar to those for SSRIs, distinctions between these groups of medications exist with respect to their side effect profiles. Undesirable weight gain is a side effect that occurs differentially among types of antidepressants and can be a common cause of noncompliance. Specifically, independent to treatment response, tricyclic antidepressants are

associated with weight gain. Whereas serotonergic medications seem not to cause weight gains and may actually result in relative weight loss [8]. In this study nausea was not as a side effect. However, Fabre showed that fluoxetine was associated more frequently with nausea, while nortriptyline was associated more frequently with dry month [11].

The paper of Abbott et al describes the pattern of remission, response, and recovery in patients with major depression who were randomized for treatment with fluoxetine or nortriptyline. In this sample, the change, in depressive symptoms were compared between treatment with fluoxetine and nortriptyline over 6 weeks. However, when we look at the more clinically important variable of recovery, then fluoxetine was superior to nortriptyline. Predicators of a poorer response to nortriptyline were gender, young age, and atypical depression [18].

While the response rate of noradrenergic antidepressants in young adults is lower, it is not clear whether this is comparable to adolescents. The reasons for a reduced response may be related to maturation of the noradernergic system in the brain. Some results of the studies of Mulde et al and Joye et al suggest that age may be a factor to be considered when choosing antidepressants for patients [19, 20].

Age and gender appear to be critical variables in understanding differential antidepressant responses to tricyclic antidepressants and selective serotonin reuptake inhibitors in melancholic depression [21].

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