Original article

Using transcranial magnetic therapy in combination with electrostimulation for correcting neuroendocrine-immune disorders in obese boys

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Received 31 March 2021, Revised 17 August 2021, Accepted 21 December 2021

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Abstract: Objective — To justify the use of low-intensity transcranial magnetic therapy (TCMT) in combination with electrostimulation (TES) for the correction of neuroendocrine-immune disorders.

Material and Methods — Fifty adolescent boys with exogenous constitutional obesity 13-15 years of age were examined. The control group consisted of 30 boys aged 13-15 years without obesity and concomitant pathology. The examination included an assessment of complaints, anamnesis of the disease, life history, objective data, hormonal status, neurotransmitters and cytokines. By random sampling, the group of obese children was divided into two subgroups: subgroup 1a (n=24), who received TCMT in combination with TES, and subgroup 1b — comparison group (n=22), who received placebo therapy with disconnected electrodes. Both groups of children received identical recommendations regarding the nutrition. The effectiveness of the therapy was evaluated after 3 months. The treatment course comprised 10 procedures. Statistical processing of the obtained data was carried out using the statistical software package Statistica 8.

Results — An increase in the levels of testosterone and β — endorphin as well as a decrease in estradiol and kisspeptin, which was accompanied by a decrease in body weight was observed in children of subgroup 1a (n=24) under the influence of TCMT in combination with TES. In subgroup 1b (n=22) receiving placebo therapy with disconnected electrodes, there was also a decrease in body weight, but at a much lower level.

Conclusion — The use of TCMT in combination with TES led to the normalization of neuroendocrine-immune disorders and contributed to weight loss.

Keywords: obesity, neuroendocrine-immune disorders, transcranial magnetic therapy, transcranial electrostimulation.

Cite as Bolotova NV, Filina NYu, Kurdiyan MS, Kompaniets OV, Garifulina LM, Meshcheryakova IYu. Using transcranial magnetic therapy in combination with electrostimulation for correcting neuroendocrine-immune disorders in obese boys. Russian Open Medical Journal 2022; 11: e0111.

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Introduction

The increasing prevalence of obesity is one of the most pressing problems of modern medicine and society. Obesity, which occurs in preschool ages as simple exogenous constitutional obesity, becomes pathological in puberty due to the appearance and aggravation of neuroendocrine and metabolic disorders [1-5].

Accumulation of body fat mass is usually associated with changes in eating behavior, resulting in excess calorie intake [6, 7].

Changes in eating behavior could be attributed to complex integrative mechanisms of interaction involving various factors such as humoral factors, immune factors and neuropeptides that have orexigenic or anorexigenic effects [8-10]. The neurotransmitter imbalance accompanying obesity contributes to the activation of orexigenic effect and a decrease in the activity of the anorexigenic neurotransmitter systems of the hypothalamus, which leads to the development of hyperleptinemia, hypercholesterolemia, dyslipidemia, arterial hypertension, impaired glucose tolerance, diabetes mellitus, sleep apnea syndrome, etc. [11].

One of the main phases of obesity therapy is behavioral and it is aimed at changing the lifestyle by first of all, changing the nature of nutrition [12, 13]. To this end, educational programs focused on rational nutrition are created to facilitate body weight reduction. However, in most cases, such measures are not enough to reduce body weight and keep it at an optimal level [14]. Considering the interesting role, the hypothalamic-pituitary system plays in regulating hunger and thirst, a methodical use of a hardware to influence these brain structures at a range of potentials could be promising and could lead to a reduction in appetite and in normalizing eating behavior. These methods include transcranial magnetic therapy (TCMT) with the effect of a traveling magnetic field and transcranial electrostimulation (TES). The rationale for using these methods originates from the fact that they reveal the peculiarities associated with energy exchange, its destructive mechanisms, as well as knowledge about the features of traveling magnetic field and electrostimulation actions. Traveling magnetic field promotes the activation of Na, K-ATPase of cell membranes, thus, improving the processes of synaptic signal transmission, therefore possessing hemodynamic and anti-inflammatory effect. The advantages of magnetic therapy include the unhindered penetration of a magnetic field into tissues and the absence of a heating effect at varying frequencies [15, 16]. TES helps normalize the condition of neurotransmitter systems directly involved in regulating eating behavior mechanisms. It has been shown that TES selectively stimulates the serotonergic, dopaminergic and opioid systems, contributing to an increase in the level of dopamine, serotonin, and beta-endorphin in the blood [17]. The combined simultaneous use of TES and magnetic therapy would most likely be more effective due to the synergy of their interaction.

Objective: To justify the use of low-intensity TCMT in combination with TES for the correction of neuroendocrine-immune disorders.

Material and Methods

This study was conducted at the Department of Propaedeutics of Children's Diseases, Children's Endocrinology and Diabetology, Saratov State Medical University under the University Clinical Hospital No. 1 named after S.R. Mirotvortseva.

Fifty obese adolescent boys 13-15 years old were examined. All children had obesity of grades 2-3. The distribution of subcutaneous fat was uneven, with a predominant accumulation in the abdomen, and some children were found to have false gynecomastia. The children had trophic skin disorders: folliculitis, single or multiple stretch marks and hyper pigmentation of natural skin folds. Average Body Mass Index (BMI) was 31.6 (30.1, 35.8) and Standard Deviation Score (SDS BMI) 2.9 (2.7, 3.3) (data presented as median with lower and upper quartiles). The criteria for participating in the study were: the age of the patient should be between 13-15 years and the existence of varying severity of obesity. The criteria for exemption were the absence of obesity, syndromic forms of obesity and the presence of obesity of varying severity.

The control group consisted of 30 boys of the same age without obesity and somatic pathology.

All children involved in this research (from 15 years of age) or their parents signed a written informed consent to participate in the study.

The study was conducted in several stages. The first stage involved the examination of complaints, anamnesis of the disease, life history, assessment of objective data, laboratory and instrumental methods of research. The parameters of height, body weight and BMI were analyzed by the method of SDS. The criterion for the diagnosis of obesity was an excess of SDS BMI of more than 2.0. The values of SDS BMI 2.0-2.5 were regarded as grade 1 obesity, SDS BMI 2.6-3.0 − grade 2 obesity, SDS BMI 3.1-3.9 − grade 3 obesity and SDS BMI≥4.0 − morbid obesity. Sexual development was assessed using the Tanner scale [18].

The investigation included a study of complaints, medical and life history, assessment of objective data, laboratory and instrumental research methods. The indicators of height, body weight, BMI were analyzed using the method of SDS and sexual development according to Tanner scale.

The state of fat and carbohydrate metabolism was assessed according to data from biochemical blood test (cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL), blood glucose, immune reactive insulin and C-

peptide) using the IMMULITE 2000 XPi and ARCHTESTo2000SR kits (Siemens, Abbot, Germany). Concentration of leptin was determined using Leptin ELISADBC, Version 10 (Germany).

Assessing the hormonal profile included determining the level of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin and estradiol using the IMMULITE 2000 XPi and ARCHTESTo2000SR kits (Siemens, Abbot, Germany).

The levels of neuropeptide kisspeptin (Kisspeptin 1 (Kiss1, Cloud-CloneCorp, China)), nerve growth factor (RayBioHumanbeta-NGFELISAKit) and β -endorphin (EIAKitforbeta-EndorphinPLI) were studied. In order to assess the cytokine status, the levels of interleukin-1 (IL-1) and interleukin-10 (IL-10) were determined using IL-1 beta ELISA Best, IL-10 ELISA Best test systems Vector-Best, Russia).

The second stage of our study involved random sampling survey aimed at correcting neuro-endocrine-immune disorders. The group of obese children was divided into two subgroups: 1a (n=24), which received transcranial magnetic therapy in combination with electrostimulation, and subgroup 1b comparison group (n=22), which received placebo therapy with disconnected electrodes. All children involved in this study received equal nutritional recommendations. Bitemporal TCMT in combination with TES was carried out using the device AMO-ATOS-E apparatus (TRIMA LLC, Saratov, registration certificate of the Ministry of Health of the Russian Federation No. FSR 209-04 781), including the attachment Ogolovye and a block of TES therapy with fronto-mastoid electrodes on the clamps of the Ogolovye terminals. The combination of a traveling magnetic field and transcranial electrostimulation was achieved using electrodes attached to the helmet straps. The scanning frequency (modulation) of the magnetic field selected was within the range of 1-12 Hz, with an induction of 45 mT on the surface of the emitter and the movement of the field from the temporal lobe to the occipital lobe synchronously to both hemispheres of the brain for 7-12 minutes (according to the bitemporal technique). TES was carried out with an output voltage of 20±10%, an average current of 15 mA, and a filling frequency of the output voltage pulse packs of 2.5±10% kHz. The course of treatment included 10 procedures.

The third stage was to evaluate the effectiveness of correcting neuro-humoral disorders after 3 months by evaluating the dynamics of previously studied indicators.

Statistical processing of the obtained data was carried out using the statistical software package Statistica 8. Data obtained from the study were presented for nonparametric tests. To compare the quantitative characteristics of the two groups, the Mann-Whitney criteria was calculated. The significance level was p<0.05. The quantitative characteristics presented as median with lower and upper quartiles – Me (LQ, UQ).

Results

Upon admission to the hospital, 70% of the boys complained of hunger and headaches and 50% of sweating, shortness of breath on exertion and constant hunger. From the anamnesis, it was observed that in 10 of the adolescents, obesity had begun developing at an early age of 2-4 years, in 25 of the adolescents at 7-8 years, and in 15 of the adolescents at 11-12 years. 80% of the children had a hereditary burden — i.e., their parents or close relatives have/had obesity, diabetes mellitus II or hypertension. All children had grade 2-3 obesity. The average BMI was 31.6 (30.1,

35.8) and SDS BMI 2.9 (2.7, 3.3). The distribution of subcutaneous fat was uneven, with most of it predominant in the abdomen. False gynecomastia was observed in half of the cases (50%). The median SDS growth was 1.9 (0.8, 2.6). The children had hyperpigmentation of natural skin folds, folliculitis and hyperhidrosis of the palms and feet. Trophic disorders in the form of single or multiple stretching bands from pearl-pink, white to red-purple color were observed in 95% of the children. Sexual development in 30 boys was at G2 and stages sensu Tanner, and in 20 boys, it was at G1 stage.

The condition of fat and carbohydrate metabolism were studied in all children, the data are presented in *Table* 1.

Indicators of carbohydrate metabolism were characterized by increased levels of basal and stimulated insulin and also basal and stimulated C-peptide. Disorders of lipid metabolism were characterized by the presence of dyslipidemia, hypercholesterolemia and hypertriglyceridemia. During an oral glucose tolerance test, 3 patients were diagnosed with type II diabetes mellitus, and no changes in the glycemic profile were detected in the rest.

Neuroendocrine-immune disorders were evaluated, the data are presented in Table 2. As can be seen from Table 2, there was a significant increase in the levels of kisspeptin, leptin, estradiol and interleukin 10 (IL-10) in the obese children and also a decrease in the levels of β -endorphin and total testosterone, which indicated the presence of a neuroendocrine-immune imbalance in this group of children. The tendency for an increment in the nerve growth factor levels and interleukin 1 (IL-1) was identified in this group of obese children, but the values, compared with the control group, were not statistically significant.

According to the study design, the correction of neuroendocrine-immune disorders was carried out in two previously described subgroups: subgroup 1a (n=24), which received therapy with combined TCMT and TES and subgroup 1b – comparison group (n=22), which received placebo therapy with disconnected electrodes. In parallel, both subgroups received equal nutritional recommendations. After 3 months, the metabolic neuroendocrine-immune parameters were evaluated.

Changes in metabolic parameters in subgroup 1a involved a 3-fold decrease in basal insulin levels, 2-fold decrease in total cholesterol and a 1.5-fold decrease in LDL and triglycerides compared to the initial values. In subgroup 1b, changes in the researched indicators were insignificant.

Under the influence of TCMT in combination with TES, children in group 1 showed an improvement in hormonal parameters and neuropeptides: an increase in testosterone and beta-endorphin, a decrease in estradiol and kisspeptin, which was accompanied by a decrease in body weight. Levels of leptin, nerve growth factor, IL-1 and IL-10 showed a tendency to decrease, but the data were not statistically significant (*Table* 3).

Thus, the correction of neuroendocrine-immune disorders by using TCMT in combination with TES led to a significant improvement in neuroendocrine-immune parameters, accompanied by a decrease in body weight in subgroup 1a. In subgroup 1b, which received placebo therapy with disconnected electrodes, there was also a decrease in body weight, but to a much lesser extent.

Table 1. The condition of fat and carbohydrate metabolism in children with exogenous constitutional obesity

Studied indicators, unit	Group of children with exogenous constitutional obesity n=50	Control group n=30	Р
Cholesterol, mmol/L	5.3 (4.6, 5.5)	4.0 (3.5, 4.1)	<0.001
Triglycerides, mmol/L	1.8 (1.6, 2.2)	1.2 (1.0, 1.4)	0.041
LDL, mmol/L	2.6 (2.1, 3.0)	2.0 (1.6, 2.3)	0.032
HDL, mmol/L	1.2 (0.9, 1.4)	1.1 (1.0, 1.2)	0.211
Basal IRI, mcm/mL	31.2 (25.0, 35.3)	16.7 (10.0, 24.0)	0.002
Stimulated IRI, mcm/mL	137.5 (110.8, 157.3)	27.8 (17.7, 46.3)	<0.001
C-basal peptide, mME / mL	2.9 (1.8, 4.5)	2.0 (1.3, 3.0)	0.040
Stimulated C-peptide, mME/mL	16.4 (14.6, 20.8)	8.7 (5.8, 12.6)	< 0.001
Blood glucose, mmol/L	4.9 (4.2, 5.2)	5.5 (4.8, 5.8)	0.015

In Tables 1, 2 and 3, data presented as median with lower and upper quartiles – Me (LQ, UQ).

Table 2. Neurohormonal-immune indicators in the studied groups

Studied indicators	Group of boys with	Control group	Р
	obesity n = 50	n = 50	P
FSH, IU/L	3.8 (3.1, 5.5)	2.8 (2.5, 3.9)	0.457
LH, IU/L	2.4 (1.2, 2.9)	3.1 (2.3, 3.3)	0.318
Testosterone, nmol/L	6.0 (2.6, 8.5)	16.6 (12.5, 17.4)	<0.001
Prolactin, nmol/mL	157.5 (116.3, 133.5)	156 (133.5, 189.0)	0.439
Estradiol, pg/mL	31.4 (28, 64)	14.5 (10.0, 24.1)	0.046
TSH, mcIU/L	1.9 (1.5, 2.5)	2.4 (1.3, 3.3)	0.213
Kisspeptin, pg/mL	144.3 (121.4, 154.5)	110.2 (94.6, 123.7)	0.001
Leptin, ng/mL	9.9 (8.4, 14.3)	8.1 (6.2, 9.9)	0.023
β-endorphin, ng/mL	5.6 (4.1, 6.8)	10.9 (10.5, 11.7)	<0.001
Nerve growth factor, pg/mL	100.4 (67.5, 111.3)	86.3 (67.5, 95.4)	0.266
IL-1, pg/mL	7.8 (4.3, 8.5)	4.9 (3.0, 11.5)	0.290
IL-10, pg/mL	19.5 (17.0, 25.9)	16.6 (11.5, 23.5)	0.025

Table 3. Dynamics of neurohormonal-immune parameters and body weight as a result of the use of combined TCMT and TES.

Indicator	Subgroup 1a initial n=24	Subgroup 1a after treatment n=24	Subgroup 1b Initial n=22	Subgroup 1b after treatment n=22	Ρ
FSH, IU/L	3.9 (3.0, 5.3)	2.9 (2.5, 3.3)	4.0 (3.7, 4.9)	3.2 (2.8, 4.0)	0.353
LH, IU/L	2.3 (1.2, 3.1)	1.9 (1.2, 2.2)	2.4 (1.6, 2.8)	1.8 (1.4, 2.3)	0.304
Testosterone, nmol/L	5.7 (2.8, 7.5)	10.1 (6.8, 11.5)	5.5 (2.6, 7.1)	6.5 (4.1, 9.3)	0.0468
Prolactin, nmol/mL	129.3 (117.5, 159.8)	120 (93.8, 149.6)	140.2 (119.5, 176.8)	138.0 (107.5, 183.2)	0.069
Estradiol, pg/mL	33.0 (27.6, 42.8)	21.0 (20.0, 25.4)	30.5 (28.7, 34.8)	26 (21.7, 32.2)	0.022
TSH, mcIU/L	2.4 (1.8, 2.6)	2.1 (1.5, 2.7)	1.8 (1.2, 2.5)	2.3 (1.5, 3.2)	0.436
Kisspeptin, pg/mL	142.4 (133.5, 146.2)	123 (114.1, 130.1)	149.5 (135.3, 153.2)	133.4 (120.2, 140.7)	0.035
Leptin, ng/mL	10.5 (8.7, 13.7)	8.4 (6.4, 12.3)	11.2 (10.4, 13.8)	10.8 (8.4, 12.8)	0.440
β-endorphin, ng/mL	4.7 (4.1, 6.9)	7.5 (6.0, 8.7)	5.2 (4.0, 7.0)	5.7 (43, 6.5)	0.046
Nerve growth factor, pg/mL	105.8 (69.1, 124.3)	90.4 (63.8, 101.3)	100.9 (67.7, 109.5)	97.7 (68.0, 106.4)	0.349
IL-1, pg/mL	7.3 (4.1, 9.1)	6.3 (5.0, 8.2)	8.3 (4.6, 9.2)	7.2 (5.6, 8.1)	0.165
IL-10, pg/mL	19.6 (16.4,25.4)	17.2 (15.7,21.7)	18.7 (17.0, 25.4)	18.3 (16.3, 24.0)	0.232
BMI, kg/m ²	31.1 (17.4, 36.3)	27.9 (24.5, 30.0)	31.4 (29.2, 36.7)	29.7 (27.9, 33.5)	0.049
SDS BMI	2.7 (2.4, 3.3)	2.3 (2.1, 2.8)	2.9 (2.2, 3.4)	2.8 (2.2, 3.2)	0.047

Discussion

The problem of obesity has become global due to a constant growth in the number of overweight people especially overweight children [19]. The nature of eating disorders, which are the basis for the accumulation of fat mass, is largely due to a neurotransmitter imbalance in the orexigenic and anorexigenic systems. Although there is practically no radical treatment for obesity, one of the promising ways of treating obesity and modulating eating behavior may be through non-invasive transcranial methods of treatment. The technologies of non-invasive brain stimulation include the following techniques: transcranial magnetic therapy (TCMT) and transcranial electrostimulation (TES).

TCMT is one of the new modern effective neuro-modulation methods designed for non-invasive magnetic pulse exposure to various regions of the cerebral cortex [20]. A large number of published research studies conducted abroad have been devoted to the use of rhythmic TCMT [21-23]. This method has been used in the treatment of many neurological diseases [24-26]. In Russia, TCMT was first used in the treatment of two (2) obese patients [27], but the method has not been practically used for treating children.

In our study, we used a combination of TCMT and TES. This combination was not chosen by chance: according to V.P. Lebedev, TES therapy was based on endorphin mechanisms, such as: analgesia, normalization of hormonal status and activation of immune mechanisms, as well as reduction in a tumor growth [28]. TES has been shown to increase the production of β -endorphin both in the CSF and in the blood [29]. The systemic nature of TES therapy is seen in the relief of various syndromes associated with a deficiency in the production of endorphins within a single medical specialty [29]. In a research by Kornilov A.A. et al., devoted to the evaluation of the effectiveness of TES for the correction of psychophysiological state of operators, it was shown that, TES had a persistent and significant positive effect on endorphin structures of the brain and on the physiological and emotional indicators of the functional structure of the operators' organism, which was able to last for up to 3 months [30]. After conducting TES procedures, the working capacity, general well-being, mood, situational and personal anxiety of the operators improved [30]. In our study, a mediator imbalance was identified in the obese boys: a decrease in the level of beta-endorphin, testosterone, and an increase in the level of estradiol, kisspeptin, leptin and IL-10. Therefore, the use of TES therapy was proven.

The pulsed magnetic field with transcranial application has an active modulating effect on the local mechanisms of microcirculation and contributed to the strengthening of sanogenic reactions [31]. The values of magnetic induction allowed us providing a sufficient depth of penetration of the magnetic field when exposed to the deep-seated diencephalic structures of the brain [31].

Under the combined influence of TCMT and TES, the overall body reaction became more active, along with neurohumoral regulation systems [32]. This was the rationale for using TCMT in combination with TES.

Conclusion

The use of TCMT in combination with TES in the obese boys led to a significant increase in the level of testosterone, beta-

endorphin and a decrease in estradiol and kisspeptin, which was accompanied by a decrease in body weight. A reduction in the level of leptin, nerve growth factor, IL-1 and IL-10 was observed, but the data were not statistically significant.

Thus, the use of TCMT in combination with TES was effective in the complex therapy of obesity in the framework of weight loss programs.

Ethical approval

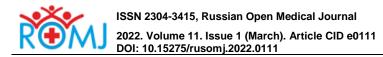
The study was approved by the Ethics Committee at SSMU for the control of research involving human subjects (Protocol No. 3 of 06 November, 2018).

Conflict of interest

The study was carried out within the framework of the Public Procurement on the topic, "Improving the Reproductive Potential of Youth Based on the Study of Neuroendocrine-Immune Relationships".

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