Effects of Human Placenta Extract Laennec on Quality of Life and Physical Performance in Patients with Chronic Fatigue Syndrome

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f patients with verified diagnosis - Chronic fatigue syndrome (CFS). ***Material and methods:*** *The study 2 patients with CFS, randomized into 2 groups: the experimental group (HPEL, 24 people) - patients d by 10 intravenous Laennec infusions, 4 ml each, 2 times/week, for 5 weeks and passive control group pers.). Before, after, and 5 weeks follow-up treatment effcacy was evaluated by severity of chronic ronic Fatigue inventory), state anxiety and depression level (STAI and STDI) and Health related Quality QoL, questionnaire SF-36v2), exercise tolerance (cardiopulmonary exercise test with gas analysis), meters.* ***Results:*** *The HPEL patients showed a signifcant reduction in index of chronic fatigue values, accompanied by signifcant decrease in situational depression, anxiety, improvements in subjective*

Chronic fatigue syndrome (CFS), despite continuing debates on etiology-pathogenesis (viral, immune, psychiatric, autonomic and endocrine dysfunctions hypotheses etc.), reappraisal of diagnostic criteria for such multisystem pathology, acquires recently growing medical and sw f Й ! ى تھ Ά | promise in the CFS treatment have naturally occurring agents, potentiating the restoration of the body's adaptive resources, in particular - human placenta extracts (HPE).

HPEs are systematically used in clinical medicine since the frst decade of the 20th century, after discovering new technics for placenta's extracts and suspensions preparation (Gromova et al., 2014). In Japan and Korea, treatments using the human placenta began in the 1950s, for improvement of hepatic functions, menopausal disorders and immunity boosting (Kong et al., 2012; Lee et al., 2011; Ware & Sherbourne, 1992). Among experimentally and clinically-based application areas for HPE are: ergogenic, neurotrophic, angiogenic, lipotropic, antioxidant, immune-

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To our knowledge, there are 2 clinical trials reporting positive consequences of short-term application of HPE in subjects with fatigue (Kong et al., 2008; Larun et al., 2016). But in both studies fatigue was not verified as CFS, improvement of fatigue was checked by self-reports scaling adapted to Koreans, and HPE were used non-systemic – by subcutaneous abdominal injections (Kong et al., 2008) or as solutions per os every day (Kuratsune et al., 1994). We hypothesized that HPE as intravenous infusions course would cause larger improvements in CFS patients in terms of fatigue reduction, HRQoL and in objective indicators of physical performance.

Therefore, we aimed to conduct a controlled trial to evaluate the efficacy and safety of HPE Laennec intravenous infusions in treatment of patients with verified diagnosis of CFS.

METHODS

Participants and Randomisation

Patients between 28 and 62 years, who attended "RHANA" clinical centre (Moscow) were invited to participate in this randomised controlled study. All volunteers underwent a routine physical examination including information on medication, medical history, physical status survey, blood determinations (red and white blood cells, haemoglobin concentration, haematocrit, total cholesterol, LDL, triglycerides, and HDL, parameters of kidney and liver, inflammatory parameters), consulting by neurologist to exclude any other neurological or psychiatric pathology then CFS. 38 patients with verified diagnosis of CFS (G 93.3), 18 men and 20 women were selected to meet inclusion criteria in accordance to 1988-Centers for Disease Control and Prevention (CDC) CFS/ME Diagnostic criteria (Revelas & Baltarestsou, 2013), revised and added by the review (Haney et al., 2015).

After signing an informed consent form all the patients have been assigned (block randomization) to two groups in proportion 2:1: 24 persons – experimental group, subjected by HPE Laennec infusions (HPEL) and 14 patients - passive control group (CTRL), not subjected by any manipulations but being tested the same days as HPEL group.

The baseline characteristics of both groups are shown in Table 1. No statistically significant differences occurred between groups in terms of age distribution, other socio-demographic characteristics and medication. However, values of key parameter for exercise tolerance - peak oxygen consumption (VO_2 peak) were significantly higher in CTRL group.

All the participants were advised not to change medications, nutrition and physical activity during the whole study period, only single doses of emergency medication in cases of high blood pressure and pain attacks were accepted, as documented in the medical recordings of the "RHANA" clinic.

The study design was approved by the local Ethics Committee in the training centre, "RHANA" clinic and performed in accordance with the ethical standards of the Declaration of Helsinki in 1975.

HPE Laennec Infusion Program

Patients of HPEL group received 10 intravenous infusions of HPE Laennec® (Manufacturer - Japan Bio Products Co., Registering certificate No. 013851/01-08, Ministry of Health, Russian Federation) slowly, in 45-50 min (40 drops/min), 4.0 ml of HPE Laennec dissolved in 250 ml of physiological solute, twice a week over 5 weeks. Two well-trained study nurses provided all the infusions and operated the therapy: before and after each infusion they measured blood pressure (BP) and heart rate (HR), collected patients' reports on possible side effects and adverse events corresponded with or as follow-up of infusions.

Evaluation of Psychological Status and Functional Exercise Capacity

All assessments including structured questionnaire, psychological testing and evaluation of the functional exercise capacity with the cardiopulmonary exercise test (CPET) were held out at the beginning, at the end after all therapy units, and at 5 weeks follow-up. The taking of blood samples was held out in the same way. Patients of CTRL group were tested twice only: at the baseline and at 5 weeks later, corresponded to the end of Laennec treatments for HPEL group.

Body weight and height (Tanita, Tokyo, Japan) and blood pressure (Omron; Omron Healthcare, Tokyo, Japan) were taken by the nurses. Blood samples were taken in the morning after an overnight fast. Serum total and high density lipoprotein (HDL) cholesterol, triglycerides and glucose concentrations were analyzed by the certified biochemical laboratory (NPO "Efs", Moscow) using standardized analytical methods on fasting blood samples.

Table 1.
Demographic information and characteristics of the subjects

Demographic and clinical information	**HPEL(n=23)**	**CTRL(n=13)**	**P value**
Sex:Male – n (%)	10 (43.5%)	7 (53%)	ns
Age, years	45.4 (30. 61)	44 (28.62)	ns
Smoking – n (%)	4 (17.4%)	3 (23%)	ns
Height, cm	171.4 (158-190)	172.9 (156-178)	ns
Weight, kg	75 (60-102)	75 (60-102)	ns
Comorbidities and medication			
Arterial Hypertension – n (%)	5 (21.7%)	2 (15.4%)	ns
Hypotensive therapy– n (%)	5 (21.7%)	2 (15.4%)	ns
Diabetes Mellitus T2 – n (%)	1 (4.3%)	-	ns
Hypoglicaemic therapy	1 (4.3%)	-	ns
Decreased VO2 peak (<84% predicted individual values), ml/kg/min	16 (69.6%)	6 (46.2%)	0.032

A structured questionnaire was used to collect socio-demographic variables, medical history and clinical data at the beginning of the study, level of Chronic Fatigue, Health-related quality of life (HRQoL), and perceived state anxiety and depression. The questionnaire was administered by the two trained study nurses and took about 60 minutes to complete. The socio-demographic characteristics included age, sex, educational level, employment, alcohol and smoking status, perceived level of Chronic Fatigue, HRQoL, and perceived anxiety and depression measures were collected via face-to-face interview.

Psychological features of CFS were assessed with the Chronic Fatigue inventory, validated on the Russian population (Lee et al., 2012). The test consists of 36 items concerning most typical subjectively assessed symptoms and complains on fatigue; the raw scores were computed by first transforming and summarized in an integral Chronic Fatigue Index (CFI).

HRQoL was measured with the Russian version of the SF-36 Health Survey. The 36 items reflect the eight scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (Torjesen, 2015). Sometimes, the SF-36 is also described as a health status instrument (Spielberg et al., 2004). As previously described, each scale is computed by first transforming the raw scores into a range with a minimum of 0 and a maximum of 100 points, higher scores indicate better functioning. Severity of depressive and anxiety symptoms was assessed with the Russian version of State Anxiety (STAI) and depression (STDI) scales of Ch.Spielberger (Lee et al., 2012; Revelas & Baltarestsou, 2013) (Table 1).

The subjects' improvement in exercise tolerance was checked by Cardiopulmonary stress test (Fitmate MED (COSMED, Italy) and treadmill Intertrack (Shiller, Switzerland). The selected exertion protocol was Bruce, duration of each workload was 3 minutes -2,4 -4,6 -7,5 -10,0 METs. Peak oxygen uptake (VO

only one - general health in HPEL patients remained noticeably higher than at the baseline. CTRLs showed no signi f cant change in the most dimensions of HRQoL (except scales of Role physical and Social functioning) in dynamics of observation.

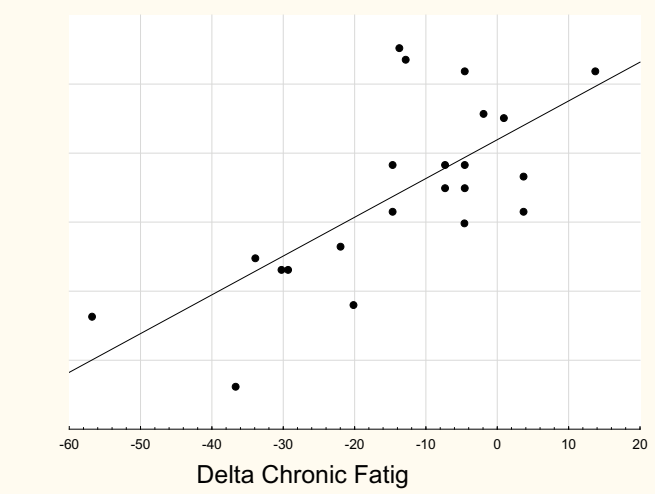
Functional Exercise Capacity

The functional exercise capacity was measured by VO_2 peak, VO_2AT, the total exercise time to exertion and other parameters of the CPET (Table 3). At the beginning, HPEL and CTRL showed no signi f cant difference. After the treatments HPEL group showed an increase in the duration of executing workloads, and in absolute and relative values of VO_2peak, which were signi f cantly high than in CTRL.

Absolute and relative oxygen consumption at the level of AT also increased noticably in HPEL (but not in CTRL) to the end of treatment and in follow-up. After all treatments, there was a statistic signi f cant difference between the groups in time to reach AT, VO_2 peak and VO_2AT (Table 3). SBP max at the maximum workload in HPEL after treatments and in follow-up decreased signi f cantly, but not in CTRL.

At the individual data dynamics at the baseline 15 HPEL patients (65%) had decreased level of aerobic capacities (VO_2

6	**% VO_2 peak**	HPEL	78.4 ± 17.4	87.2 ± 17.2*#	85.9 ± 16.9*
		CTRL	85.2 ± 14.6	77.5 ± 10.1	-
7	**VO2AT, ml/kg/min**	HPEL	17.3 ± 3.6	19.9 ± 4.3*	20.4 ± 4.9*
		CTRL	21.8 ± 2.8	19.5 ± 2.4	-
8	**% VO_2AT**	HPEL	66.4 ± 5.3	70.1 ± 5.9*#	71.6 ± 5.1*,**
		CTRL	72.8 ± 9.5	64.5 ± 9.9	-
9	**SBP max, mmHg**	HPEL	162.5 ± 17.4	145.8 ± 16.3*#	142.6 ± 9.0*
		CTRL	157.1 ± 11.8	160.5 ± 14.9	-
10	**DBP max, mmHg**	HPEL	87.2 ± 8.5	83.7 ± 5.7	92.3 ± 6.1**
		CTRL	98.1 ± 8.1	96.6 ± 8.3	-



%VO_2 peak, in contrary, increased from 6 (46%) at the baseline to 8 (62%) at the end.

We discovered a high significant negative relationship between the changes of the Chronic Fatigue Index (between baseline and at the end of treatment) and the changes of Mental Health subscale scores in HRQoL and also between the changes of CFI and the Physical Functioning subscale scores (Figure 1). We also found a significant positive relationship between the differences of the CFI and changes in State Depression score and also between the delta CFI and the State Anxiety score.

There were no significant changes in the immune, hormonal and haematological parameters in HPEL and CTRL during the study period and in follow-up, which may be due to a pronounced inter-individual variability recorded parameters and confirm the absence of specific laboratory indicators of immune response and their combinations in the diagnosis of CFS. Positive shifts were

only in cholesterol metabolism (a signi f cant reduction in total cholesterol from 5.76 ± 1.18 to 4.83 ± 1.07 Mmol/L, $p \leq 0.042$ and LDL cholesterol from 3.55 ± 1.18 to 2.93 ± 0.99 Mmol L $p \leq 0.039$), that con f rms hepatoprotective and normalizing lipid metabolism properties of Laennec (Stauber et al., 2013; Torjesen, 2015).

DISCUSSION

Chronic Fatigue Syndrome is a serious, disabling disorder, expressed in multiple symptoms affecting individual health condition. Aside from the adverse effects to patients' health, sequela of the disorder include a negative impact on emotional, social and physical functioning, quality of life in general. Based on the results of previous pilot trials with HPE (Dudnik et al., 2008; Lee et al., 2012) we introduced the method of CFS treatment with the course of intravenous HPE Laennec infusions.

We found statistically signi f cant relevant improvements in self-reported characteristics of fatigue levels and HRQoL after relatively short course of only 10 Laennec infusions in 5 weeks and in follow-up. Similar results have been reported by Kang-Kon Lee et al. on fatigue recovery in 294 subjects, but after 4 weeks of HPE drinkable solutes of Unicenta (HPE enriched by vitamins and caffeine) (Larun et al., 2016). In aforementioned study fatigue recovery was assessed via score changes in the Checklist of individual strength (CIS), based on subjects' self-reports, and fatigue was not veri f ed by neurologist as CFS.

We observed well correlated improved scores in CFI and in HRQoL subscales in sample group with veri f ed primary diagnosis of CFS. Besides such an inprovements in CFI were correlated with corresponded decrease in perceived symptoms of depression and anxiety. Such data can be explained in part by multidirectional relationship between HRQoL, depression and physical health in different patients' categories (Spielberg et al., 2004). In CFS subjects HPE infusions reduce fatigue, potentiate physical f tness which, in turn, alleviates depressive symptoms and improves HRQoL, especially mental and emotional components.

To our knowledge this is the f rst study that investigated the effects of HPE Laennec intravenous infusions on CFS patients' physical functioning and exercise tolerance assessed in objective parameters. We observed signi f cant increase in HPEL subjects' aerobic capacity and exercise performance to the end of the treatment period and in 5 weeks follow-up without any additional exercise interventions, while these parameters were unchanged signi f cantly in CTRL.

There are several studies demonstrating positive effects of physical training on fatigue recovery, depression and anxiety level, and HRQoL in CFS patients (Brouwers et al., 2002; Klasnja et al., 2014; Torjesen, 2015). Klasnja A. et al. demonstrated graded exercise therapy has a positive effect on both physical and psychological state of CFS patients (Klasnja et al., 2014). As shown in systematic review of Larun L. et al., exercise therapy is most effective in CFS patients with respect to self-perceived HRQoL and physical functioning in comparison with cognitive-behavioral therapy and other strategies (Larun et al., 2016). But improvements needs some time and studies with a long-term intervention of more than 3 months showed the best effects.

As demonstrated in our study, similar effects with potentiation in physical work capacity, as well as in improvement of HRQoL and fatigue recovery may result from HPE Laennec infusions alone, without graded exercise interventions and within shorter period of time. In concordance to Kong et al., who did not f nd any changes in risk factors for cardiovascular disease in elderly subjects after HPE course (Kong et al., 2008; Kong et al., 2012), we observed objectively registered improvements in parameters of exercise tolerance and lipid metabolism.

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be the mean of choice in complex treatment and rehab programs

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