A randomised controlled trial of combined EEG feedback and methylphenidate therapy for the treatment of ADHD

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Summary

PURPOSE: To evaluate the efficacy of combined methylphenidate and EEG feedback treatment for children with ADHD.

METHODS: Forty patients with ADHD were randomly assigned to the combination group (methylphenidate therapy and EEG feedback training) or control group (methylphenidate therapy and non-feedback attention training) in a 1:1 ratio using the double-blind method. These patients, who met the DSM-IV diagnostic criteria and were aged between 7 and 16 years, had obtained optimal therapeutic effects by titrating the methylphenidate dose prior to the trial. The patients were assessed using multiple parameters at baseline, after 20 treatment sessions, after 40 treatment sessions, and in 6-month follow-up studies.

RESULTS: Compared to the control group, patients in the combination group had reduced ADHD symptoms and improved in related behavioural and brain functions.

CONCLUSION: The combination of EEG feedback and methylphenidate treatment is more effective than methylphenidate alone. The combined therapy is especially suitable for children and adolescents with ADHD who insufficiently respond to single drug treatment or experience drug side effects.

Keywords: ADHD; EEG-feedback; methylphenidate

Introduction

Electroencephalography (EEG) feedback is based on the principle of operant conditioning and achieves its therapeutic purposes by selective training to reinforce brain waves of a certain frequency [1]. A number of studies have found that strengthening sensorimotor rhythm (SMR) wave while inhibiting theta wave by EEG feedback is effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [2–5]. EEG feedback can improve ADHD core symptoms [6–7] and intelligence quotient (IQ) [8–11], which results in long-term steady improvement on emotional, behavioural, and academic performance, as well as improved cognition and performance in daily activities. The effectiveness rate is as high as 60–70%. Our group previously compared the efficacy of EEG feedback and methylphenidate [12], and demonstrated that both treatments are comparably effective on their own strengths. In the present study, we performed a rigorous double blind, randomised controlled trial to assess the efficacy of the combined therapy in the treatment of ADHD.

Subjects and methods

Subjects

A total of 64 paediatric patients were initially included in the trial. Among them, 54 were male (84.4%) and 10 were female (15.6%). The ages of the patients ranged from 7 to 16 years with an average of 10.6 ± 2.8. These patients were diagnosed with ADHD by paediatric psychiatrists at the Peking University Sixth Hospital clinic between September 2003 and June 2006. The diagnosis was in accordance with the diagnostic criteria for ADHD as defined in the U.S. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [13]. The patients' clinical symptoms were evaluated using the paediatric Clinical Diagnostic Interview Scale (CDIS) [14]. These patients were randomly divided into two groups after informed consent was obtained from their parents. Thirty-two patients were assigned to the combination group (methylphenidate therapy and EEG feedback training) and the remaining 32 patients were assigned to the control group (methylphenidate therapy and non-feedback attention training). All patients completed 40 sessions of EEG feedback or non-feedback attention training, as well as assessments prior to the treatment and after the treatment. One patient in the combination group and three patients in the control group dropped out during the follow-up period. Patients were excluded from the study if they met one of the following conditions: (1) younger than 7 years old, (2) afflicted by severe mental illness, (3) showed predominantly fast β waves upon EEG examination, or (4) IQ <80.

The two groups of patients were not statistically different in terms of baseline age, gender, ADHD subtypes, EEG types, core symptoms, behavioural problems, social function, brain function, drug side effects, general body condition, laboratory tests, and methylphenidate dosage (P >0.05, table 1).

Methods

Informed consent has been received from all participants and the ethics of current study was approved as part of Peking University Health Science Centre 2003-2005 2.1.1 evidence-based medicine research project.

Randomised grouping and blind experimental design
Before receiving EEG treatment or non-feedback attention training, patients had been treated with methylphenidate and the optimal therapeutic effects were obtained by titrating the dose of methylphenidate (i.e., further increasing the amount of methylphenidate no longer increased the efficacy or caused side effects). Patients were assigned to A (combination) and B (control) groups in a 1:1 ratio using a block randomisation method. Opaque envelopes were used for randomisation. The two envelopes were labeled "A" and "B", respectively, and the randomisation programme was designed by the Epidemiology Centre of Peking University Third Hospital. Random numbers were generated by computer software and sealed in the two envelopes. Patients (as well as their families) and efficacy evaluators were blindly selected.

EEG feedback and non-feedback attention training
All training was performed on an Autogenic A620 EEG feedback therapeutic apparatus (Rayfield Technology Inc., USA). For EEG feedback training, the 4-8 Hz θ wave was suppressed while 12-15 Hz SMR was strengthened. For non-feedback attention training, the threshold was set to non-feedback status. Instructions and game sequences were unified. Patients received the training 2 to 5 times per week and each training session lasted 25 to 35 minutes.

Methylphenidate dose adjustment
The starting dose was 5-10 mg once a day. The dose could be increased by 5 mg per week until the optimal dose (best therapeutic effect with the fewest side effects) was achieved. The maximum dose taken per day was not more than 60 mg. The two groups had been maintained on the optimal methylphenidate doses by dosage titration and received EEG feedback or non-feedback attention training in the subsequent five months, during which the dosage could be further adjusted to maintain maximum efficacy. At the end of the training, the minimum effective dose was used for maintenance therapy.

Assessment methods

Core symptoms and related behavioural problems
ADHD symptoms were assessed using the DSM-IV parent-teacher questionnaire for ADHD [15]. The related behavioural problems were assessed with Conners' Parent-Teacher Questionnaire [16, 17], Rutter Children's Behaviour Questionnaire [18], and Achenbach Child Behaviour Checklist [19].

Social function
Social function was assessed using the peer interactions assessment scale [20], school report card, and global assessment of functioning (GAF) scale [13].

Brain function
Brain function was assessed using the encephalofluctuograph technology (ET). EEG was performed on an HY9212 ET apparatus (Huayang Technology Inc., China) [21, 22].

Drug dosage and side effects
Methylphenidate dosage was recorded and the side effects were evaluated using the side effect scale of stimulant medication [23].

Statistical analyses
Data were processed and analysed using SPSS11.5 software. Qualitative data were compared using independent samples t tests and χ^2 tests and are expressed as the mean ± standard deviation (X ± s). Non-normal distributed data were analysed using the independent samples rank sum test. Paired samples were analysed using the Wilcoxon signed-rank test.

Results

Assessment of core symptoms and behavioural problems
In the follow-up sessions, the combination group showed significant improvement compared to the control group in attention deficit scores, hyperactivity/impulsivity scores, and total score in the ADHD parent-teacher questionnaire, as well as improved hyperactivity scores in Conners'

Table 1: General patient characteristics of the two groups of patients at baseline.

	Comb. (n = 32)	Control (n = 32)	Z/χ^2	p
Age range (years old)	7–17	7–16		
Average age ($\overline{x} \pm s$) $^\triangledown$	10.8 ± 2.6	10.4 ± 2.9	0.586	0.560
Male to female ratio	4.3:1	7:1		
Male (%)*	26 (81.3)	28 (87.5)	0.470	0.220
Less than ten years old	14	15		
ADHD subtypes*			0.390	
ADHD-HI	2	1		
ADHD-I	21	21		
ADHD-C	9	10		
Abnormal EEG (%)*	7 (21.2)	6 (18.8)	0.10	0.230

Note: $^\triangledown$non-normal data distribution analysed with independent samples rank sum test, *χ^2 test. Comb., the combination group.

Parent-Teacher Questionnaire compared to the control group (p <0.05, table 2).

Social function assessments

In the peer interactions assessment scale, the combination group had significantly lower scores than the control group in follow-up studies (p <0.001, table 3).

In the GAF scale, the combination group performed significantly better than the control group after 40 sessions of treatment as well as in follow-up sessions (p <0.001, table 3).

Brain function assessment

For the average dominant probability of α wave components, the dominant probability of 8 Hz wave decreased significantly in patients of the combination group, from 24.2% ± 11.9% (baseline) to 21.8% ± 10.4% (after 40 sessions, p <0.05) and 20.4% ± 12.6% (in follow-up sessions, p <0.01), respectively.

For major and auxiliary frequencies of α-wave, in follow-up sessions, the major frequency of α-wave of the patients in the combined group increased from 9.0 ± 0.3 Hz to 9.6 ± 1.2 Hz, which was higher than the control group (p <0.01).

Assessment of drug dosage and side effects

Some patients in the combination group lowered the dose of methylphenidate from 19.6 ± 9.8 mg prior to treatment to 15.2 ± 8.2 mg in follow-up sessions, whereas the dose for the control group was 19.2 ± 7.3 mg in follow-up. The difference between the two groups was statistically significant (p <0.05, table 4).

In this study, the most common side effects were decreased appetite (53.1%), irritability (56.3%), followed by nail bit-ing (37.5%), dizziness (34.4%), and fatigue (32.8%). The extent of reaction positively correlated with the methylphenidate dose. The incidence rate of side effects in the combination group was 53% after 40 sessions and 42% in follow-up versus 67% and 61%, respectively, in the control group.

Discussion

Stimulants are currently the first choice of medication to treat ADHD. However, because stimulants can affect appetite and sleep, and potentially affect development as well, the treatment generally results in poor patient adherence [24]. Therefore, EEG feedback is considered a very promising alternative and auxiliary therapy [25–27]. Many controlled studies have shown that a combination of medication and EEG feedback can improve ADHD symptoms with similar effectiveness [28–32]. Based on the results from previous studies [12, 33], we confirmed the effectiveness of combining EEG feedback and methylphenidate treatment to improve ADHD symptoms in a strict double-blind, randomised controlled trial.

This study has also determined that the combined therapy is superior in terms of improvement on core symptoms, related behavioural problems, and brain function. The advantages persisted even after treatment ceased. Some patients reduced the dose of methylphenidate and the side effects were ameliorated following the combined therapy. In light of China's cultural background, long-term clinical use of stimulant medication in children has been restricted due to parents' concerns, and the combination therapy would more practical in this situation.

Table 2: DSM-IV ADHD and Conners' questionnaire results at various time points.

	Baseline		After 40 sessions of treatment		Follow-up	
	Comb.	Control	Comb.	Control	Comb.	Control
Attention deficit score (parent)	23.5 ± 4.2	22.9 ± 6.1	22.6 ± 3.7	23.9 ± 6.0	21.6 ± 4.5	25.7 ± 4.7***
Attention deficit score (teacher)	24.3 ± 4.7	22.5 ± 5.8	21.2 ± 4.6	23.6 ± 6.3	19.9 ± 3.9	25.4 ± 3.6***
Hyperactivity and impulsivity (parent)	18.5 ± 5.0	18.1 ± 6.0	16.6 ± 4.7	17.3 ± 6.3	16.0 ± 4.0	19.2 ± 6.1*
Hyperactivity and impulsivity (teacher)	20.3 ± 6.6	18.7 ± 6.2	16.8 ± 5.6	18.4 ± 6.5	16.1 ± 6.5	19.8 ± 6.1*
DSM-IV total score (parent)	42.3 ± 7.5	41.0 ± 9.9	38.6 ± 7.8	41.2 ± 9.9	37.9 ± 6.5	44.9 ± 8.5 ***
DSM-IV total score (teacher)	44.3 ± 9.5	41.6 ± 10.6	37.9 ± 8.7	41.8 ± 11.1	35.0 ± 7.4	43.7 ± 9.8***
Conners' Hyperactivity score (parent)	5.3 ± 3.1	4.6 ± 3.1	3.3 ± 2.5	4.5 ± 2.9	3.0 ± 2.4	4.4 ± 3.0*
Conners' Hyperactivity score (teacher)	10.9 ± 5.6	8.7 ± 5.4	8.0 ± 5.4	9.3 ± 5.0	6.4 ± 3.8	9.6 ± 4.5**

Note: normal distribution data analysed with independent samples t-test.
* p <0.05, **p<0.01, ***p<0.001

Table 3: Peer interactions scale and GAF results at various time points.

	Baseline		After 40 sessions of treatment		Follow-up	
	Comb.	Control	Comb.	Control	Comb.	Control
Peer interactions scale	10.6 ± 5.8	9.3 ± 5.4	7.5▽	9.5	6.3 ± 3.9	10.9 ± 5.8***
GAF△	63.0 ± 3.4	63.3 ± 6.2	66.6 ± 4.0	60.5 ± 5.5***	69.0 ± 6.8	59.6 ± 6.3***

Note: *p<0.05, **p<0.01, ***p<0.001; △normal distribution data analysed with independent samples t-test. ▽non-normal data distribution analysed with independent samples rank sum test.

Table 4: Comparison of median drug dosages (mg).

Treatment period	Comb.	Control	Z	p
Baseline	19.6 ± 9.8	18.6 ± 7.3	0.472	0.639
After 40 sessions of treatment	15.2 ± 8.2	19.2 ± 7.3	–2.054	0.044
Follow-up	12.7 ± 9.2	20.0 ± 6.8	–4.426	0.000

Note: M is the median. Drug doses are non-normal distributed data and were analysed with an independent samples rank sum test.

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