발기부전 환자에서 홍삼농축분말의 유효성 및 안전성: 다기관, 무작위배정, 이중맹검, 위약 대조 임상연구

Efficacy and Safety of Red Ginseng Extract Powder in Patients with Erectile Dysfunction: Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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Purpose: To evaluate the safety and efficacy of red ginseng extract powder (OKBT) for treating erectile dysfunction.
Materials and Methods: Sixty-nine adult patients with mild to moderate erectile dysfunction of various etiologies were randomized to receive placebo or red ginseng extract powder. The red ginseng extract powder used in the present study was named OKBT. The primary efficacy parameter was response to the International Index of Erectile Function (IIEF) erectile function domain at baseline and week 8. Other IIEF domain scores were evaluated as secondary parameters. For safety evaluation, we performed history taking, physical examination, clinical laboratory tests, and hormonal tests at baseline and week 8.
Results: There were no significant differences in the patients' characteristics between the 2 groups. After 8 weeks of administration, primary efficacy (erectile function domain) and all secondary efficacy domains were significantly improved in the OKBT group compared with the placebo group ($p < 0.05$). Notably, even the domain related to sexual desire, frequency and degree of sexual desire, was also improved in the OKBT group ($p < 0.001$). There were no significant adverse reactions with OKBT administration, and there were also no significant differences in the results of laboratory tests between the 2 groups after administration.
Conclusions: Our data show that red ginseng extract powder can be used as an alternative remedy for Korean men suffering from mild to moderate erectile dysfunction. **(Korean J Urol 2009;50:159-164)**

Key Words: Ginseng, Erectile dysfunction, Treatment efficacy

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Introduction

Erectile dysfunction is a common disease that affects approximately 150 million men worldwide. The prevalence of erectile dysfunction is higher in the presence of physiological or psychiatric factors such as increasing age, obesity, diabetes, high blood pressure, and depression.[1] Domestic reports

indicate that more than half of men over 30 years of age suffer from erectile dysfunction, and it is reported that this is closely related not only to increasing age but also to an increase in the occurrence of adult diseases.[2-4]

In Korea, folk remedies for erectile dysfunction use various medicinal ingredients such as ginseng, red ginseng, deer antlers, lyceum, *Cornus* fruit, *Rubus coreanus* fruit, *Cuscuta* seed, and *Schizandra*, while in other countries, herbal medicines such as *Lepidium meyenii* extract [5] or *Ferula hermonis* root extract [6] are used as drugs to improve sexual function. In particular, ginseng is a representative herbal medicine that has been used for a long time in oriental herbal treatments for the prevention and treatment of various diseases, and the effectiveness of ginseng and red ginseng has been reported in animal experimentation as well as in clinical settings.[7-8] However, clinical studies of the safety and efficacy of these herbal medicines for the treatment of erectile dysfunction are lacking. We therefore investigated the safety and efficacy of red ginseng extract powder in clinical application.

Materials and Methods

1. Study Population and Assessment

Study participants were selected from among patients admitted to 2 university hospital urology departments with the chief complaint of continuous erectile dysfunction for at least 3 months from June to October 2007. The study population included 73 adult men, each of whom were fully informed of the purpose of this clinical trial, decided to participate of their own will, and signed a written consent. Each study participant had maintained a single female sex partner for more than 6 months. Erectile dysfunction was defined as the lack of arousal of sufficient penile erection, or the failure to maintain the penile erection for satisfactory sexual intercourse. The degrees of erectile dysfunction were categorized according to the investigatory categories of the International Index of Erectile Function (IIEF) survey and were based on the erectile function domain score; 17 points or more was classified as slight, 11–16 points as moderate, and 0–10 points as high level. High-level erectile dysfunction patients were excluded from the target population of this clinical trial. Moreover, patients who were diagnosed with cardiovascular diseases such as stroke, cardiac infarction, or unstable angina, and those who had used phosphodiesterase-5 (PDE-5) inhibitors or vasodilator self-injection for the treatment of erectile dysfunction in the 2 weeks prior to the start of the clinical trial were excluded from the target population as well. The cause of erectile dysfunction was diagnosed based on the patients' history, physical examination, laboratory results, and the existing diagnostic examination method. If, based on the detailed medical history and consultation, the cause of erectile dysfunction was determined to be due to psychological reasons or interactions with

people, it was defined as psychogenic impotence, and if accompanied by congenital causes, it was defined as complex erectile dysfunction.

The selected subjects were divided into the red ginseng extract powder (OKBT; 200 mg/capsule, 2 times per day, 4 capsules per day) oral administration group and the placebo group, in a randomized and double-blinded manner. Safety and efficacy assessments and examinations were carried out on the subjects during hospital visits before treatment and after 8 weeks of treatment.

The efficacy of treatment was assessed on the basis of the IIEF survey criteria. The erectile function domain of the IIEF was the primary efficacy assessment variable, and other areas of the IIEF, such as orgasmic function, sexual desire, intercourse satisfaction, and the overall satisfaction were secondary efficacy assessment variables.

For the assessment of safety, examinations of patient history, vital signs, and electrocardiograms were carried out before treatment and after 8 weeks of treatment. In addition, the clinical examination included hematology and blood clotting evaluations, blood chemistry testing, urinalysis, HbA1C, total testosterone, and prostate-specific antigen testing. Participants were educated to report abnormal reactions that occurred during or after the administration of drugs. The whole process of the clinical trial was under the supervision of the clinical trials judging committee of each hospital.

2. Drug Manufacture Method

The red ginseng extract powder used in this research, named OKBT was produced by the following refinement process for strengthening of the effective ingredients. Dried ginseng (1 kg) was concentrated by extracting it twice for 3 h each time in 90% ethanol at 60°C, to obtain approximately 100 g of extract. This was dissolved in water, adsorbed by passing through a column filled with the DIAION HP-20 ion exchange resin (Mitsubishi Chemicals Corp., Tokyo, Japan), and then desorbed with 95% ethanol to yield 30 g of a complex ginsenoside mixture which was over 90% pure and contained Rb1, Rb2, Rc, Rd, Re, Rg1, Rf, and small amounts of other ginsenosides. Complex ginsenoside (12 g) was then reacted with beta-glucosidase from *Bacillus* sp. (75°C; 12 h; pH, 6.0) to increase the content of the ginsenoside Rd to over 40%. Ten grams of ginsenoside were obtained from this step, which were then reacted with 10% acetic acid solution 2 1 (80°C; 12 h). After adsorption on a DIAION HP-20 ion exchange resin column, the sample was desorbed with 95% ethanol to yield a 90% pure ginsenoside mixture containing 150 mg Rg2, 110 mg F4, 120 mg Rg6, 2.32 g Rg3, 0.84 g Rg5, 1.27 g Rk1, 1.73 g Rh1, 1.1 g Rh4, 0.73 g Rk3, 80 mg Rh2, 20 mg Rh3, 20 mg Rk2, 40 mg PPT, and 510 mg of other components. The experimental drug OKBT was produced by

mixing 100 mg of this final complex ginsenoside product with 100 mg of 4- to 5-year-old root ginseng extract powder (1:1 weight ratio). For the placebo, 200 mg of microcrystalline cellulose, which has a scent and flavor identical to OKBT, was added. The OKBT and placebo drugs used in this study were provided by BTGin (Geumsan, Korea).

3. Statistical Analysis Method

Clinical trial data of all participants were assessed according to grouping. Continuous data are presented as the mean and standard deviation, and categorical data are presented as frequency and ratio. The differences between the 2 groups were compared using Student's *t*-test for continuous data, and Fisher's exact test for categorical data.

Linear by linear association was used to analyze improvements, if any, as a result of treatment, and analysis of covariance (ANCOVA) was used to assess efficacy. In order to regulate the influence of the mean score before treatment, comparison analysis was performed on the mean score after treatment for each group. A p-value less than 0.05 was used to determine that the results were statistically significant, and the statistics program SPSS 12 (SPSS Inc, Chicago, USA) was used for all statistical tests.

Results

1. Clinical Characteristics

Seventy-three erectile dysfunction patients were enrolled and separated into 2 groups; 37 patients were administrated with OKBT and the other 36 with placebo. Of these subjects, 69 patients completed the medicine efficacy and safety assessment after 8 weeks of treatment, including 35 patients in the OKBT group and 34 in the placebo group). The other 4 patients were discontinued from the clinical trial due to consent withdrawal.

The participant age, marital status and length, and spouse age were not noticeably different between the 2 groups ($p > 0.05$). Drinking history was not noticeably different between the 2 groups, but there were more past smokers in the OKBT group, and more current smokers in the placebo group, resulting in a statistically significant difference between the 2 groups ($p = 0.012$). Categorization of the cause of erectile dysfunction did not show a difference between the 2 groups ($p = 1.000$), and total serum testosterone and prostate specific antigen levels were all in the normal range in both groups with no noticeable differences ($p > 0.05$; Table 1).

Table 1. Characteristics of patients

Characteristics	OKBT (n=35)	Placebo (n=34)	p-value
Mean age (years)[a]	53.2±9.7	50.8±8.0	0.256[b]
Marital status			
Mean duration (years)[a]	26.1±10	23.1±8.4	0.169[b]
Mean age of spouse (years)[a]	50.2±8.9	48.4±7.7	0.362[b]
Smoking history (%)			0.012[c]
Smokers	4 (11.4)	14 (41.2)	
Ex-smokers	23 (65.7)	12 (35.3)	
Never smoked	8 (22.9)	8 (23.5)	
Alcohol history (%)			0.296[c]
Drinker	27 (77.1)	22 (64.7)	
Past drinker	4 (11.4)	3 (8.8)	
No drinker	4 (11.4)	9 (26.5)	
Diabetes mellitus (%)	10 (28.6)	5 (14.7)	0.244[c]
Hypertension (%)	8 (22.9)	9 (26.5)	0.785[c]
Etiology of erectile dysfunction (%)			1.000[c]
Psychogenic	16 (45.7)	15 (44.1)	
Organic	17 (48.6)	18 (52.9)	
Mixed	2 (5.7)	1 (2.9)	
Testosterone (ng/ml)[a]	4.5±2	4.7±1.8	0.695[b]
PSA (ng/ml)[a]	1.4±1.4	1.0±0.7	0.215[b]

OKBT: red ginseng extract powder, PSA: prostate-specific antigen, [a]: mean±SD, [b]: Student's t-test, [c]: Fisher's exact test

Table 2. Change from baseline in IIEF erectile score

IIEF questionnaire	Change from baseline in IIEF score (%)			p-value
	No increase	1	≥2	
Q1				<0.001[a]
OKBT	13 (37.1)	12 (34.3)	10 (28.6)	
Placebo	27 (79.4)	5 (14.7)	2 (5.9)	
Q2				<0.001[a]
OKBT	11 (31.4)	13 (37.1)	11 (31.4)	
Placebo	27 (79.4)	5 (13.9)	2 (5.9)	
Q3				0.016[a]
OKBT	18 (51.4)	9 (25.7)	8 (22.9)	
Placebo	28 (82.4)	3 (8.8)	3 (8.8)	
Q4				0.016[a]
OKBT	17 (48.6)	10 (28.6)	8 (22.9)	
Placebo	27 (79.4)	4 (11.8)	3 (8.8)	
Q5				<0.001[a]
OKBT	10 (28.6)	15 (42.9)	10 (28.6)	
Placebo	27 (79.4)	7 (20.6)	0 (0.0)	
Q6				<0.001[a]
OKBT	8 (22.9)	18 (51.4)	9 (25.7)	
Placebo	27 (79.4)	7 (20.6)	0 (0.0)	
Q7				0.016[a]
OKBT	12 (34.3)	15 (42.9)	8 (22.9)	
Placebo	26 (76.5)	2 (5.9)	6 (17.6)	
Q8				<0.001[a]
OKBT	15 (42.9)	9 (25.7)	11 (31.4)	
Placebo	27 (79.4)	6 (17.6)	1 (2.9)	
Q9				0.006[a]
OKBT	20 (57.1)	8 (22.9)	7 (20.0)	
Placebo	28 (82.4)	6 (17.6)	0 (0.0)	
Q10				0.001[a]
OKBT	14 (40.0)	13 (37.1)	8 (22.9)	
Placebo	27 (79.4)	6 (17.6)	1 (2.9)	
Q11				<0.001[a]
OKBT	9 (25.7)	16 (45.7)	10 (28.6)	
Placebo	28 (82.4)	5 (14.7)	1 (2.9)	
Q12				0.001[a]
OKBT	13 (37.1)	14 (40.0)	8 (22.9)	
Placebo	28 (82.4)	3 (8.8)	3 (8.8)	
Q13				0.033[a]
OKBT	14 (40.0)	15 (42.9)	6 (17.1)	
Placebo	25 (73.5)	5 (14.7)	4 (11.8)	
Q14				0.001[a]
OKBT	13 (37.1)	14 (40.0)	8 (22.9)	
Placebo	29 (85.3)	2 (5.9)	3 (8.8)	
Q15				0.002[a]
OKBT	12 (34.3)	15 (42.9)	8 (22.9)	
Placebo	23 (67.6)	10 (29.4)	1 (2.9)	

IIEF: International Index of Erectile Function, OKBT: red ginseng extract powder, [a]: Linear by linear association test

Table 3. Results for primary efficacy (erectile function domain) analysis

Group	Baseline	Last observ.	p-value
OKBT (n=35)[a]	17.2±9.4	23.2±7.3	0.003[b]
Placebo (n=34)[a]	17.7±8.2	19.6±8.3	

IIEF: International Index of Erectile Function, Last observ.: last observation after 8 weeks, OKBT: red ginseng extract powder, [a]: mean±SD, : analysis of covariance (ANCOVA) test

Table 4. Results of the secondary efficacy (IIEF domain except erectile function) analysis

Domain	Group	Baseline	Last observ.	p-value
Intercourse satisfaction[a]	OKBT (n=35)	6.5±3.6	9.7±2.9	0.009[b]
	Placebo (n=34)	7.2±3.7	8.6±3.2	
Orgasmic function[a]	OKBT (n=35)	6.1±3.6	7.7±2.5	0.021[b]
	Placebo (n=34)	6.7±3.0	7.1±3.0	
Sexual desire[a]	OKBT (n=35)	4.9±1.8	6.9±1.6	<0.001[b]
	Placebo (n=34)	5.6±1.9	5.8±1.8	
Overall satisfaction[a]	OKBT (n=35)	5.2±2.4	6.9±2.3	0.024[b]
	Placebo (n=34)	5.5±1.9	6.1±2.1	

IIEF: International Index of Erectile Function, Last observ: last observation after 8 weeks, OKBT: red ginseng extract powder, [a]: mean±SD, [b]: analysis of covariance (ANCOVA) test

Table 5. Results for adverse events in overall cases

Adverse events	OKBT (n=35)	Placebo (n=34)
Respiratory system disorder (%)		
Acute nasopharyngitis	0	3 (8.8)
Rhinitis	1 (2.9)	0
Skin and appendages disorder		
Eczema	1 (2.9)	0
Skin disease	1 (2.9)	0
Gastrointestinal system disorder		
Diarrhea	1 (2.9)	0
Anal bleeding	0	1 (2.9)
Central and peripheral nervous system disorder		
Voice disorders	1 (2.9)	0
Visual system disorder		
Ophthalmalgia	1 (2.9)	0
Genital system disorder		
Perineal pain	1 (2.9)	0
Generalized disorder		
Chest pain	1 (2.9)	0
Urologic system disorder		
Renal stone	0	1 (2.9)
Total (%)	8 (23.2%)	5 (14.5)

OKBT: red ginseng extract powder

2. Analysis of Improvement After Treatment

We determined whether there was an increase in IIEF erectile score after treatment, compared to the score before treatment. The results show that in all IIEF categories, there was a noticeable increase in the IIEF erectile score in the OKBT group compared to the placebo group. ($p < 0.05$; Table 2). However, for Q3 and Q9, the IIEF erectile score increased in less than 50% of the patients after OKBT treatment.

3. Primary Efficacy Assessment Variable: Erectile Function Domain

In order to regulate the influence of the score before treatment, covariance analysis was performed. The results show that compared to the placebo group, the OKBT group shows a noticeably higher mean score in the erectile function domain after treatment ($p = 0.003$; Table 3).

4. Secondary Efficacy Assessment Variables: Intercourse Satisfaction, Orgasmic Function, Sexual Desire, and Overall Satisfaction

We assessed the efficacy of treatment in terms of secondary variables such as intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction using covariance analysis. The results show that in all domains, the OKBT group had a noticeably higher mean score after treatment compared to the placebo group ($p = 0.009$, 0.021, < 0.001, and 0.024 respectively; Table 4).

5. Drug Safety

During the 8-week treatment period using OKBT and placebo, a total of 14 cases of abnormal reactions were seen in 11 subjects, of whom 8 (23.2%) were from the OKBT group, and 5 (14.5%) were from the placebo group. These reactions were not specifically associated with the experimental drug and there were no serious abnormal reactions (Table 5). A comparison of laboratory examination results of

each group from the 8-week follow-up showed no differences in any category except in general blood WBC counts.

Discussion

With the increase in adult diseases due to industrialization, the increase in mean age, and changes in social perspectives such as a reluctance to discuss erectile dysfunction, there is an increase in the number of patients visiting the hospital with sexual dysfunction as their chief complaint. Currently, the major primary treatment drug for erectile dysfunction is an oral PDE-5 inhibitor, which inhibits PDE-5 in the smooth muscle of the corpus cavernosum penis, prevents the breakdown of cGMP, and allows relaxation of the smooth muscle and the continuous dilation of penis blood vessels[9] However, in the case of the oral erectile dysfunction drugs, side effects such as indigestion, headache, facial flushing, and rhinitis occur, and severe visual disability or cardiovascular side effects occur on rare occasions.[10-15] In contrast, herbal remedies for erectile dysfunction have the advantages of relatively high treatment efficacies with negligible side effects, which is the reason why many are used traditionally. A recent report of Kam et al.[16] shows that cornus fruit complex extract powder significantly improves sexual function without causing abnormalities in hematology or blood chemistry examinations. This sexual function improvement effect of cornus fruit complex extract powder was seen vividly in a group with severe sexual dysfunction, and caused slight side effects that were relieved without any treatment; indicating that cornus fruit complex extract powder is safe and causes significant sexual function improvement.

There has been a report that ginseng affects the major causes of erectile dysfunction such as high blood pressure, high cholesterol level, aging, and other metabolic diseases by decreasing glucose level and blood pressure, and it has been proven that there is an improvement in cholesterol metabolism, a decrease in peripheral blood vessel dilation, and decreased peripheral resistance of the respiratory system, resulting in improvement in the peripheral blood circulation. Based on these results, numerous studies of the effects of ginseng on penis erection are being carried out. [17-18] The treatment mechanism of ginseng in the case of erectile dysfunction involves an increase in the production of nitric oxide (NO), which improves abnormalities in blood vessel endothelial cells and smoothens blood circulation by decreasing peripheral blood vessel dilation and peripheral resistance. Moreover, in the case of red ginseng, which is produced by baking through steaming of ginseng or other methods, there are fewer side effects due to its constitution than with unrefined ginseng, from the perspectives of oriental medicine. Further, it is known that during the steaming and drying process, certain ginsenoside components are eliminated or newly formed,

increasing the effectiveness of treatment. Animal experimentation results using red ginseng show that it affects NO and calcium transport channels, resulting in relaxation of the corpus cavernosum penis smooth muscles. Particularly, the saponin differentiation product of red ginseng increases the relaxation and internal pressure of the corpus cavernosum penis smooth muscles, which in turn enhances the erectile ability of the penis, and this effect is confirmed to be different depending on its components. [19-21]

Based on these findings, we used the IIEF survey to assess the efficacy and safety of OKBT in clinical applications by comparing treatment efficacies between the OKBT and placebo groups. There was a significant treatment effect in the OKBT group than in the placebo group in the assessment of primary efficacy on the erectile function domain. Additionally, the OKBT group showed statistically significant treatment effects compared to the placebo group in the assessment of secondary efficacy, and there were no drug-related abnormal reactions or special side effects regarding the drug's safety assessment. Interestingly, the OKBT group showed a significant treatment effect compared to the placebo group with respect to the frequency and relativity of sexual desire. In traditional medicine, which uses phytochemicals extracted from esculent plants, disease is defined as inability of the body to control appropriate overall functioning, and traditional medicine focuses on curing this root cause of disease. Therefore, traditional medicine approaches erectile dysfunction from the perspective that there is a partial disability in the body. Indeed, protodioscin extracted from *Tribulus terrestris* L. is known to enhance sexual desire[22]; other reports indicate that nutritional supplements including ginseng significantly increase sexual desire in females.[23-24] These results may be related to our observation of increased sexual desire in the OKBT group; additional research involving a larger study group is needed in this area. High-level erectile dysfunction patients were excluded from this study, and in certain categories of the IIEF, there were cases in which more than half of the patients who received OKBT treatment did not improve; this poses limits to the use of OKBT as an erectile dysfunction drug. However, OKBT is safe and has been determined to significantly improve sexual function in patients with slight and moderate level erectile dysfunction.

Conclusion

Red ginseng extract powder had a significant effect on overall sexual function in patients with slight and moderate level erectile dysfunction, without any toxic side effects, compared to the placebo group; in particular, an enhancement of sexual desire was observed. Further studies involving more patients and including high-level erectile dysfunction patients are required, and efforts should be made to discover the mechanisms underlying the enhancement of

sexual desire. However, it may be used as an alternative drug for patients who have side effects or repulsion to oral erectile dysfunction treatment.

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