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ORIGINAL CONTRIBUTION

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Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder

An open label maintenance study

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Abstract *Background* The aim of the study was to investigate safety, efficacy and tolerability of risperidone in comparison with haloperidol in the long-term treatment of autistic disorder. *Methods* This was an open-label continuation study of the randomized, double-blind, controlled trial of risperidone and haloperidol study for 12 week in autistic children and adolescents. A total of 28 subjects between 8 and 18 ages with autistic disorder were enrolled to the open label phase of the study. Behavioral rating scales (Clinical Global Impression Scale [CGI-I], Ritvo-Freeman Real Life Rating Scale [RF-RLRS]), Aberrant Behavior Checklist [ABC], Turgay DSM-IV Pervasive Developmental Disorder Rating Scale [TPDDRS]) and safety assessment scales (Extrapyramidal Symptoms Rating Scale [ESRS], UKU-Side Effect Rating Scale) were performed at 12, 16, 20 and 24 weeks, following the 12 week double-blind phase. Risperidone and haloperidol treatments were applied with a once daily dosage regimen as 0.01–0.08 mg/kg/day. *Results* Risperidone led to a significant greater reduction on CGI scale. There was significant improvement on RF-RLRS sensory motor and language subscale and ABC scores in risperidone group. Weight gain was observed more frequently in the haloperidol group at week 24. *Conclusions* These results demonstrate that risperidone is more efficacious and well tolerated than haloperidol in the long-term maintenance treatment of autistic disorder.

Key words autistic disorder – risperidone – haloperidol

Introduction

Autistic disorder (AD) is a neuropsychiatric syndrome characterized by impairment in social interaction, delays and deviancies in communication, and restricted and repetitive patterns of interests and behaviors. It is classified among the pervasive developmental disorders (PDD) in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [3]. In addition to core symptoms, autistic children and adolescents have serious behavioral disturbances, such as: self-injury, hyperactivity, irritability, labile mood, severe tantrums, aggression and stereotypical behavior, which can profoundly impair their functioning [37].

Medication, though not curative, is used clinically to decrease these disruptive symptoms [7, 9]. The most studied medication for use in children and adolescents with AD is typical neuroleptic, haloperidol. The efficacy of haloperidol and its superiority over placebo was established in this population, especially for the reduction of the behavioral symptoms [4, 5, 13, 31]. The extrapyramidal system (EPS)

side effects, including acute dystonias and tardive dyskinesia, limit its use in pediatric patients [4, 8, 20]. Therefore, atypical antipsychotics are preferred in the treatment of psychiatric disorders of children and adolescents. Because, they are less likely to cause similar side effects [15].

Risperidone, an atypical antipsychotic, is especially effective on 5HT2A and D2 receptors. At least six open label studies [10, 17, 23, 25, 27, 30] have shown that risperidone is an effective and well tolerated treatment for children and adolescent with AD or pervasive developmental disorder (PDD). It was reported that double-blind placebo controlled studies of risperidone in autistic children are the most appropriate method for testing the safety and efficacy [33]. Results from double-blind placebo controlled studies [26, 29, 34] suggest that risperidone can be used as a safe and effective agent to improve behavioral symptoms in children and adolescents with AD or PDD. There are no published clinical trials comparing risperidone with haloperidol in autistic children and adolescents.

The aim of our study was to evaluate the safety and efficacy of risperidone in the long-term treatment by comparing to haloperidol in autistic children and adolescents. Haloperidol was used as a control treatment, as it has been shown to be effective in treating children with AD.

Methods

Subjects

The subjects included in the double-blind study were children and adolescents with a primary diagnosis of AD according to the DSM-IV criteria [3]. The blinded study started with 32 patients at the baseline. Two patients did not continue follow-up visits, and two other patients withdrew their consents before randomization. Of the 32 patients (26 boys and 6 girls), 28 (22 boys and 6 girls) continued the open label phase after completing the double-blind phase. The ages of the subjects ranged from 8 to18.

Diagnoses were made by the consensus between two child psychiatrists. To be included in the study, each child had to (a) satisfy the DSM-IV criteria for autistic disorder, (b) be 8–18 years or (c) have his or her parents' informed consent, and (d) agree to be followed-up. Children were excluded from the study if they (a) also had epilepsy, (b) had a concomitant neuropsychiatric illness (such as attention deficit and hyperactivity disorder, Tourette syndrome, etc.), (c) demonstrated a psychotic disorder or symptoms, or (d) had other pervasive developmental disorders.

Design

This study was planned as the second phase of a twelve-week prospective, randomized, double-blind controlled study performed to compare the efficacy and safety of risperidone and haloperidol in children and adolescents diagnosed with AD according to DSM-IV criteria. After the 12-week double-blind and controlled phase, the second 12-week open-label and maintenance phase was conducted and the study was completed at the end of the 24th week. After double-blind phase, patients were administered same medication and recruited to the open label maintenance phase. The long-term the efficacy and safety of the drugs were evaluated at 12, 16, 20 and 24 weeks' visits.

The physical and neurological examinations and the vital signs (weight, height, pulse, systolic and diastolic blood pressure) of the patients were carried out at week 12. They were repeated at weeks 16, 20 and 24. Complete blood cell count, serum aspartate-amino transferase (AST) and alanine-amino transferase (ALT), serum prolactin, electroencephalogram (EEG), and electrocardiogram (EKG) examinations were also evaluated at 12th week. They were repeated at week 24.

This study was conducted in accordance with the ethical principles in the Declaration of Helsinki and the Good Clinical Practice guidelines established at the International Conference on Harmonization. We received approval of the study's protocol and addenda from the Independent Ethics Committee or Institutional Review Board. The young patients themselves were unable to give consent because of their disabilities. Instead, we obtained informed consent from their parents.

Medication

In the 1st phase (double-blind study) thirty patients were randomized to receive either haloperidol or risperidone. Following the randomization, risperidone or haloperidol was started at 0.01 mg/kg/day. Daily dose was doubled every 4 days. If tolerated, it was increased to a maximum dosage of 0.08 mg/kg/day at the end of the first 2 weeks. At week 12, the dosage for both treatment permitted by study protocol was 0.08 mg/kg/day. However, the maximum dose was not reached in all patients in either risperidone or haloperidol group due to their adverse effects. In the open-label phase, the patients were administered the same titration of the same medication. The patients also continued to use antianalgesics, antipyretics, decongestants and antibiotics administered by other doctors throughout the study. Anticholinergic agents

were prescribed to those who exhibited extrapyramidal symptoms but not as prophylactic drugs.

Measurements

Behavioral rating scales

Clinical Global Impression Scales-Improvement (CGI-I) [19], Ritvo-Freeman Real Life Rating Scale (RF-RLRS) [16], Aberrant Behavior Checklist (ABC) [1, 2] and Turgay DSM-IV Pervasive Developmental Disorder Rating Scale (TPDDRS) [36] were used for assessing the efficacy of the drugs at week 12 of the double-blind study. Efficacy measurements were repeated at weeks 16, 20 and 24.

Clinical global impression scales-improvement (CGI-I): CGI-I, a single item scale, rates behavior from 1 ("very much improved") to 7 ("very much worsened"). This instrument has been extensively used in psychopharmacologic studies of PDD or AD in children and adolescents [14, 25, 30].

Ritvo-freeman real life rating scale (RF-RLRS): This scale was developed to evaluate the effects of the treatments on symptomatic behaviors in patients with AD [16]. This scale has been used to measure the change in behavioral symptoms of children and adolescent with AD [28, 32].

RF-RLRS included subscales for assessing sensorymotor behaviors (e.g., rocking, hand flapping, pacing) (subscale-I), social relatedness (e.g., appropriate response to interaction and to events in the environment, initiation of appropriate physical interactions) (subscale-II), affectual reactions (e.g., abrupt changes in affect, crying, temper outbursts) (subscale-III), sensory responses (e.g., being agitated by noises, rubbing surfaces, sniffing self or objects) (subscale-IV), and language (e.g., communicative use of language, initiation of appropriate verbal communication) (subscale-V). The all subscales were scored on a four-point scale: 0 indicated "never", 1 signified "infrequently", 2 indicated "frequently" and 3 represented "almost always". A mean score for each subscale was determined by adding the individual ratings (0–3) for each behavior in the scale and dividing by the number of behaviors on that scale. The score on the RF-RLRS increases as the number and frequency of the severity of the AD symptoms. A mathematical sign correction to subtract normal behavior was made on subscales II, IV and V; this could result in negative values some subscales. For each subscale, absolute changes from baseline at each week were calculated by subtracting the baseline value from the value observed in a given week. The scale was administered at baseline (at week 0) and at the end of weeks 12, 16, 20 and finally 24 during the continuation phase of the study.

Aberrant behavior checklist (ABC): ABC is a rating scale for the assessment of treatment effect [1, 2]. It has been widely used in drug treatment studies in children and adolescent with autism [6, 26, 34]. ABC included subscales for assessing irritability, social withdrawal, stereotypic behavior, hyperactivity and inappropriate speech (total 58 items). ABC scale scores are calculated by adding all the responses (scored 0–3) to each question. Percent changes from baseline at each week were calculated by dividing the absolute change from baseline in a given week to the observed value at baseline.

Turgay DSM-IV pervasive developmental disorder rating scale (TPDDRS): This scale was based on DSM-IV criteria for PDD and all of the DSM-IV symptoms for PDD were asked to autistic children's mother or father [36]. The all items were scored on a four-point scale: 0 indicated "never", 1 signified "infrequently", 2 indicated "frequently" and 3 represented "almost always". TPDDRS scores are calculated by adding all the responses (scored 0–3) to each question. Absolute changes from baseline at each week were calculated by subtracting the baseline value from the value observed in a given week.

Safety assessment measures

Extrapyramidal Symptoms Rating Scale (ESRS) [11], and UKU Side-Effect Rating Scale [22], were applied for assessing safety of the drugs at each visit.

Extrapyramidal symptoms rating scale (ESRS): The ESRS consisted of a questionnaire on parkinsonian symptoms, a physician's examination of parkinsonism, distonia, and dyskinetic movements [11, 12]. From the individual items of the ESRS, total scores were performed for the questionnaire on parkinsonian and dystonic symptoms, the physician's evaluation of parkinsonism (acute distonia was included), and for dyskinetic movements. In addition, a factor score for hypokinesia was formed from the summed scores for expressive automatic movements, bradykinesia, rigidity, gait, and sialorrhea [12]. This questionnaire has been used for the presence and severity of the EPS side effects in psychopharmacologic studies in children with PDD or AD [34] and in adults with schizophrenia [12].

UKU side-effect rating scale: The UKU Side Effect Rating Scale was applied to evaluate the safety of the both drugs. This instrument comprised a total of 48 symptoms, arranged into four groups: psychic, neurological, autonomic and other (mainly dermatological and sexual) side effects. The severity of each side effect was rated on a scale from 0 (none) to 3 (severe). The scale was completed by mothers or fathers of the children and adolescents. The UKU was an inclusive

instrument with high reported reliability and validity [21].

Statistical analysis

The data were analyzed according to the intent-to-treat principle. Continuous variables are presented by means of summary statistics. This (unless otherwise stated) refers to the number of patients (n), mean, standard deviation (SD), minimum, median, and maximum. Categorical data are presented using either absolute and relative frequencies or contingency tables.

To look at efficacy, we set alpha at 0.05 and did a two-tailed analysis. Baseline was defined as week 0 (before medication) and the end-point was defined as week 24. The baseline and end-point (24th week) values were compared using the Wilcoxon matched pairs signed rank test in each study group (within group). The comparison of the mean values between the two groups was made by the Mann–Whitney-U test (between groups). The distributions and description for the outcome parameters were provided for each visit. In the assessment of statistical significance, $p \leq 0.05$ was used.

Results

Subjects

A total of 27 of 28 subjects completed the open-label study. One subject continued on risperidone was excluded from our final analysis from 24th week evaluation because of lack of efficacy data. Three cases of haloperidol group were administered anticholinergic agents because of EPS symptoms. The age, gender and weight characteristics of the subjects have been shown on Table 1.

Medication dosage

Medication dosage ranged from 1.0 to 6.0 mg/day (mean = 2.7 ± 1.3 mg/day) in the haloperidol group (n = 15), and 1.2–3.8 mg/day (mean = 2.5 ± 0.7 mg/day) in the risperidone group (n = 13) in the open-label continuation study.

Measures

Efficacy

CGI: Degree of improvement was superior in the risperidone group compared to the haloperidol group at week 24 (p = 0.0186).

RF-RLRS: The change in RF-RLRS sensory-motor subscale scores between the baseline and week 24 was statistically significant in the risperidone group (p = 0.018), but not in the haloperidol group (p = 0.16; Table 2). The mean values of RF-RLRS language subscale scores showed a significant increase at week 24 from baseline in the haloperidol group (p = 0.0074; Table 2). On the other hand, in the risperidone group, there was a moderate decrease at the same period, but this was not statistically significant (p = 0.5616; Table 2). When both groups were compared as regards RF-RLRS language subscale scores, there was a statistically significant improvement in the risperidone group (p = 0.014; Table 2), but not in any of the other subscales (Fig. 1).

ABC: The change from baseline risperidone group was significant at week 24 (p = 0.0029); but was not significant in the haloperidol group (p = 0.53; Table 2). The changes of ABC scores were not significantly different between the two study groups at week 24 (p = 0.0746) (Fig. 2).

TPDDRS: The difference between the baseline and week 24 scores was statistically significant both in the risperidone and haloperidol group (p = 0.0012 and p = 0.049 respectively, Table 2) (Fig. 2).

Table 1 Description of the sample

	Risperidone (n = 13)	Haloperidol (n = 15)	p value
Age			
Mean (SD)	10.2 (±2.8)	10.9 (±2.9)	0.253*
Range	7–15	7–17	
Gender			
Male	9	13	0.371**
Female	4	2	
Weight (kg)			
At week 0 (mean ± SD) Range	33.3 ± 9.1 (18–53.3)	42.1 ± 17.9 (18–87)	0.198**
At week 24(mean ± SD) Range	37.5 ± 8,9 (28–58)	48.4 ± 18,2 (26–93)	0.299**

*Mann–Whitney U non-parametric test; **χ^2 (2-sided)

Table 2 Change from baseline (at week 0) in the efficacy measurements at study endpoint (at week 24)

Efficacy measure	Risperidone		Haloperidol		p^a values
	Baseline	Endpoint	Baseline	Endpoint	
RF-RLRS (Sensory-motor)	0.90 ± 0.52	0.44 ± 0.42**	0.69 ± 0.47	0.57 ± 0.48	0.1828
RF-RLRS (Social)	0.62 ± 0.50	0.69 ± 0.42	0.50 ± 0.41	0.68 ± 0.59	0.6141
RF-RLRS (Affect)	1.09 ± 0.41	1.27 ± 0.37	1.05 ± 0.61	1.36 ± 0.68	0.6141
RF-RLRS (Sensory)	0.98 ± 0.46	0.82 ± 0.35**	0.86 ± 0.44	0.81 ± 0.59	0.7551
RF-RLRS (Language)	0.52 ± 0.37	0.44 ± 0.33	0.15 ± 0.44	0.32 ± 0.51*	0.0414
ABC (Total)	85.6 ± 27.3	52.0 ± 14.9*	67.1 ± 25.1	58.1 ± 32.2	0.0746
TPDDRS	91.5 ± 20.1	67.2 ± 17.0*	77.6 ± 23.1	66.2 ± 26.4**	0.0594

*$p \leq 0.01$, **$p \leq 0.05$ Wilcoxon test; [a]Mann–Whitney *U* Test

Safety

ESRS: There were no statistically significant difference baseline and week 24 scores within groups or between groups. *Three cases of haloperidol group were administered* anticholinergic agents because of EPS symptoms.

UKU-Side Effect Rating Scale: Among all the items of the side effect screening scale only the 'weight gain' item was significantly different between the study groups at week 24 ($p = 0.0414$). Weight gain was observed more frequently in the haloperidol group.

Vital Signs and Laboratory Findings: Neither group developed severe adverse events. When the serum prolactin levels were compared at the end of the 24th week and at the baseline, it was significantly high in the haloperidol group at the end of the 24th week ($p = 0.0092$); but not in the risperidone group ($p = 0.0712$). The change from baseline for weight values were statistically significant in both haloperidol and risperidone group at 24 weeks ($p = 0.0007$ and $p = 0.0060$, respectively). There was no statistically difference between the two groups for serum prolactin levels ($p = 0.5480$) and weight values ($p = 0.2995$) at the end of the study.

Other Common Side Effects: Other reported side effects were constipation (29%), enuresis nocturna (20%), blunt affect (20%), difficulty sleeping (20%), increased appetite (26.7%), and upper respiratory tract infection (URTI) (53.35) in the haloperidol group. The risperidone group developed constipation (23.1%), enuresis nocturna (23.1%), and URTI (53.8%).

Discussion

The outcomes of our prospective, open-label, side to side comparison study support that risperidone is more effective and safer than haloperidol in the long-term maintenance treatment of autistic children and adolescents because of lower incidence of side effects. In this trial, risperidone was more efficacious than haloperidol in reducing scores on the CGI-I and on the subscale for language (subscale V) on the RF-RLRS (Fig. 1). Additionally, risperidone was found effective for improving scores on the subscale sensory motor behaviors (subscale I) on the RF-RLRS (Fig. 1), on the ABC and on the TPDDRS (Fig. 2). However, haloperidol was effective for decreasing only on TPDDRS, risperidone's efficacy was trending towards statistical significance compared with haloperidol ($p = 0.0594$). In open-label [17, 23, 25, 27, 30] and double-blind, controlled studies [26, 29, 34] have been shown that risperidone was efficacious in the treatment of children and adolescents with AD. There are no other published treatment studies of risperidone in comparison with haloperidol in children and adolescents with AD. In our study, we found that risperidone was beneficial in treating for autistic children and adolescent. Additionally, although, haloperidol was the most studied and most commonly used agent in the treatment of AD in the previous years, risperidone was superior to it.

Our finding that risperidone was more effective than haloperidol in the long-term treatment of AD for CGI-improvement scores confirms results of prior studies reporting the efficacy of risperidone in the long-term treatment [23, 25, 38]. Achieving better results in maintenance treatment suggests that risperidone may be preferred to haloperidol, which was a common classical psychotropic drug in the treatment of AD.

RF-RLRS sensory-motor subscale evaluates stereotypical movements and motor behaviors observed in AD [16]. By using RF-RLRS sensory motor subscale, we determined that, though risperidone decreased stereotypical-motor behaviors in the long-term, haloperidol did not make any difference (Fig. 1). This finding corroborates the open-label short-term studies [17, 27], the long-term studies [17, 38], and the double-blind, placebo controlled short/long-term studies [28, 29, 34], all of which shown that risperidone was effective in the improvement of behavioral symptoms including stereotypical motor activities of AD. In addition to this, our result

supports the publication suggesting that risperidone remained efficacious in the long-term treatment [23, 25, 29, 38]. It's a different and important point in present study that haloperidol did not improve sensory-motor behaviors of the autistic children and adolescents in the long-term use. Our result is that a decrease on sensory motor subscale (subscale I) in risperidone group was similar to findings of the study by the Autism Network of the Research Units on Pediatric Psychopharmacology (RUPP-2005) [29]. They determined a reduction in sensory-motor subscale on RF-RLRS comparing risperidone to placebo. Additionally, they found that risperidone more efficacious than placebo for improving scores in affectual reactions (subscale III) and sensory responses (subscale IV) on RF-RLRS, but they did not find a statistically significance in language (subscale V) and social withdrawal (subscale II). Interestingly, we found a significant improvement with risperidone on language subscale when compared to haloperidol (Fig. 1). Although in the risperidone group, mean scores of RF-RLRS language subscale did not show statistically significant improvement at the end of the 24th week, they tended to decrease compared with the baseline scores as seen in Table 2. On the other hand, in the haloperidol group unlike the risperidone group, patients' language functions significantly deteriorate ($p = 0.0074$) (increase in the RF-RLRS language subscale scores) at week 24 from baseline, which suggests that risperidone is statistically more beneficial than haloperidol ($p = 0.0414$) on language functions. This result does not necessarily means that "risperidone improves language functions in AD". However, it may suggest that risperidone has more positive effects on language functions of autistic patients than haloperidol. This is an important issue for selection of medication in the treatment of AD.

The other finding of the present study that risperidone was efficacious not only on sensory-motor activities but also on behavioral disturbances assessed with ABC in the maintenance treatment support the short-term studies [6, 26, 34] and long-term studies [23, 25, 38] conducted on this topic. Nevertheless, in mentioned studies in which other scales and ABC were used to assess behavioral problems, certain target symptoms such as irritability and hyperactivity were aimed, and the effects of risperidone were studied on these symptoms. Therefore, what behavioral problems of autistic children would benefit from risperidone were also clarified by these studies. However, our results suggest that risperidone generally decreases behavioral symptoms in ABC without definite target symptoms. This could be considered as a limitation since there is no any definite target symptom; it is difficult to specify where risperidone could be utilized.

Today AD is diagnosed by DSM-IV criteria. Although both drugs decrease TPDDRS scores, which determine the severity of AD by DSM-IV diagnosis criteria of AD [34], it was determined that risperidone was superior to haloperidol nearly significantly ($p = 0.0594$). This may suggest that risperidone is generally more effective than haloperidol in the improvement of symptoms of autism, but it is difficult to define the specific symptoms in which risperidone is efficacious.

Our findings on side effects of the long-term uses of risperidone and haloperidol in children and adolescents show that risperidone has fewer side effects than haloperidol, and thus more tolerable in this age group. The most marked result regarding side effects observed in both groups is the weight gain. Weight gain during risperidone administration is a result, which has been confirmed in several studies [23, 24,

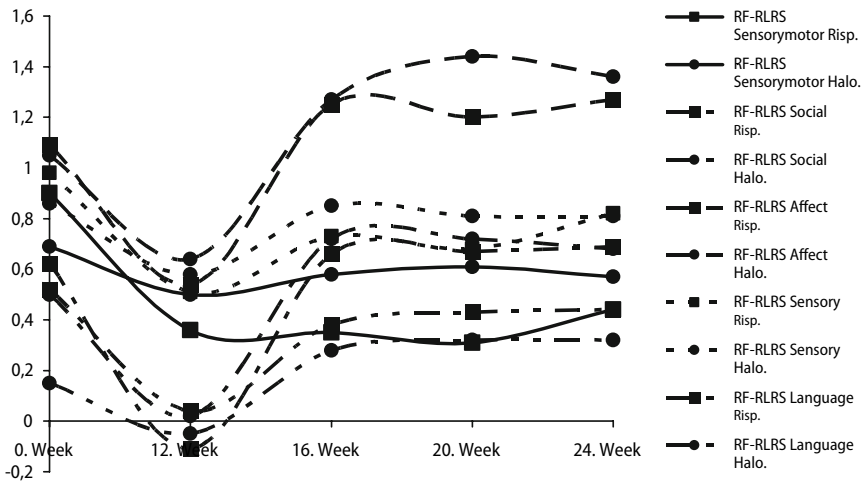

Fig. 1 RF-RLRS scores during the different time points of the study

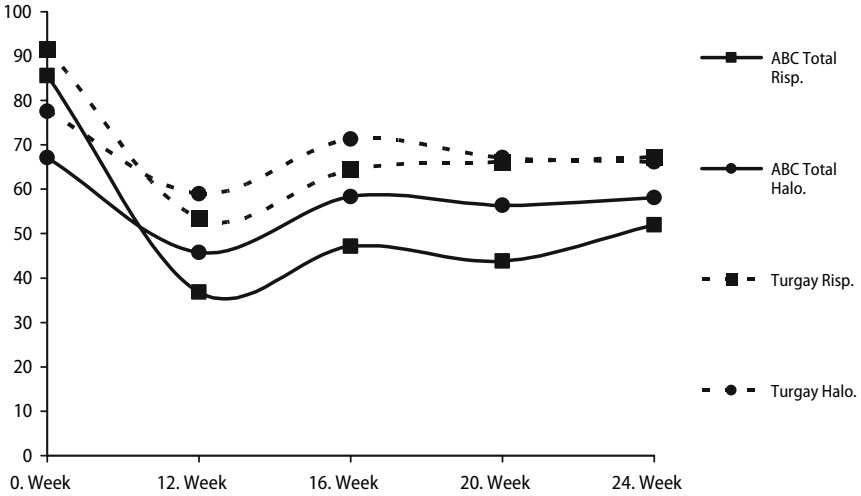

Fig. 2 ABC and Turgay PDD-DSM-IV scores during the different time points of the study

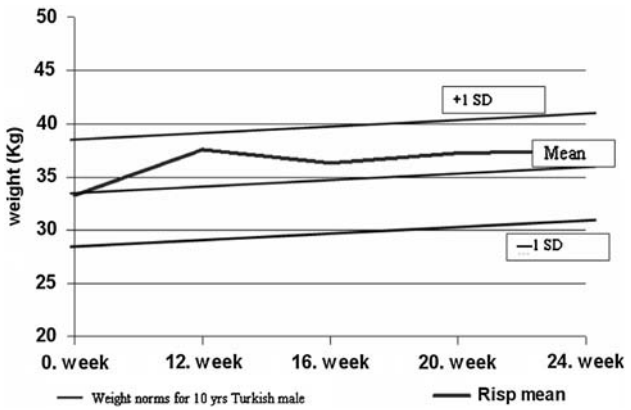

Fig. 3 Absolute and expected weight gain in Risperidone group during 24 week

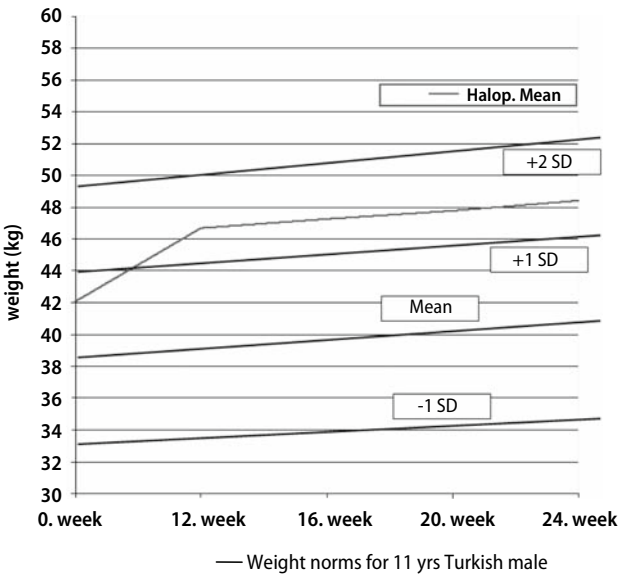

Fig. 4 Absolute and expected weight gain in Haloperidon group during 24 week

34, 38]. There is also some publication reporting that haloperidol and other classical antipsychotics may cause weight gain [18, 35]. It's interesting in this study that 'weight gain' item on the UKU Side Effect Rating Scale, which completed by mothers or father of the children, was observed more frequently in the haloperidol group. However, this data does not seem to be an objective data because of the change of the mean values from baseline for weight is not statistically significant between the two groups at the end of the study ($p = 0.2995$). Martin et al. studied weight changes for six months among risperidone treated youths with autism. They found that, risperidone causes weight gain in excess of developmentally expected norms that follows a curvilinear trajectory and decelerates over time [24]—However both risperidone and haloperidole did not cause weight gain in excess of developmentally expected norms in our study (Figs. 3 and 4)—Martin et al. reported that, rapid weight gain was occurred in the risperidone group during first 2 months of the study, similarly we observed rapid weight gain in both two treatment groups at the beginning of the study (Figs. 3, 4). Weight gain stopped after 12th week of risperidone treatment despite in haloperidole group weight gain continued to increase until 24th week.

Another finding on side effects of this study was that prolactin level was significantly increased in the haloperidol group at the end of the study; but not in risperidone group. However, there was not a significant difference between the two groups. In both group, there was no clinical manifestation of hyperprolactinemia. This finding is similar to the changes of the serum prolactin levels determined in the study carried out by Gagliano et al. in order to evaluate the efficacy and adverse effects of risperidone in 24 autistic chil-

dren [17]. In their open-label study, serum prolactin levels increased with risperidone treatment, at the end of the 12th week but measurements obtained at the end of the 24th week showed a decline in serum prolactin levels of some patients. In our controlled study, we saw increased prolactin levels only in haloperidol group at week 24. No severe EPS side effects were observed either in the risperidone group or in the haloperidol group. Minimal side effects associated with EPS were observed in the haloperidol group; however, this was considered statistically insignificant.

Conclusions

The consequences of this study suggest that in the long-term treatment of AD, risperidone is more effective and safer than haloperidol in the long-term maintenance treatment. However, in the assessment of efficacy and safety of risperidone in autistic children and adolescents, a great number of long-term studies should be performed on a large case series including placebo controls.

Limitations: The limitation of our study was that there was no statistical analysis in terms of the level of intelligence. Behavioral symptoms of mentally retarded children may be different and the response to psychopharmacological treatment may be different. This limitation could affect the findings.

Clinical Implication: This study reveals that, in the long-term maintenance treatment of AD, risperidone is more effective and well tolerated than haloperidol, the most frequent studied and effective psychopharmacological agent of previous years.

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