Effect of Human Placental Extract on Quality of Life in Postmenopausal Woman

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Abstract

Objective: We aimed to evaluate the effect of Human placental extracts (HPE) on the quality of life (QOL) in postmenopausal Korean women aged over 40 years, using Women's Health Questionnaire (WHQ) and Nottingham Health Profile (NHP).

Methods: 100 volunteers over the age of 40 who had menopausal symptoms were recruited, and 60 women contributed to the analyses. The women were randomly assigned to receive subcutaneous injection of either placebo (normal saline) or HPE for 2 weeks by patient-blind method. To assess the QOL, we used WHQ and NHP translated into Korean. We applied WHQ and NHP at baseline, 2 weeks and 6 months after injections.

Results: 46 women participated in the final analysis (24 in the HPE group and 22 in the placebo group). The scores of WHQ and NHP were not significantly different between the HPE and the placebo groups at baseline. After 2 weeks, the score for sleep (NHP Part I) of HPE group was significantly improved (p=0.029). After follow-up period of 6 months, the score changes for pain (NHP Part I, p=0.048) and sleep (WHQ, p=0.004) of HPE group were significantly improved, but not in the placebo group.

Conclusion: HPE injections were partially effective in QOL improvement of postmenopausal women.

Key words: Human placental extracts, Quality of life, Postmenopausal women.

Introduction

Placenta obtained on delivery has been used traditionally for treatment of disease, such as anxiety disorder, epilepsy, dementia, chronic bronchitis, and general weakness in Korea. We could find some records about treatment with human placenta from Korean traditional herbal-medical textbook. The method to extract human placenta was developed in Japan, and Ministry of Health approved its clinical use in 1956. After approval, Human placental extracts (HPE) had been widely used in various clinical settings in Japan. HPE were known to have a lot of bio-active and therapeutic elements. So far, various growth factors, cytokines, hormones, peptides, lipids, nucleic acids, vitamins and minerals were identified (1, 2). In addition, HPE might contain unknown traces, and have the promising effect such as anti-inflammatory, anti-mutagenic, anti-anaphylactic and anti-oxidative (3, 4).

HPE began to be imported to Korea for treatment of chronic liver disease since 1994. Additionally, Korean physicians began using HPE to improve menopausal symptoms since 2003. The indications of HPE are now expanding to cover various disease entities, such as liver dysfunction, sexual dysfunction, ageing, fatigue syndrome and cosmetic problems of skin, although there are few evidence on HPE efficacy. Most of the studies were performed in animal or experimental based settings (5). Some authors reported the availability of HPE on the skin-whitening effect by anti-melanin action (6), and others insisted that HPE were effective on the hypopigmentation disorders by stimulation on melanocytes (7-9).

The objectives of the present study were to evaluate the effect of HPE on the quality of life in postmenopausal women aged over 40 years, using Women's Health Questionnaire (WHQ) and Nottingham Health Profile (NHP).

Material and Methods

Study participants

100 volunteers over the age of 40 who had menopausal symptoms were recruited in one university hospital in Seoul, Korea from July to August, 2007. We only included women who be-

came to be menopausal spontaneously within 5 years and who have more than 20 points in Kupperman's index. This study was approved by the Hospital Ethics Committee of Inje University Sanggye-Paik Hospital, Seoul, Korea.

After exclusion of women with a past history or current condition such as allergy to drug, cancer, thyroid disease, uncontrolled hypertension, complicated diabetes, uncontrolled dyslipidemia, neuropsychiatric disorder, systemic infections, hysterectomy, oophorectomy, hepatic or renal dysfunction, drug abuse, hormone therapy within 1 month, endometrial thickness over 5mm, abnormal Pap smear result within 6 months, vaginal bleeding and experience to be treated with HPE, 60 women contributed to the analyses. We randomly assigned subjects into 2 groups, which were HPE and placebo group. In addition, 14 participants were excluded for final analyses as one showed hematuria during the study, another one withdrew participation, and 12 did not complete questionnaire. Finally, we could assign 24 into HPE group and 22 into placebo group.

Study protocols

The women were randomly assigned to receive subcutaneous injection of either placebo (normal saline) or HPE for 2 weeks. From August to September, 2007, HPE or placebo was injected twice or three times weekly (6 times totally) by patient-blind method. To assess quality of life, we used WHQ and NHP, which were translated into Korean. We applied the 2 questionnaires for three times, which were at baseline, 2 weeks later and 6 months after injections. We measured pulse rate, body temperature, the height and weight of the women at baseline and calculated body mass index (BMI) (weight [kg]/ height [m^2]). Blood pressure was measured with a mercury blood pressure gauge in sitting position at rest. Laboratory variables assessed at baseline of the study using blood glucose, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum total bilirubin, lipid profile, serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In addition, we measured socioeconomic indicators such as marital status, monthly incomes and educational status. Marital status was divided into maintaining and non-maintaining group (unmarried, divorced, bereaved and separated).

Study tools

WHQ is a measure of mid-aged women's emotional and physical health (10). Since its publication in 1992 the WHQ has been widely used in multinational clinical trials, in epidemiological studies as well as in the evaluation of non-medical treatments. In particular the WHQ included quality of life measure in trials of hormonal preparations for peri- and postmenopausal women. The questionnaire was developed in English and standardized on a sample of women aged 45–65 years. It is reliable, valid and sensitive to detect change, and now available in 27 languages. The WHQ is a 36-item questionnaire assessing nine domains of physical and emotional health rated on four point scales. The nine domains are depressed mood (6 items), somatic symptoms (7 items), anxiety/fears (4 items), vasomotor symptoms (2 items), sleep problems (3 items), sexual behavior (3 items), menstrual symptoms (4 items), memory/ concentration (3 items) and attractiveness (3 items). The four point scales (yes definitely, yes sometimes, no not much, no not at all) are reduced to binary options (0/1) and the subscale items are summated and divided by the number of items in each subscale. We used 32 items except menstrual symptoms, translated into Korean, which was proved to have validity and reliability by Lee et al (11).

NHP is a two-part self-completed questionnaire. Part I assesses perceived health along six dimensions (Energy, Sleep, Emotional Reactions, Pain, Physical Mobility and Social Isolation). Each dimension consists of a number of statements which respondents are asked whether they apply to them or not. Each statement is weighted to produce a scoring system ranging from zero (no problems) to 100 (all the stated problems). Part II asks about the effect any ill-health has on seven areas of daily life. We used the NHP translated into Korean, which was proved to have validity and reliability by Moon et al (12).

Statistical analyses

We used SAS software for Windows version 9.1 (SAS institute, Cary, USA). We used χ^2-test and Fisher's exact test for comparison of HPE with placebo at baseline. We measured both pre and post injection scores, and difference of score changes to assess the effect of HPE on quality of life. We used Wilcoxon signed ranks test for comparison pre and post injection scores within groups, and Mann-

Whitney U test for the difference in score changes between baseline and after the study. All values are median (range) and a p value of less than 0.05 was considered to be statistically significant.

Results

Baseline clinical characteristics

In Table 1, 14 women did not complete the study because of several reasons as described above. Therefore, 46 women participated in the final analyses (24 in the HPE group and 22 in the placebo group). The age, weight, height, BMI and scores for WHQ and NHP were not significantly different between the HPE and placebo groups. In socioeconomic indicators, marital status and monthly incomes were not different, but educational levels were lower in placebo groups (p=0.018).

There were no serious adverse effects except only mild local symptoms such as pain on injection site, redness, itching, bruising. Additionally, one woman in the HPE group showed hematuria during the study period, and excluded from analysis. The incidence rate of adverse effects was not significantly different between two groups.

Short-term changes of quality of life after injections

To assess short-term changes of quality of life, we applied WHQ and NHP after 2 weeks from injections. The NHP Part I scores were significantly different in total Part I scores (before, 188.2 vs. after 2 weeks, 139.1, p=0.002), physical mobility (12.5 vs. 12.5, p=0.021), pain (25.0 vs. 12.5, p=0.005), sleep (40.0 vs. 20.0, p=0.029) and energy (66.7 vs. 33.3, p=0.018) in HPE group. In placebo group, total Part I scores (181.9 vs. 148.3, p=0.044) and

Table 1. Basic characteristics of study subjects (n=46).

Characteristic	HPE group (n=24)	Placebo group (n=22)	P value
Age(years, mean±SD)	54.6±2.0	53.9±2.3	0.442*
Weight(Kg)	55.7±5.9	57.2±5.3	0.295*
Height(Cm)	156.8±5.3	156.0±3.4	0.446*
BMI(Kg/m^2)	22.6±2.0	23.5±2.2	0.156*
Marital status, N(%)			0.659†
Married	17(70.8)	10(45.5)	
Unmarried	3(12.5)	3(13.6)	
non-response	4(16.7)	9(40.9)	
Degree of education, N(%)			0.018†
<middle school	2(8.3)	7(31.8)	
high school	14(58.3)	4(18.2)	
University	3(12.5)	2(9.1)	
non-response	5(20.8)	9(40.9)	
Income, N(%)			0.342†
<200(10 thousand won/month)	8(33.3)	7(31.8)	
200-400	7(29.2)	4(18.2)	
>400	4(16.7)	0	
non-response	5(20.8)	11(50.0)	
Women's Health Questionnaire(mean±SD)	83.6±15.5	77.5±14.6	0.222‡
Nottingham health profile(Ⅰ)(mean±SD)	214.2(12.5-478.9)	169.9(0-350.9)	0.276‡
Nottingham health profile(Ⅱ)(mean±SD)	2.6±2.3	2.2±2.4	0.488‡

HPE: Human placental extract, BMI: body mass index.
**by χ^2-test, †by Fisher's exact test, ‡by Wilcoxon signed ranks test.*

energy (50.0 vs. 33.3, p=0.017) were significantly different. There were no significant differences in the NHP Part II scores in both groups. On the other hand, the WHQ scores were not significantly different in each item in both groups (Table 2).

Long-term changes of quality of life after injections

To assess long-term changes of quality of life, we applied WHQ and NHP again after 6 months from injections. The NHP Part I scores were significantly different in total Part I scores (before, 188.2 vs. after 6 months, 128.9, p=0.002), physical mobility (12.5 vs. 12.5, p=0.038), pain (25.0 vs. 12.5, p=0.006), sleep (40.0 vs. 20.0, p=0.029), energy (66.7 vs. 33.3, p=0.018) and social isolation (20.0 vs. 0.0, p=0.033) in HPE group. On the other hand, in placebo group, there were no significant differences in each item. In addition, there were no significant differences in the NHP Part II scores in both groups. The WHQ scores were not significantly different in almost each item in both groups (Table 3).

Comparison for short-term changes of WHQ and NHP scores after injection

We compared score changes between HPE and placebo groups to assess the differences in two groups after 2 weeks from injections. The greater the score changes, the greater the improvement of quality of life. There were no significant score changes between HPE and placebo groups in NHP, except sleep (HPE, 0.0 vs. placebo, 0.0, p=0.033). In WHQ, items of cognitive difficulties (p=0.056) and sleep problem (p=0.077) seemed to be different marginally, but we could not find any more differences between two groups (Table 4).

Comparison for long-term changes of WHQ and NHP scores after injections

We compared score changes between HPE and placebo groups to assess the differences in two

Table 2. The comparison of treatment response between the two study groups after 2 weeks.

Measurements (No. of items)	HPE group, median(range)		P value*	Placebo group, median (range)		P value*
	Baseline	After 2 weeks		Baseline	After 2 weeks	
Nottingham health Profile(I)	188.2 (12.5-478.9)	139.1 (0-426.4)	0.002	181.9 (0-350.9)	148.3 (0-281.1)	0.044
physical mobility(8)	12.5(0-50)	12.5(0-50)	0.021	0.0(0-50)	0.0(0-37.5)	0.431
pain(8)	25.0(0-100)	12.5(0-87.5)	0.005	12.5(0.87.5)	12.5(0-62.5)	0.156
sleep(5)	40.0(0-80)	20.0(0-60)	0.029	20.0(0-60)	20.0(0-60)	0.366
energy(3)	66.7(0-100)	33.3(0-100)	0.018	50.0(0-100)	33.3(0-100)	0.017
social isolation(5)	20.0(0-100)	20.0(0-60)	0.069	20.0(0-100)	0.0(0-60)	0.499
emotional reaction(9)	33.3(0-88.9)	22.2(0-88.9)	0.252	44.4(0-88.9)	22.2(0-77.8)	0.051
Nottingham health Profile(II)(7)	2.0(0-7)	1.0(0-7)	0.090	1.0(0-7)	1.0(0-7)	0.101
Women's Health Questionnaire	82.0(51-107)	79.5(48-109)	0.136	80.5(50-98)	77.0(43-101)	0.548
somatic symptom(7)	19.0(7-26)	19.0(10-27)	0.221	16.0(7-24)	16.0(7-26)	0.215
depressed mood(7)	17.0(10-26)	16.5(9-23)	0.062	16.5(7-22)	15.5(7-20)	0.509
cognitive difficulties(3)	8.5(5-12)	8.5(4-12)	0.216	8.0(3-11)	9.0(3-12)	0.216
anxiety/fears(5)	12.0(8-17)	12.0(7-18)	0.776	11.0(5-17)	11.0(7-15)	0.599
sexual functioning(3)	7.0(0-12)	7.5(0-12)	0.924	7.0(1-12)	7.5(2-10)	0.676
vasomotor symptom(2)	6.0(2-8)	6.0(2-8)	0.371	6.5(2-8)	5.5(4-8)	0.082
sleep problem(3)	9.0(5-12)	8.0(5-12)	0.094	7.5(4-11)	8.5(3-12)	0.354
attraction(2)	5.0(2-9)	5.0(2-8)	0.668	5.0(2-8)	5.0(3-8)	0.147

**by Wilcoxon signed ranks test.*

Table 3. The comparison of treatment response between the two study groups after 6months.

Measurements (No. of items)	HPE group, median (range)		P value*	Placebo group, median (range)		P value*
	Baseline	After 6 months		Baseline	After 6 months	
Nottingham health Profile(I)	188.2 (12.5-478.9)	128.9 (0-330.9)	0.002	181.9 (0-350.9)	132.7 (23.6-321.1)	0.232
physical mobility(8)	12.5(0-50)	12.5(0-50)	0.038	0.0(0-50)	12.5(0-50)	0.785
pain(8)	25.0(0-100)	12.5(0-87.5)	0.006	12.5(0.87.5)	12.5(0-100)	0.824
sleep(5)	40.0(0-80)	20.0(0-80)	0.029	20.0(0-60)	20.0(0-80)	0.952
energy(3)	66.7(0-100)	33.3(0-100)	0.018	50.0(0-100)	33.3(0-100)	0.240
social isolation(5)	20.0(0-100)	0.0(0-80)	0.033	20.0(0-100)	0.0(0-60)	0.051
emotional reaction(9)	33.3(0-88.9)	22.2(0-66.7)	0.117	44.4(0-88.9)	22.2(0-55.6)	0.131
Nottingham health Profile(II)(7)	2.0(0-7)	1.0(0-6)	0.100	1.0(0-7)	2.0(0-7)	0.977
Women's Health Questionnaire	82.0(51-107)	80.0(50-105)	0.339	80.5(50-98)	83.0(45-100)	0.702
somatic symptom(7)	19.0(7-26)	19.0(9-27)	0.542	16.0(7-24)	18.0(8-24)	0.948
depressed mood(7)	17.0(10-26)	16.0(10-21)	0.081	16.5(7-22)	16.0(8-21)	0.746
cognitive difficulties(3)	8.5(5-12)	9.0(5-12)	0.486	8.0(3-11)	8.0(3-12)	1.000
anxiety/fears(5)	12.0(8-17)	12.0(8-17)	0.749	11.0(5-17)	12.0(7-16)	0.917
sexual functioning(3)	7.0(0-12)	7.5(0-11)	0.507	7.0(1-12)	9.0(3-11)	0.253
vasomotor symptom(2)	6.0(2-8)	6.0(3-8)	0.774	6.5(2-8)	6.0(4-8)	0.839
sleep problem(3)	9.0(5-12)	8.0(5-12)	0.090	7.5(4-11)	9.0(4-12)	0.024
attraction(2)	5.0(2-9)	5.0(2-7)	1.000	5.0(2-8)	5.0(3-8)	0.230

**by Wilcoxon signed ranks test.*

groups after 6 months from injections. There were no significant score changes between HPE and placebo groups, except pain (HPE, 12.5 vs. placebo, 0.0, p=0.048) of NHP Part I and sleep (HPE, 1.0 vs. placebo, -1.0, p=0.004) of WHQ (Table 5).

Discussion

Although there is few evidence about its effects so far, Human placental extracts (HPE) are now expanding to cover various disease entities, such as liver dysfunction, sexual dysfunction, aging, fatigue syndrome and cosmetic problems of skin. Earlier studies suggested that HPE has anti-inflammatory properties and HPE has been assumed to have anti-ageing action via fibroblast proliferation and growth-promoting effect (13, 14). In addition, some authors reported effects of HPE on chronic non-healing wounds (15, 16). Kong et al. suggested that menopausal symptoms and fatigue in middle-aged Korean women improved after 8 weeks of HPE treatment (17). But research evidence of these effects is still lacking. The quality of life, including not only objective, but also subjective feeling of well-being, is very broad concept. Therefore, evaluation of subjective well-being sense is important when we assess the quality of life. In this study, we investigated whether significant changes of the quality of life occur after HPE treatment, and we focused well-being sense mainly rather than bioactivity or analysis for sub-elements of HPE. As a short-term result, we could observe significant improvements of NHP Part I scores in total Part I scores (p=0.002), physical mobility (p=0.021), pain (p=0.005), sleep (=0.029) and energy (p=0.018) in HPE group. In placebo group, total Part I scores (p=0.044) and energy (p=0.017) were significantly different. These results seemed to be maintained after 6 months later. But with comparison for changes of WHQ and NHP scores between HPE and place-

Table 4. The comparison of short-term score change between the two study groups after 2 weeks.

Measurements (No. of items)	HPE group short-term score change, Median (range)	Placebo group short-term score change, Median (range)	P value*
Nottingham health Profile(I)	48.6(-86.6~249.1)	22.8(-69.4~187.9)	0.456
physical mobility(8)	0.0(-12.5~25.0)	0.0(-25.0~37.5)	0.324
pain(8)	12.5(-12.5~37.5)	0.0(-25.0~50.0)	0.427
sleep(5)	0.0(-20.0~80.0)	0.0(-40.0~20.0)	0.033
energy(3)	0.0(-33.3~44.5)	33.3(-33.3~100.0)	0.647
social isolation(5)	0.0(-40.0~60.0)	0.0(-40.0~60.0)	0.470
emotional reaction(9)	11.1(-33.4~44.5)	11.1(-33.4~55.6)	0.631
Nottingham health Profile(II)(7)	1.0(-6.0~6.0)	0.0(-1.0~4.0)	0.540
Women's Health Questionnaire	3.0(-28.0~21.0)	3.0(-20.0~17.0)	0.552
somatic symptom(7)	1.5(-12.0~6.0)	1.0(-4.0~7.0)	0.947
depressed mood(7)	2.0(-8.0~8.0)	0.0(-7.0~8.0)	0.347
cognitive difficulties(3)	0.0(-3.0~3.0)	-0.5(-5.0~3.0)	0.056
anxiety/fears(5)	0.0(-6.0~5.0)	0.0(-6.0~3.0)	0.947
sexual functioning(3)	0.0(-4.0~4.0)	0.5(-6.0~7.0)	0.797
vasomotor symptom(2)	0.0(-2.0~3.0)	0.5(-2.0~2.0)	0.378
sleep problem(3)	0.5(-3.0~6.0)	0.0(-5.0~3.0)	0.077
attraction(2)	0.0(-4.0~3.0)	-0.5(-3.0~4.0)	0.322

**by Mann-Whitney U test.*

bo groups after injections, we could only find partial score changes in sleep (p=0.033) of NHP part I as a short-term result, pain (p=0.048) and sleep (0.004) of NHQ as a long-term results. These might be due to high prevalence of pain and sleep disorder, and the other items such as physical mobility, emotional reaction, depressed mood, energy and anxiety were thought to be dispersed widely according to personal susceptibility. We have to consider other medical and social conditions such as comorbidities of osteoarthritis and other degenerative disease, therapeutic modality, degree of labor, personal susceptibility and medication history when evaluating pain. Similarly, the considerations for stress, emotional status, sleep quality and medication history are essential when we evaluate the HPE effect on sleep. Therefore, we could not conclude that the above changes were totally due to HPE injections.

The difference of score changes between WHQ and NHP were higher than expected, and these trends were sustained during the study period. It seems to be due to simplicity of NHP and complexity of WHQ.

We acknowledge some strengths and limitations of this work. To our knowledge this study is the first prospective one that assessed the effects of HPE on the quality of life in postmenopausal women. Furthermore, we rechecked the questionnaires after 6 months to find out the long-term effect of HPE.

The current study has several limitations. First is the lack of objective assessment on quality of life. We used only questionnaire scores to assess the quality of life change. Postmenopausal symptoms are subjective feeling, so we cannot conclude that the questionnaire score changes represent degree of quality of life exactly. Also it could be due to the placebo effect related to psychological support. Second, the results could not represent other socio-medical conditions that could impact on the quality of life of participants (11). Finally, the

Table 5. The comparison of long-term score change between the two study groups after 6 months.

Measurements (No. of items)	HPE group long-term score change, Median (range)	Placebo group long-term score change, Median (range)	P value*
Nottingham health Profile(I)	48.0(-115.5~293.6)	43.4(-206.2~245.0)	0.361
physical mobility(8)	0.0(-12.5~25.0)	0.0(-25.0~37.5)	0.135
pain(8)	12.5(-25.0~50.0)	0.0(-62.5~62.5)	0.048
sleep(5)	0.0(-20.0~40.0)	0.0(-40.0~60.0)	0.122
energy(3)	33.3(-33.3~66.7)	16.7(-66.7~100.0)	0.957
social isolation(5)	20.0(-40.0~80.0)	0.0(-40.0~60.0)	0.536
emotional reaction(9)	11.1(-33.3~77.8)	11.1(-44.5~66.7)	1.000
Nottingham health Profile(II)(7)	1.0(-5.0~5.0)	0.0(-5.0~5.0)	0.096
Women's Health Questionnaire	4.5(-30.0~34.0)	1.0(-47.0~18.0)	0.314
somatic symptom(7)	0.5(-14.0~10.0)	1.0(-10.0~7.0)	0.608
depressed mood(7)	2.0(-6.0~9.0)	-1.0(-11.0~9.0)	0.423
cognitive difficulties(3)	0.0(-5.0~3.0)	0.0(-6.0~3.0)	0.710
anxiety/fears(5)	0.0(-6.0~7.0)	0.0(-9.0~6.0)	0.813
sexual functioning(3)	0.0(-5.0~5.0)	-1.0(-7.0~8.0)	0.210
vasomotor symptom(2)	0.0(-3.0~3.0)	0.0(-3.0~2.0)	0.756
sleep problem(3)	1.0(-3.0~3.0)	-1.0(-6.0~2.0)	0.004
attraction(2)	0.0(-2.0~5.0)	0.0(-2.0~4.0)	0.437

**by Mann-Whitney U test.*

number of participants was small and the results could not represent general population.

Recently, the usage of oral preparation of HPE is also available in the clinics beside the subcutaneous injection. In Korea, there are few approved statistical outcomes for HPE usage, under the circumstances where the large number of people are favorable using herbal medicines, we can easily assume that the numbers of using HPE will be more than we expected. Although there are some studies which have been shown safety features about usage of HPE[18], some still make concerns about the side effects (19,20).

Conclusion

HPE injections were partially effective in QOL improvement of postmenopausal women. Large population oriented clinical trials to confirm the efficacy and the safety of HPE should be performed.

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