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Human Placental Extract as a Subcutaneous Injection is effective in Chronic Fatigue Syndrome.

: A Multi-center, Double-Blind, Randomized, Placebo-Controlled Study

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## Summary

Chronic Fatigue (CF) is a common reason for consulting a physician due to affecting quality of life, but only a few effective treatments are available. The aim of this study was to examine the effectiveness of subcutaneous injection of the human placental extract (HPE) on medically indescribable cases of CF and safety in a randomized, double-blind, placebo-controlled clinical trial. A total of seventy eight subjects with CF were randomly assigned to either a HPE group or a placebo group. Subjects in the HPE group were treated with HPE three times a week subcutaneously for 6 weeks, whereas those in the placebo group with normal saline. Then, the Fatigue Severity Scale (FSS), Visual Analog Scale (VAS) and Multidimensional Fatigue Inventory (MFI) were measured in both CF group and chronic fatigue syndrome (CFS) and idiopathic chronic fatigue (ICF) subgroup. The FSS, VAS and MFI score at baseline were not different between the HPE and placebo group in total subjects with CF. In CFS group, the FSS ( $p= 0.0242$ ), VAS ( $p=0.0009$ ) and MFI ( $p= 0.0159$ ) scores measured at the end of the study period decreased more in the HPE group than in the placebo group when compared with those at the baseline. There were no significant differences between the HPE group and placebo group in the mean change from baseline in FSS, VAS, and MFI in subjects with ICF during the study period. The subcutaneous injection of HPE was effective in the improvement of CFS.

Keywords: Chronic Fatigue Syndrome; Randomized Clinical Trials; Complementary and Alternative Medicine

## Introduction

Chronic fatigue (CF) is a subjective feeling of emptiness or a lack of power that can affect one's daily life during or after work longer than 6 months.<sup>1)</sup> Medically indescribable cases of chronic fatigue can be classified into chronic fatigue syndrome (CFS) and idiopathic chronic fatigue (ICF).<sup>2)</sup> CFS is a clinically defined condition characterized by long-lasting (at least 6 months) severe disabling fatigue and associated symptoms such as memory and concentration difficulties, post-exertion malaise, sore throat, tender cervical or axillary lymph nodes, muscle aches, joint pain, sleep disturbances, and headache.<sup>3)</sup> If a patient does not meet all the criteria for CFS described above, he/she is diagnosed with ICF.<sup>2)</sup> Several treatments for this condition have been explored, but, none has shown persistent or consistently significant outcomes in this patient population.<sup>4,5)</sup> In addition, a recent review of CFS treatments also proved limited evidence for the effectiveness of Complementary and Alternative Medicine (CAM) therapy in relieving symptoms of CFS.<sup>6)</sup>

As a kind of CAM therapy, the human placental extract (HPE) is currently used in various consumer products such as pharmaceuticals, cosmetics, hair care products, and health tonics. In South Korea, the HPE has been used in skin care and for recovery from fatigue symptoms or allergy in many primary care settings. Indeed, a recent study demonstrated that the oral HPE was effective in the improvement of fatigue symptoms in Korean population.<sup>7)</sup> However, the effect of HPE as a subcutaneous injection on CFS & ICF patients remains unclear. Therefore, we conducted a randomized, double-blind, placebo-controlled clinical trial to determine whether subcutaneous injection of HPE improved fatigue symptoms via score changes in Fatigue Severity Scale (FSS), Visual Analog Scale (VAS) and Multidimensional Fatigue Inventory (MFI) in total subjects with CFS and ICF including subgroup analysis. In addition, the safety of the placental extract was investigated by analyzing AEs, vital signs, and laboratory test results.

## Materials and Methods

### *Study design*

Of the subjects who visited one of two medical centers (Sungkyunkwan Univ. Kangbuk Samsung Hospital and Ajou Univ. Hospital) in Korea from January 14, 2013 to September 2, 2013, those who met the criteria for CFS or ICF [Centers for Disease Control and Prevention (CDC), 1994] were enrolled in this study. Chronic fatigue patients aged 20-65 years old were recruited and initial screening included a medical history, physical examination, and laboratory test.

We excluded subjects who met at least one of the following criteria: 1) elevated liver enzymes: aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $>2 \times$  upper limit of normal, 2) abnormal renal function (creatinine  $>2 \times$  upper limit of normal), 3) Beck Depression Inventory (BDI) II  $\geq 29$ , 4) subjects who were diagnosed as follows: diabetes, malignant tumor, tuberculosis, multiple sclerosis, hypothyroidism, major depressive disorder, bipolar disorder, schizophrenia, delusional disorder, dementia, severe obesity (BMI  $\geq 45$  kg/m<sup>2</sup>), fatty liver, liver cirrhosis, chronic renal failure, subject on dialysis, and phenylketonuria, 5) subjects who were judged by investigators to be difficult to participate in the study due to severe metabolic diseases, cardiovascular/cerebrovascular diseases, systemic infectious diseases, and gastrointestinal diseases that may cause physical and mental fatigue, 6) pregnancy, breast feeding, or women of childbearing age without a suitable contraceptive, 7) previous record of hypersensitivity to HPE or other animal derivatives.

A sample size of 27 patients in each group was determined to be sufficient to detect a difference of one on mean change from baseline in FSS between the HPE group and placebo group, assuming a power of 80% and a significance level of 5% (power=80%,  $\alpha=0.05$ ). Considering 30% withdrawal rate, 39 patients in each group were planned for assignment.

Of the eighty three subjects who underwent the screening process, five applicants were

excluded (not eligible for inclusion/exclusion criteria). Therefore, seventy eight subjects were enrolled in the present study and randomly assigned to a HPE group (n = 39) or a placebo group (n = 39) by block randomization (Fig 1).

Of the seventy eight subjects, 73 subjects completed this study, as 5 subjects were withdrawn due to consent withdrawal, unpermitted medication, and others. All the subjects completed an informed consent form before participating in the study, and the study was conducted after the approval of the Institutional Review Board (IRB) of every participated medical center.

We measured the height and weight at baseline and at the end of the study and calculated body mass index (BMI) [BMI is defined as weight (kilograms) per square of height (metre)]. Blood pressure was measured with a mercury blood pressure gauge in the sitting position at rest. Serum biochemistry variables assessed at baseline and at the end of the study included hemoglobin, platelet count, white blood cell count, AST, ALT, total bilirubin, Fasting Blood Glucose (FBG), blood urea nitrogen (BUN) and creatinine.

### *Study protocol*

The subjects were randomly assigned to receive subcutaneous injection of either placebo (normal saline, Lot No. 30402) or HPE for 6 weeks. During the study period, 4 mL was injected three times weekly. The HPE was supplied as a glass ampule containing a slightly opaque yellowish brown solution, while colorless normal saline was used as placebo. This color and description gap is directly observable. Hence, the surface of syringes was covered with opaque film, and subjects were randomly assigned under double-blind conditions. On the third week of the study period, their physical condition, vital signs, degree of fatigue severity, serious life events, and AEs were checked. Their laboratory test results, degree of fatigue severity, serious life events, and AEs were also checked after the completion of the

six-week study period.

HPE (Laennec<sup>®</sup>, Lot No. 30405, the commercially available hydrolysate of human placenta manufactured by GCJBP Corporation in Yongin, Korea) is an aqueous extract of human placenta that is used for improvement of chronic liver diseases with the approval of the Ministry of Food and Drug Safety. HPE is extracted from umbilical cord through heating and adding acid for hydrolysis, and composed of proteins of molecular weight (MW) 10–100 kDa, minerals, amino acids, and steroid hormones.<sup>8)</sup>

Human placentas collected at the time of full-term delivery were immediately placed on ice. The placentas were then cut into pieces, extracted with water, and the aqueous extract was sterilized and sealed in ampules. Before this procedure fresh placentas were tested for human immunodeficiency virus and hepatitis B and C viruses. In addition, product sterilization and virus tests were performed.<sup>9)</sup>

To assess the degree of fatigue symptoms, we used the FSS to measure degree of fatigue severity.<sup>10,11)</sup> The usefulness of this scale was recently investigated in Korea; using the FSS index of 3.22 as the cutoff point, sensitivity was 84.1% and specificity was 85.7% for the HPE group and placebo group.<sup>12)</sup> The FSS contains nine items, each of which is ranked for degree of severity using a scale of 1 (none) to 7 (very severe); the score is the average of the nine items. We also used the VAS to assess the degree of fatigue, using a scale of 0 (no fatigue) to 10 (very severe fatigue). Additionally, we used the MFI score that is a 20-items, self-report instrument for measuring degree of fatigue severity.<sup>13)</sup> It covers the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. All items are scored on a five-point Likert scale ranging from 1 (yes, that is true) to 5 (no, that is not true). Subscale scores (range 4–20) are calculated as the sum of item ratings and a total fatigue score (range 20–100) is calculated as the sum of subscale scores.

Higher scores indicate a higher level of fatigue.

### *Statistical analysis*

We used SPSS software for Windows version 17.0. Baseline characteristics were analyzed in the HPE and Placebo group with unpaired t test or Wilcoxon rank sum test for continuous variables, and with Chi-square test or Fisher exact test for categorical variable. We used paired-samples t tests or Wilcoxon signed rank test for the difference in FSS, VAS and MFI scores between at baseline and after the study within groups. We used unpaired t test or Wilcoxon rank sum test for comparison of mean change of fatigue scales between two groups during study period. All of these statistics also were used for subgroup analysis (CFS and ICF group). All values are mean  $\pm$  SD. A *p*-value of less than 0.05 was considered to indicate statistical significance.

## **Results**

### *Baseline clinical characteristics*

The mean age of the HPE group ( $38.74 \pm 10.83$  y) was similar to that of the placebo group ( $38.67 \pm 9.64$  y) in total subjects ( $p = 0.8886$ ; Table 1). There were also no significant differences between the HPE and placebo groups in gender, BMI, BDI II and blood pressure. In addition, there were no significant differences between the HPE and placebo groups in baseline biochemistry characteristics, including white blood cell count, hemoglobin, platelet count, AST, ALT, FBG, BUN, creatinine, and total bilirubin. All these values were within normal range. The mean FSS, VAS and MFI scores were not significantly different between the HPE and placebo groups at baseline in total subjects (HPE vs. placebo: for FSS,  $4.97 \pm 0.96$  vs.  $4.82 \pm 1.13$ ,  $p = 0.5271$ ; for VAS,  $72.26 \pm 14.03$  vs.  $71.64 \pm 10.91$ ,  $p = 0.2440$ ; for MFI,  $2.91 \pm 0.49$  vs.  $2.94 \pm 0.60$ ,  $p = 0.8048$ ). These clinical characteristics and fatigue

scores at baseline were also not significantly different between the HPE and placebo groups in both CFS and ICF groups (data not shown).

#### *Change in degree of fatigue severity*

There were no significant differences between the HPE group and placebo group in the mean change of FSS, VAS and MFI in total subjects with CF and ICF subgroup (data not shown). However, in CFS subgroup, the FSS score at the end of the study period (HPE,  $3.24 \pm 1.28$ ; placebo,  $4.09 \pm 1.22$ ) was significantly lower than that at baseline (HPE,  $5.29 \pm 0.91$ ; placebo,  $5.13 \pm 0.82$ ) in both the HPE and placebo groups ( $p < 0.0001$  and  $p = 0.0016$  by paired-samples t tests) (Fig. 2A). There was a significant difference between the two groups in the mean change in FSS score during the study period (HPE,  $-2.05 \pm 1.43$ ; placebo,  $-1.04 \pm 1.30$ ;  $p = 0.0242$  by unpaired t tests). The VAS scores in the two groups were significantly decreased (scores at baseline vs. at the end of the study: HPE group,  $76.11 \pm 8.99$  vs.  $39.89 \pm 24.28$ ,  $p < 0.0001$ ; placebo group,  $73.24 \pm 8.56$  vs.  $59.90 \pm 18.20$ ,  $p = 0.0004$ ) (Fig. 2B). The mean change in VAS between the baseline and the end of the study period was significantly different between the HPE and placebo groups (HPE vs. placebo:  $-36.21 \pm 26.20$  vs.  $-13.33 \pm 17.16$ ,  $p = 0.0009$  by unpaired t tests). The MFI score measured at the end of the study period decreased by 2.28 points ( $\pm 0.57$ ) in HPE group, and by 2.70 points ( $\pm 0.52$ ) in the placebo group compared to that at the baseline (HPE,  $2.85 \pm 0.47$ ; placebo,  $2.99 \pm 0.61$ ). The MFI score decreased with statistical significance in both groups six weeks after the subcutaneous injection of study solution (HPE,  $p < 0.0001$ ; placebo,  $p = 0.0004$ ) (Fig. 2C). In addition, there were significant differences in the mean scores of FSS, VAS, and MFI between HPE and placebo groups at the end of study (FSS,  $p = 0.0378$ ; VAS,  $p = 0.0052$ ; MFI,  $p = 0.0200$ ).



### *Safety Assessment*

There were no significant changes in vital sign and biochemistry in the HPE group and placebo group in total subjects during the study period, including white blood cell count, hemoglobin, platelet count, AST, ALT, total bilirubin, FBG, BUN and creatinine (Table 2). No statistically significant difference in the percentages of the subjects who experienced AEs was found between the groups ( $p = 0.8199$ ) (Table 3). Statistically significant difference in the adverse drug reaction (ADR) expressions was also not found between the groups ( $p = 0.4935$ ). These drug safeties between the groups were also observed in both CFS and ICF groups (data not shown). In this clinical trial, there was no one who experienced either serious adverse events (SAEs) or withdrawal due to AEs.

The most frequently experienced AEs overall [experienced by 46.15% (18 subjects) of the HPE group and 43.59% (17 subjects) of placebo group] were infection and infestations, skin and subcutaneous disorders, general disorders and administration site conditions, and respiratory, thoracic and mediastinal disorders accounted for 17.95 % (7 subject), 7.69 % (3 subject), 7.69 % (3 subject), and 7.69 % (3 subject) respectively, in HPE group. On the other hand, infection and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and nervous system disorders accounted for 17.95 % (7 subjects), 12.82 % (5 subjects), 7.69 % (3 subjects), and 7.69 % (3 subjects) respectively, in placebo group.

### **Discussion**

In the present study, the fatigue symptoms in CFS but not ICF were found to be improved in middle-aged Korean after they received HPE for 6 weeks. The vital sign, laboratory test results and AE frequency in the HPE group was similar to those in the placebo group. The present study has the strength of the first randomized, double-blind, placebo-controlled clinical study evaluating the effect of HPE as a subcutaneous injection on CFS patients, and a

significant favourable impact on fatigue symptoms and degree of its severity assessed subjectively by FSS, VAS, and MFI is valuable.

The possible underlying mechanisms to explain the observed link between HPE and CFS are as follows. First, while emotional stress is one of the common major causes of CFS, abnormal immune function, immune activation, and various microbial infections are also considered to be the causes of CFS.<sup>14)</sup> Previous studies suggested that HPE has anti-inflammatory properties, thereby resulting in fatigue symptom improvement.<sup>15,16)</sup> HPE significantly inhibits carrageenin and prostaglandin E1-induced edema in rats. This degree of HPE effect was almost the same as that in the diclofenac sodium treated group.<sup>15)</sup> HPE has been used in many countries for the treatment of chronic wounds,<sup>17-19)</sup> and it improves or eradicates oral mucositis in cancer subjects who undergo chemotherapy and/or radiotherapy.<sup>20,21)</sup> Therefore, the anti-inflammatory properties of HPE improve chronic inflammation, which is one of the causes of CFS. The second possible reason for the HPE effect on CFS could be its ability to improve immunity. One of the causes of CFS is impaired immune function. The HPE products used for the present study contained 6.14 pg/mL of interleukin-2 (IL-2)<sup>8)</sup> and IL-2 is one of the cytokines that are used for improving immune function.<sup>22)</sup> These may explain the effectiveness of HPE in the improvement of CFS observed in the present study.

This study showed that both various blood chemistry test results and SAE in the HPE treated group were similar to those in the placebo group, and that the frequency of its AEs was also low. In fact, as the HPE is extracted from body tissues, thorough management and regulation of raw material collection and manufacturing are required.

Previous clinical studies on the HPE were mainly conducted to investigate its effects on hepatic dysfunction,<sup>23)</sup> menopausal disorder,<sup>9)</sup> and skin whitening.<sup>24, 25)</sup> The present study is valuable as a multi-center, double-blind study that first assessed the effectiveness and safety

of the subcutaneous injection of HPE on CFS. Furthermore, the results of this study are valuable because they can provide more treatment options to subjects with CFS in the current situation wherein only a few effective treatments are available for CFS. However, the present study did not show for the effectiveness of HPE subcutaneous injection in ICF subjects. This finding may be due to different study subjects because the clinical characteristics of CFS were distinguished from ICF.

The current study has several limitations. First, the number of participants was small, and the results could not represent a long-term effect because of the 6-week duration of the study. Second, this study was conducted using an imprecise outcome measure. Not only is degree of fatigue severity measured subjectively, but it varied greatly and is influenced by emotional state. Accordingly, this study couldn't exclude placebo effect through 6 weeks in both the HPE and placebo groups. These limitations may obscure the treatment effect of HPE unless sample sizes are large. Therefore, a further multi-center, and large population-based study is needed to answer the questions developed from the present data.

In conclusion, this is the first study showing the effectiveness of subcutaneous injection of HPE on CFS. The subcutaneous HPE injections were beneficial for alleviating CFS complaints after 6 weeks. And various serum chemistry results on laboratory in the HPE group were also showed no difference than in the placebo group. Thus, the results of this study may support the prescription of subcutaneous injection of HPE for CFS-related symptoms.

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**Conflict of Interest**

All authors received a research grant from Green Cross Corporation & GCJBP Corporation.

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Table 1. Subject characteristics at baseline

	HPE (n = 39)	Placebo (n = 39)	<i>p-value</i>
Age (in years)	38.74 ± 10.83	38.67 ± 9.64	0.8886
Female (%)	29 (74.36)	32 (82.05)	0.4106
BMI (kg/m <sup>2</sup> )	22.08 ± 2.48	21.87 ± 3.18	0.3901
SBP (mmHg)	112.05 ± 11.39	112.49 ± 9.78	0.8566
DBP (mmHg)	70.03 ± 9.69	68.95 ± 8.90	0.6108
WBC (×10 <sup>3</sup> /uL)	5.77 ± 1.46	5.91 ± 1.29	0.6498
Hematocrit	40.15 ± 3.72	39.84 ± 3.65	0.7089
Platelet	221.13 ± 47.00	232.74 ± 50.51	0.2484
AST (U/L)	19.90 ± 3.34	21.23 ± 6.08	0.8098
ALT (U/L)	17.23 ± 6.31	17.92 ± 7.79	0.8531
Total Bilirubin	0.86 ± 0.28	0.76 ± 0.23	0.0855
FBG	93.97 ± 8.55	90.95 ± 7.03	0.1495
BUN	12.92 ± 3.73	13.48 ± 3.19	0.4731
Creatinine	0.82 ± 0.17	0.78 ± 0.16	0.4051
FSS	4.97 ± 0.96	4.82 ± 1.13	0.5271
VAS	72.26 ± 14.03	71.64 ± 10.91	0.2440
MFI	2.91 ± 0.49	2.94 ± 0.60	0.8048

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBG, fasting blood glucose; BUN, Blood urea nitrogen; FSS, Fatigue Severity Scale; VAS, Visual Analog Scale; MFI, Multidimensional Fatigue Inventory.

Mean ± SD



Table 2. Change of vital sign and biochemistry in the two study groups

	HPE (n = 39)			Placebo (n = 39)			<i>p-value</i> <sup>b</sup>
	Baseline	End	Difference <sup>a</sup>	Baseline	End	Difference <sup>a</sup>	
SBP	112.05	109.39	-2.97	112.49	108.95	-3.54	0.8172
(mm Hg)	± 11.39	± 10.40	± 9.85	± 9.78	± 10.91	± 11.44	
DBP	70.03	68.34	-1.84	68.95	69.10	0.15	0.4292
(mm Hg)	± 9.69	± 8.47	± 10.86	± 8.90	± 7.86	± 11.17	
WBC	5.77	5.74	-0.04	5.91	5.70	-0.25	0.5334
(×10 <sup>3</sup> /uL)	± 1.46	± 1.65	± 1.52	± 1.29	± 1.52	± 1.30	
Hematocrit	40.15	39.70	-0.30	39.84	39.46	-0.22	0.8573
	± 3.72	± 3.90	± 1.75	± 3.65	± 4.09	± 1.89	
Platelet	221.13	219.97	-1.08	232.74	233.41	-1.38	0.8611
	± 47.00	± 48.85	± 22.86	± 50.51	± 57.83	± 29.23	
AST (U/L)	19.90	18.53	-1.18	21.23	19.24	-2.00	0.4847
	± 3.34	± 3.28	± 2.86	± 6.08	± 3.80	± 5.16	
ALT (U/L)	17.23	14.97	-1.74	17.92	16.32	-1.89	0.4089
	± 6.31	± 5.34	± 4.00	± 7.79	± 6.61	± 4.83	
Total	0.86	0.80	-0.06	0.76	0.66	-0.10	0.5856
Bilirubin	± 0.28	± 0.24	± 0.26	± 0.23	± 0.22	± 0.30	
FBG	93.97	91.84	-2.21	90.95	89.35	-1.86	0.4078
	± 8.55	± 9.79	± 9.97	± 7.03	± 8.85	± 9.46	
BUN	12.92	12.74	-0.08	13.48	13.91	0.54	0.3472
	± 3.73	± 3.47	± 2.22	± 3.19	± 3.86	± 3.32	
Creatinine	0.82	0.79	-0.02	0.78	0.81	0.02	0.0662
	± 0.17	± 0.18	± 0.09	± 0.16	± 0.19	± 0.09	

SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBG, fasting blood glucose; BUN, Blood urea nitrogen.

a Change from baseline (after baseline).

b P values are for the comparison between groups (change from baseline).

Table 3. Summary of adverse events

Adverse Event		HPE (n = 39)	Placebo (n = 39)	<i>p-value</i> <sup>a</sup>
Adverse event (AE)	n (%)	18 (46.15)	17 (43.59)	0.8199
Serious adverse event (SAE)	n (%)	0 (0.00)	0 (0.00)	
Adverse drug reaction (ADR)	n (%)	2 (5.13)	0 (0.00)	0.4935
Withdrawal due to adverse events	n (%)	0 (0.00)	0 (0.00)	

a Chi-square test or Fisher's exact test

Fig 1.

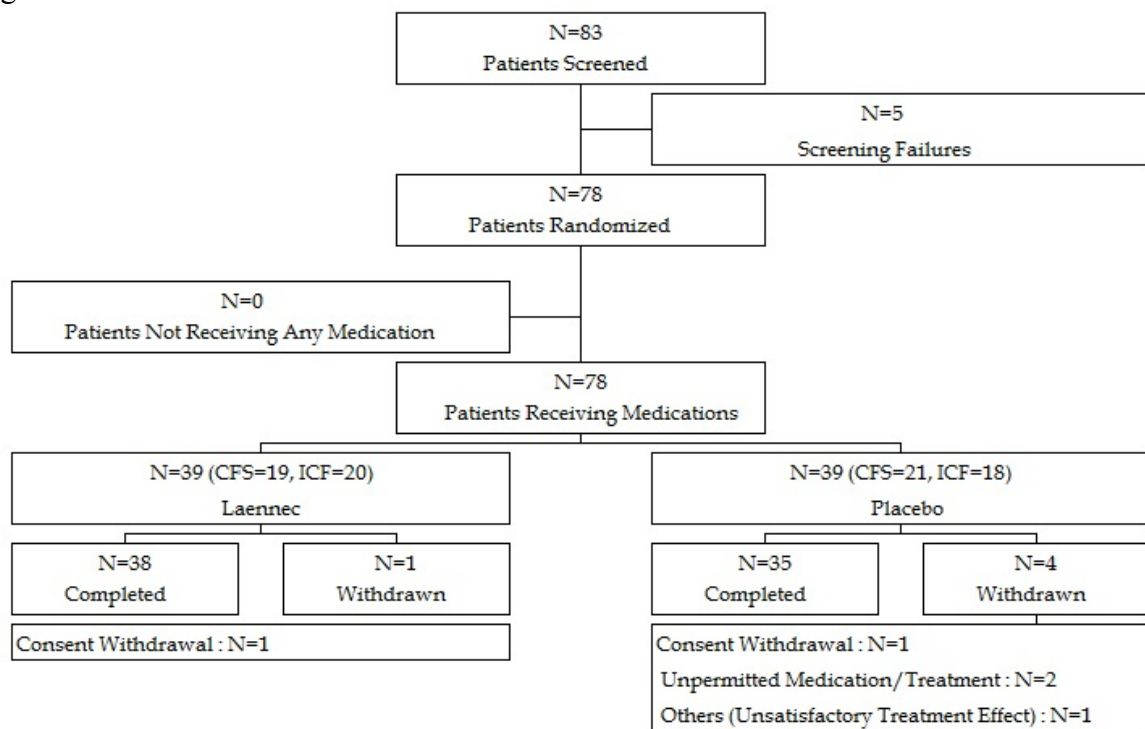
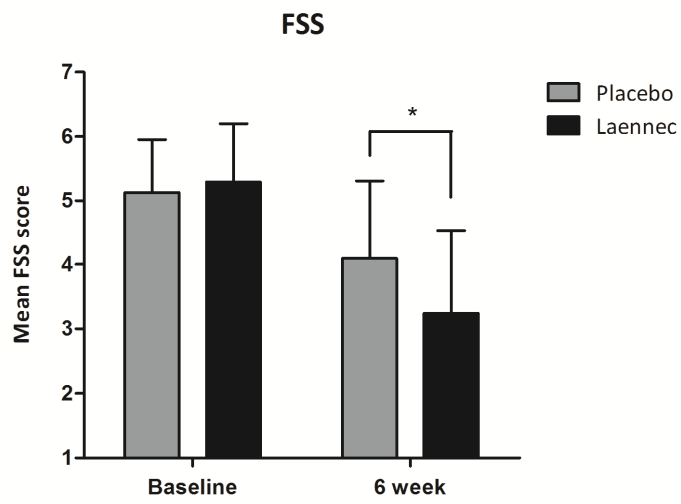
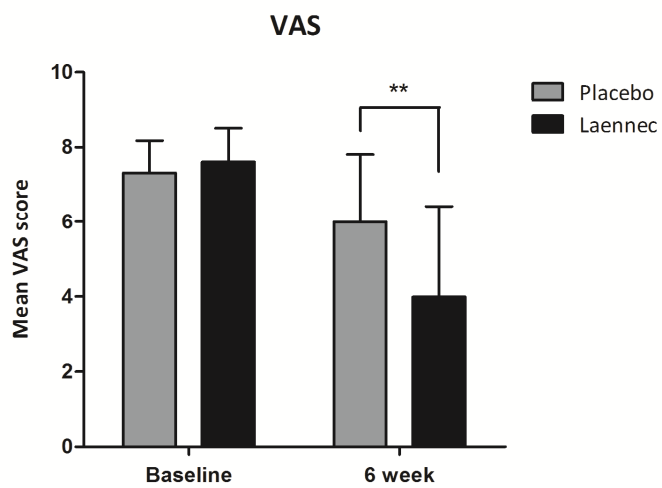


Fig 2.

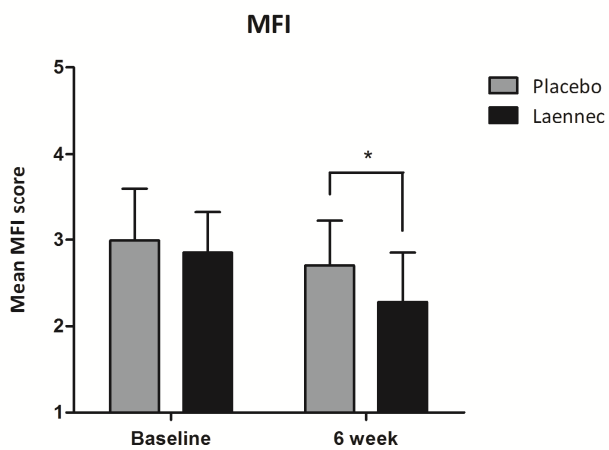
A



B



C



## Figure legends

Fig 1. Flow chart for this study

Fig 2. Change in Fatigue Severity Scale (FSS) score (A), Visual Analog Scale (VAS) (B) and Multidimensional Fatigue Inventory (MFI) (C) of fatigue severity in the two study groups in subjects with CFS.

\* comparison of mean scores between HPE and placebo groups at the end of study (FSS,  $p=0.0378$ ; MFI,  $p=0.0200$ )

\*\* comparison of mean scores between HPE and placebo groups at the end of study (VAS,  $p=0.0052$ )

HPE; human placental extract.