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Osmotic Release Oral System Methylphenidate is More Effective Than Immediate Release Methylphenidate: A Retrospective Chart Review in Turkish Children with Attention Deficit Hyperactivity Disorder

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ÖZET:

OROS-Metilfenidat IR-Metilfenidattan daha etkilidir: Dikkat eksikliği hiperaktivite bozukluğu olan Türk çocuklarında retrospektif bir araştırma

Amaç: Bu çalışmanın amacı DEHB olan Türk çocuklarında IR-MPH ile karşılaştırıldığında OROS-MPH'nın etkinlik ve güvenliğinin değerlendirilmesidir.
Yöntem: Ayaktan hasta kliniğine ilk kez başvuran ilkokul çağındaki çocukların tıbbi kayıtları gözden geçirilmiş, OROS-MPH alan 67 çocuk ile IR-MPH alan 47 çocuk çalışmaya alınmış, DEHB için tedavi gören toplam 114 çocuk 8 hafta boyunca takip edilmiştir.
Bulgular: Hem aile hem de öğretmen değerlendirmelerinde Turgay DSM-IV'e Dayalı Çocuk ve Ergen Davranım Bozuklukları Tarama ve Değerlendirme Ölçeği puanlarında 8 hafta sonunda azalma izlenmiştir ($p<0.001$). Başlangıç-8. hafta ortalama dikkatsizlik puan karşılaştırmalarında OROS-MPH'nın IR-MPH'a göre hem öğretmen ($p=0.007$) hem de aile ($p=0.015$) formlarında daha üstün olduğu tespit edilmiştir. OROS-MPH ve IR-MPH'nın ikisi de iyi tolere edilmiştir ve yan etki profilleri benzer çıkmıştır.
Sonuç: OROS-MPH'nın Türk çocuklarında DEHB semptomlarının tedavisinde etkin ve güvenli olduğu görülmüştür.

Anahtar sözcükler: Dikkat Eksikliği Hiperaktivite Bozukluğu, metilfenidat, çocuklar

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ABSTRACT:

Osmotic Release Oral System Methylphenidate is more effective than Immediate Release Methylphenidate: a retrospective chart review in Turkish children with attention deficit hyperactivity disorder

Objective: The aim of this study was to evaluate the efficacy and safety of osmotic release oral system methylphenidate (OROS-MPH) compared with immediate release methylphenidate (IR-MPH) in Turkish children with attention deficit hyperactivity disorder (ADHD).
Method: The medical records of primary school-aged children, who were first-time referrals to the outpatient clinic, were reviewed; 67 children receiving OROS-MPH and 47 children receiving IR-MPH were recruited for the study. A total of 114 children receiving treatment for ADHD were evaluated over 8 weeks.
Results: The total Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale scores from both the parent and teacher forms decreased significantly in both groups over 8 weeks ($p<0.001$). OROS-MPH was found to be superior to IR-MPH when comparing baseline-to-8th-week- mean inattention score changes on both the teacher ($p=0.007$) and parent ($p=0.015$) forms. OROS-MPH and IR-MPH were both well tolerated, with similar side-effect profiles.
Conclusion: OROS-MPH was found to be effective and safe in the treatment of ADHD symptoms in Turkish children.

Keywords: Attention Deficit Hyperactivity Disorder, methylphenidate, children

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INTRODUCTION

Among the neurodevelopmental disorders of childhood, attention deficit hyperactivity disorder (ADHD) is the flagship diagnosis, with an estimated worldwide prevalence of approximately 5%[1]. Although this disorder is observed in childhood and adolescence, among the most important clinical implications are its long-term effects, which extend into adulthood[2]. ADHD is generally associated with emotional and cognitive problems[3,4] and may often be associated with

deficiencies or retardation in motor development or coordination[5,6]. These negative effects present cumulatively as academic underachievement in school-aged children, which generally continues into adolescence[7]. Eventually, ADHD in adulthood may be associated with occupation-related failures[8].

ADHD causes disruptions in the individual's academic, social, and occupational life, and it may also affect other family members and threaten relationships[9]. ADHD may also be an early sign of subsequent psychiatric disorders, such as antisocial personality disorder[10].When all these aspects are considered together, achieving successful treatment of ADHD becomes crucial.

Methylphenidate (MPH) is a potent dopamine and noradrenergic reuptake inhibitor, and it is the most widely used treatment for ADHD[11,12]. Clinical studies show that stimulants improve academic performance[13,14], and, in 1996, a multimodal treatment study of ADHD (MTA) demonstrated that a three-times-daily regimen of immediate-release methylphenidate (IR-MPH) was the gold standard treatment for ADHD[15]. The major shortcoming of this daily dosing, however, is the problem of adherence to the medication regimen. Especially in school-aged children, the major responsibility for assuring safe treatment, with no discontinuation, is left to the teachers, which is not a reliable solution. The demand for a method of guaranteeing stable dosing of IR-MPH treatment has resulted in a better solution, namely the development of extended-release MPH formulations.

After two generations of extended-release formulations (i.e., the first one used a wax matrix system and the second one used biphasic release of both immediate- and extended release coated molecules) the third generation of MPH was manufactured as an osmotic release oral system (OROS) that uses osmotic pressure to achieve controlled delivery of medication, with a half-life of 6.4 hours[12]. This long plasma half-life of OROS-MPH provides all-day activity in patients, and clinical studies show that the efficacy of OROS-MPH is at least comparable to that of IR-MPH in both children[16] and adolescents[17]. MPH is regarded as a well-tolerated and safe drug; nevertheless, approximately one quarter of children cannot tolerate stimulant medications. Whether the choice of treatment is IR- or OROS-MPH, this intolerance is generally related to higher doses of the drug, and both forms of MPH have similar adverse drug reaction rates[18].

Current research comparing the efficacy and safety of MPH formulations in Turkish children is very limited. A literature search of national databases revealed only an eight-week, open-ended study that included 83 children between 7 and 14 years of age. In the study, OROS-MPH and IR-MPH were both found to be effective according to the evaluations of physicians and families, and no significant differences were found with respect to efficacy and adverse effects[19]. Due to this lack of data in Turkish children, in the current study, we aimed to evaluate the efficacy and reliability of OROS-MPH according to families, teachers, and clinicians, as well as to evaluate its efficacy and adverse effects compared with IR-MPH, in a population of Turkish children with ADHD. As the current literature suggests, biological diversities affect sensitivities to and side effects of psychotropic medications[20], and adverse events observed from stimulant medications are generally dose-dependent[21]. For these reasons, we aimed to contribute to the variety of knowledge in the literature by presenting comparisons of these two medications in a less well-studied population.

METHODS

Sample

This study included 122 children between 7 and 15 years of age who were first admitted to the Child and Adolescent Psychiatry Department of Ege University Medical Faculty between January and June 2010 and were diagnosed with ADHD according to the Schedule for Affective Disorders and Schizophrenia for School Aged Children (Kiddie-SADS). The children had not been diagnosed with a psychotic disorder, bipolar

disorder, a pervasive developmental disorder, or mental retardation (defined as having an IQ lower than 80), and they were not taking another medication for anxiety, depression, or other disruptive behavior disorders. The study groups included participants taking OROS-MPH (n=68) and IR-MPH (n=54) who met the inclusion criteria.

Study Design

In this study, the hospital records of cases were retrospectively reviewed. Participants who met the inclusion criteria, had complete records for the initial, 4th-week, and 8th-week visits, and began treatment with 5 mg twice daily (10 mg/day) of IR-MPH or 18 mg/day of OROS-MPH were enrolled in the study. Drug doses were arranged according to the manufacturers' directions. A pediatrician performed the physical examination, assessed heart rate, blood pressure, and weight at the 1st-and 8th-week visits and took laboratory measurements.

Evaluation Scales

Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV) (clinician and parent forms): This scale was first developed by Turgay to screen for disruptive behavior disorders, and Ercan et al. conducted a Turkish validity and reliability study. It includes 41 questions assessing the following areas: 9 for attention deficit, 9 for hyperactivity and impulsivity, 9 for oppositional defiant disorder, and 15 for conduct disorder. Each question is rated as 0= none, 1= some, 2= quite, or 3= much.

Clinical Global Impression-Improvement and Severity (CGI-I, CGI-S) Scales: These scales were developed by Guy[22] for use in clinical trials to evaluate the course of psychiatric disorders in all ages. The CGI-S was used at the first week, and the CGI-S and CGI-I were used at the 8th week evaluations. A physician administered the CGI scales during semi-structured interviews. The CGI-I evaluates improvement as 1= very much improved, 2= quite improved, 3= minimally improved, 4= no change, 5= minimally worsened, 6= quite worsened, or 7= very much worsened.

Side Effect Assessment

A methylphenidate side effect scale that was designed for this study was used in each clinical interview, and questions regarding the presence of any side effects were asked of both the patients and parents, with responses noted. Mild side effects were managed by dosage regulation or changes in the daily drug intake times. At the end of 8 weeks, all the parents were asked to complete the methylphenidate side effect assessment scale.

Statistical Analyses

All statistical analyses were performed using SPSS for Windows, version 15.0, software (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using a chi-square test, numerical variables in independent groups were compared using Student's t-test, and drug efficacies over consecutive follow-ups were compared with a paired samples t-Test. Normal distributions of numerical variables were evaluated by a general examination of data by the Kolmogorov-Simirnov or Shapiro-Wilk tests, Detrented Plot graph, Coefficient of Variation, Histogram, and Skewness and Kurtosis evaluation.

Ethics Statement

Local approval was obtained from hospital administration for using the data on the Hospital Information System retrospectively.

RESULTS

This study included 122 children (OROS-MPH: 68 and IR-MPH: 54) between 7 and 15 years of age who met the inclusion criteria. The mean age of the participants was 9.1±1.7 years. Participants in the OROS-MPH group used MPH at a mean dose

Table 1: Sociodemographic and clinical characteristics (n=122)

	OROS-MPH	IR-MPH	t	p
Age (years)	9.3±1.8	8.9±1.7	1.31	0.190
Drug dose (mg/day)	30.8±11.5	27.5±6.1	1.9	0.058
Total IQ score	98.2±16.5	99.4±12.8	0.26	0.796
Gender			χ^2	p
Boys	85% (n=58)	74% (n=40)	3.03	0.082
Girls	15% (n=10)	26% (n=14)		
ADHD sub-type				
Combined type	91% (n=62)	87% (n=47)	0.54	0.462
Predominantly Inattentive Type	9% (n=6)	13% (n=7)		

Student's-t test for numerical data; Chi-square test for categorical data.

Table 2: Comparison of the OROS-MPH and IR-MPH treatments (n=122)

	OROS-MPH		IR-MPH		
	Baseline Mean±SD	8th Week Mean±SD	Start Mean±SD	8th Week Mean±SD	p
T-DSM-IV Attention Problem					
Parent report	16.3±4.8	7.2±4.7	17.2±4.8	10.9±5.9	0.015
Teacher report	15.9±4.8	7.7±4.7	16.1±6.7	10.7±6.6	0.007
T-DSM-IV Hyperactivity					
Parent report	15.4±6.1	6.7±4.9	18.1±5.2	10.8±5.9	0.240
Teacher report	14.9±9.4	5.9±5.8	16.3±7.9	9.7±5.7	0.152
T-DSM-IV Oppositional Defiance					
Parent report	11.0±5.9	4.6±4.6	13.5±5.7	7.7±5.1	0.639
Teacher report	9.6±6.8	3.5±4.3	11.0±7.3	6.1±4.6	0.322
T-DSM-IV Conduct Problems					
Parent report	3.5±3.8	1.3±2.7	4.6±4.1	2.1±2.1	0.716
Teacher report	3.9±3.9	1.1±1.9	4.9±5.1	1.8±2.3	0.695
T-DSM-IV Total					
Parent report	45.9±16.0	18.3±14.7	53.3±15.7	28.6±16.2	0.485
Teacher report	44.7±18.7	18.5±14.6	49.1±22.3	28.6±6.1	0.114
CGI-Severity	6.1±0.7		5.9±0.6		0.287
CGI-Severity		2.2±1.2		2.8±1.1	0.011
CGI Improvement		1.8±0.9		2.3±1.2	0.014

Paired samples t test, p<0.05

of 30.8±11.5 mg/day, and those in the IR-MPH group took 27.5±6.1 mg/day, such that the MPH doses were not statistically different between the groups (t=1.90, p=0.058). Gender, age, total IQ score (according to the WISC-R), and ADHD sub-group distribution were not statistically differed between the study groups (Table 1).

Efficacy Measures

Both study groups showed significant decreases in parent-teacher T-DSM-IV total scores and all sub-scale scores at the 8-week evaluation compared with the initial evaluation (p<0.001 for all). The OROS-MPH group showed a 60% decrease (28.1 points) and the IR-MPH group showed a 40% decrease (22.3 points) in parent T-DSM-IV total scores, but no significant difference was found between the groups (p=0.485). Similarly, the OROS-MPH and IR-MPH groups showed decreases of 61% (27.5 points) and 42% (22 points), respectively, in teacher T-DSM-IV total scores, and there was no significant difference between the groups (p=0.144). In addition, there were no statistically significant differences between the groups in hyperactivity, oppositional defiance, and conduct scores according to the T-DSM-IV scale (Table 2).

Table 3: Adverse effects (n=122)

	OROS-MPH		IR-MPH	
Adverse Effect	**n**	**%**	**n**	**%**
Any	52	76.0	43	79.6
Loss of appetite	47	68.5	37	69.1
Weight loss	25	36.8	15	27.8
Stomachache	16	23.5	12	22.5
Nausea	14	20.6	8	14.8
Constipation	10	14.7	13	24.1
Emotional change*	22	32.4	30	51.9
Irritability	30	44.1	24	44.4
Increased mobility	22	32.4	14	25.9
Headache	16	23.5	21	38.9
Insomnia	19	27.9	23	42.6
Withdrawal	21	30.9	9	16.7
Tic 2	3	1	2	

Chi-square, *p<0.05

OROS-MPH was found to be more effective (p=0.015) in improving the parent T-DSM-IV attention deficit scores compared with IR-MPH. Similarly, OROS-MPH was more effective (p=0.007) in improving the teacher T-DSM-IV attention deficit scores compared with IR-MPH (Table 2).

The CGI-Severity scores at the first evaluation were similar in both study groups (OROS-MPH: 6.1±0.7, IR-MPH: 5.9±0.6; t=1.16, p=0.287), but at the 8-week evaluation, the IR-MPH group (2.8±1.1) had significantly higher scores than the OROS-MPH group (2.2±1.2) (t=-2.57, p=0.011).

The evaluations at the 8th week revealed statistically significant differences between the groups with respect to CGI-Improvement scores (OROS-MPH: 1.8±0.9, IR-MPH: 2.3±1.2; t=-2.48, p=0.014). With CGI-I scores of 1 and 2 considered as representing a good treatment response, 80.8% of children in the OROS-MPH group and 59.6% of children in the IR-MPH group achieved good improvement, and this improvement was statistically significant (χ^2=6.57, p=0.009) (Table 2).

Adverse Effects

At least one adverse effect was reported in 76% of the OROS-MPH group and in 79.6% of the IR-MPH group. No severe or life-threatening adverse effects were reported in either group. Emotional changes were significantly more frequent in the IR-MPH group compared with the OROS-MPH group (51.9% and 32.4%, respectively; p=0.030), but other adverse effects were similar between the groups (Table 3). Eighty-eight percent of the adverse effects in the OROS-MPH group and 86% of those in the IR-MPH group decreased or disappeared over time.

DISCUSSION

This study aimed to address the paucity of knowledge on the safety and efficacy of OROS-MPH in Turkish pediatric patients with ADHD. Overall, the results revealed that OROS-MPH significantly decreased the symptoms of attention deficit, hyperactivity/impulsivity, oppositional defiance, and conduct disorders.

Current research on the efficacy of OROS-MPH suggests that this treatment is effective in reducing the core symptoms of ADHD and significantly improves attention and behavioral problems[17,23]. Similarly, a recent paper by a Turkish group suggested that OROS-MPH was effective in the treatment of ADHD according to parents, and clinical impression measures[19]. We found in our study that OROS-MPH was more effective than IR-MPH according to the CGI-I, CGI-S, and parent-teacher T-DSM-IV attention deficit scales. The mean scores of the OROS-MPH group on the

T-DSM-IV, including the total, hyperactivity, oppositional defiance, and conduct disorder scale scores, were slightly higher than those of the IR-MPH group, although the differences were not statistically significant. Because the OROS-MPH has a longer duration of effect, teachers and families may give higher scores to patients on this treatment, which may be a reason for the higher scores that we found in our study. Another reason for these findings may be that IR-MPH must be used more than once a day and compliance with this regimen may be disrupted when patients are in school. Despite the knowledge that a three-times-daily dosing of MPH is the most effective method of drug delivery, it is also a known and reported fact that doses administered during the school day are generally the most neglected doses because of the psychosocial aspects of medication usage by children for a psychiatric problem[24]. Furthermore, fluctuations in the plasma concentrations of short-acting MPH may cause symptom deterioration and adverse effects, which must be accounted for in the clinical interpretations of significant differences between the two drugs[25].

After OROS-MPH was introduced into the market, most patients, parents, teachers, and clinicians welcomed this new formulation, which can provide symptom relief with a once-daily dosing[26]. Additionally, patients reported that shifting to OROS-MPH resulted in improvements in their daily lives[27]. These intended shifts may be related to ease of use as well as increased efficacy due to elongated effect durations. However, there are debates in the current literature related to compliance with this extended-release formulation of MPH. A recent meta-analysis revealed that, according to some studies, there was no significant difference in compliance between the ER- and IR-MPH formulations[12]. In contrast, another study comparing IR- and OROS-MPH reported that the results clearly support a greater efficacy of OROS-MP, due to both compliance and elongated effect duration that lasts throughout the day and early evening[28]. Our results also support this favorable outcome of OROS-MPH.

One of the major concerns related to treatment choice is adverse effects. According to our results, adverse events and their frequencies were similar between OROS-MPH and IR-MPH, but emotional changes were more frequent with IR-MPH. In contrast to our findings, a previous study reported that emotional changes were more frequent with OROS-MPH, although the difference was not significant[19]. We think that emotional changes were seen in the IR-MPH group more frequently due to fluctuations in plasma concentrations associated with its more-than-once-daily use.

The most frequently reported adverse effect was loss of appetite in both groups in our study. Current data in the literature on the adverse effects of OROS- and IR-MPH generally focus on two prevalent effects, namely decreased appetite and insomnia[29]. Other reported prevalent adverse effects of OROS-MPH include headaches and abdominal pain[30,31]. These side effects were generally reported to be present in 10-25% of patients. However, our study revealed that appetite loss was seen in 69.1% of children taking OROS-MPH. This value is higher than those in the literature, but is consistent with a previous report on Turkish children with ADHD, which reported appetite loss in 57.1% of children[19]. This high prevalence of appetite loss associated with MPH treatment in our population may be related to nutritional factors, eating habits, or genetic characteristics of the population, which should be clarified by further studies.

Another significant finding of the current study is that OROS-MPH and IR-MPH were both effective in Turkish children with ADHD, despite their use at lower doses compared with the doses used in the MTA (1999) and Hechtman (2004) studies (34.4 and minimum of 35.8 mg/day, respectively). Current data suggest that there are no criteria for determining the optimal dose in psychostimulant therapy, and the dose can be escalated until a significant decrease in symptoms is obtained or a severe adverse effect is observed[32]. A previous study showed that a daily dose of 24.8±8.1 mg of IR-MPH was sufficient to control ADHD symptoms in the Turkish population, whereas another study conducted with OROS-MPH reported that a daily

dose in the range of 18-36 mg is adequate to control ADHD symptoms[19]. Including our study, three studies have revealed that lower doses of MPH are effective in the treatment of ADHD compared with Western populations. Another study conducted by Lee et al. similarly found that lower doses of OROS-MPH (18-36 mg/day) were effective and reliable in Korean children[33]. It is known that pharmacogenetic characteristics are deterministic of the response to MPH[34]. The dose differences across populations may be related to the genetic characteristics of the populations, and further pharmacogenetic studies are needed to clarify the treatment responses to MPH in different populations.

Limitations

A major limitation of this study is its retrospective nature; thus, randomized, double-blind, prospective studies are needed to generalize these findings. Another important limitation of our study is our inability to assess treatment adherence in both medication groups.

Competing interests

While making the study no support has been taken. Eyup Sabri ERCAN is in charge in the advisory board of Lilly and Janssen-Cilag, and the other authors declare no competing financial interests.

Authors' contributions

All authors contributed to, read and approved the final version of the manuscript. UAA drafted the manuscript, ESE designed the study and revised the manuscript critically for important intellectual content, EE contributed to the data collection and participated in the statistical analysis, DY analyzed the data, interpreted the results and wrote the results section, and BKB contributed to the data collection and conducted the literature search.

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