Complementary Therapies in Clinical Practice 21 (2015) 61–67

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

journal homepage: www.elsevier.com/locate/ctcp

Ginkgo biloba in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. A randomized, placebo-controlled, trial

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Keywords:
Ginkgo biloba
Complementary therapies
Herbal medicine
Attention deficit disorder with hyperactivity
Methylphenidate

A B S T R A C T

Objective: To evaluate the efficacy of *Ginkgo biloba* as a complementary therapy for attention-deficit/hyperactivity disorder (ADHD).
Methods: Children and adolescents with ADHD received methylphenidate (20–30 mg/day) plus either *G. biloba* (80–120 mg/day) or placebo for 6 weeks. Parent and teacher forms of the ADHD Rating Scale-IV (ADHD-RS-IV) were completed at baseline, week 2, and week 6. Treatment response was defined as 27% improvement from baseline in the ADHD-RS-IV.
Results: Compared with placebo, more reduction was observed with *G. biloba* regarding ADHD-RS-IV parent rating inattention score (-7.74 ± 1.94 vs. -5.34 ± 1.85, $P < 0.001$) and total score (-13.1 ± 3.36 vs. -10.2 ± 3.01, $P = 0.001$) as well as teacher rating inattention score (-7.29 ± 1.90 vs. -5.96 ± 1.52, $P = 0.004$). Response rate was higher with *G. biloba* compared with placebo based on parent rating (93.5% vs. 58.6%, $P = 0.002$).
Conclusions: The *G. biloba* is an effective complementary treatment for ADHD. Further studies with longer treatment duration are warranted in this regard. IRCT2014111519958N1.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in children. Symptoms are persistent and mainly include inattention, hyperactivity, and impulsivity [1]. The estimated worldwide prevalence of ADHD is about 5.3% in children and adolescents of the general population [2]. This disorder significantly impairs the academic and psychosocial functioning of the child [3–5] and results in high global burden [6].

Management of ADHD consists of both pharmacological and behavioral interventions [7]. Stimulants such as methylphenidate and non-stimulants such as atomoxetine (selective norepinephrine-reuptake inhibitor) are recommended by the current practice guidelines for the treatment of ADHD [7]. However, up to 30% of the patients have no satisfactorily response to these drugs, must avoid stimulant therapy, or may not tolerate drugs' common side effects such as appetite loss and sleep problems [8]. Accordingly, a large number of families use complementary or alternative medicines (CAM) for treatment of their children with ADHD. Common applied CAM methods include vitamins, minerals, and dietary modifications and supplements [9]. Although families report beneficial effects of a number of these CAM methods, there is lack of well-designed studies in this regard.

Herbal therapy is a common used CAM method in the treatment of ADHD [9]. Proposed mechanisms of action for the applied herbs include increasing serotonin level, central stimulating, anti-depressant, and anxiolytic effects, and improving cognitive

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http://dx.doi.org/10.1016/j.ctcp.2015.04.001
1744-3881/

performance [10]. However, limited controlled trials are conducted on the efficacy of herbal medicines in the treatment of ADHD. Although a number of herbs are reported to be beneficial, clear conclusion could not be made due to limited number of studies and methodological inadequacies [11].

Ginkgo biloba (Ginkgoaceae; Maidenhair tree) is a native plant of China which has been used for centuries in Traditional Chinese Medicine. Seeds and leaves of the plant are used for therapeutic purposes. The known and main active ingredients of the plant are flavone glycosides and terpene lactones [12]. Clinical studies have evaluated the efficacy of *G. biloba* extracts for a variety of disorders such as anxiety and depression [13], Alzheimer's disease and dementias [14], memory impairment [15], and cerebral insufficiency [16]. Animal studies have shown that *G. biloba* increases central dopaminergic activity [17] which is implicated in the pathophysiology of ADHD [18]. Considering its effects on cognitive functions as well as safety and tolerability, *G. biloba* is an attractive herbal medicine to be investigated in the treatment of ADHD.

A number of open-label trials have reported beneficial effects of *G. biloba* for the treatment of ADHD in children [19–21]. In contrast, the randomized controlled trial conducted by Salehi et al. [22] found no efficacy for *G. biloba* as a monotherapy when compared with methylphenidate. However, it is not clear if *G. biloba* is effective as a complementary method in treatment of ADHD. Therefore, we aimed to evaluate the efficacy of *G. biloba* as a complementary therapy to methylphenidate in treatment of ADHD in children and adolescents. We hypothesized that combined treatment of *G. biloba* and methylphenidate is superior to methylphenidate alone in reducing symptoms of ADHD.

2. Materials and methods

2.1. Participants and study setting

This randomized, double-blinded, placebo-controlled, clinical trial was conducted on children and adolescents with ADHD referring to the Department of Child and Adolescent Psychiatry at the Noor University Hospital in Isfahan city (Iran) between September and December 2014. Inclusion criteria were a) age between 6 and 12 years, b) diagnosis of ADHD by a child and adolescent psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [23], and c) the Children's Global Assessment Scale (CGAS) score of <80 indicating decreased general function [24]. Exclusion criteria were any evidence of mental retardation (IQ $\leq$ 70), type I bipolar disorder, psychosis, pervasive developmental disorders, organic brain disease, seizure, or cardiovascular disease. The study protocol was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from parents. The study was registered at the Iranian Registry of Clinical trials (http://www.irct.ir, registration number: IRCT2014111519958N1).

2.2. Interventions

The herbal medicine used in this study was an extract of the *G. biloba* leaves standardized by flavonoid glycoside 24% and terpene lactone 6%. The solvents used in the extract are ethanol and water and the herbal-to-extract ratio is 4:1 (Ginko T.D.^{TM}, Tolid-Daru Co., Tehran, Iran). After a two-week psychiatric drug free baseline period, participants were randomized into the *G. biloba* and placebo groups. All children were treated by methylphenidate (Ritalin®, NOVARTIS, Switzerland) with a total dose of 20 mg/day (10 mg/b.i.d) for those with body weight of <30 kg, and 30 mg/day (10 mg/t d s) for those >30 kg. Dosage was increased gradually by 10 mg/week up to the assigned total dose. Children in the *G. biloba* group received enteric coated tablets of *G. biloba* with a total dose of 80 mg/day (40 mg/b.i.d) for those with body weight of <30 kg, and 120 mg/day (40 mg/t d s) for those >30 kg. Dosage was gradually increased by 40 mg/week up to the assigned total dose. This dosage regimen was determined according to previous studies [22]. Children in the placebo group received placebo tablets (School of Pharmacy, IUMS, Isfahan, Iran) which were filled with starch and lactose and identically sized and colored to match the *G. biloba* tablets. Participants consumed medicines for a total of 6 consecutive weeks and continued treatment with methylphenidate thereafter.

The study was designed as to be a randomized and double-blinded trial with two parallel arms. Randomization was done using the random allocation software producing a table with two alphabets which were randomly distributed among consecutive numbers [25]. Patients were consecutively entered into the study and were assigned an order number and received the intervention based on the allocation sequence. The randomization and allocation process was done by a psychologist who was not involved in participants' recruitment, treatment, or follow-up. The assignments were kept in sealed and opaque envelopes until the point of data analysis. Also, the outcome assessor was not aware about the study arms.

2.3. Measurements

All participants were visited and interviewed at baseline by a Child and Adolescent Psychiatrist (FSh). Physical examination was done and a standard 12-lead electrocardiogram was obtained to evaluate any evidence of cardiovascular disease. Parents were interviewed by a general psychiatrist (MR) to gather data on demographic characteristics, ADHD symptoms duration and severity, past medical and drug history, and global functioning of the child. Weight was measured using a single calibrated scale. Participants were visited again at 2 weeks and 6 weeks after medication to evaluate the following treatment outcomes.

2.3.1. The ADHD rating Scale-IV (ADHD-RS-IV), parent and teacher ratings

The ADHD-RS-IV is a widely applied instrument for the assessment and rating of the ADHD symptoms. It evaluates 18 symptoms of ADHD (defined by the DSM-IV-TR) and consists of two sub-scales including inattention and hyperactivity–impulsivity. Response to each item is graded from 0 (never) to 3 (always). The total score ranges from 0 to 27 for each sub-scale and from 0 to 54 for the total scale. The ADHD-RS-IV can be completed by teachers as well as by clinicians interviewing with the parents [26,27]. The validity and reliability of the ADHD-RS-IV is established and studies have indicated an appropriate responsiveness to treatments [26]. The ADHD-RS-IV was completed by parents (with interview) and teachers at baseline, and then at week 2 and week 6 after treatment.

2.3.2. Children's Global Assessment Scale

The CGAS is widely used by mental health professionals to measure general (psychosocial) functioning of children. It consists of ten categories of general functioning with scores ranging from 1–10 to 91–100; there are 10-score intervals between each category [24]. The CGAS was completed during an interview with parents at baseline and then at week 6 after treatment.

2.3.3. Side effects

Side effects were assessed by a psychiatrist at week 2 and week 6 after treatment.