ORIGINAL ARTICLE

Effects of Korean Red Ginseng on Semen Parameters in Male Infertility Patients: A Randomized, Placebo-Controlled, Double-Blind Clinical Study*

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ABSTRACT **Objective:** To investigate the effects of Korean red ginseng (KRG) on semen parameters in male infertility patients in a randomized, double-blind, placebo-controlled study. **Methods:** A total of 80 male infertility patients with varicocele were recruited from April 2011 to February 2012. The subjects were then divided into the following four groups: non-varicocelectomy (V)+placebo (P) group, V+P group, non-V+KRG group (1.5-g KRG daily), and V+KGR group (1.5-g KRG daily). Semen analysis was performed and hormonal levels were measured in each treatment arm after 12 weeks. **Results:** All groups but not the non-V+P group, showed significant improvements in sperm concentrations, motility, morphology, and viability at the end of the study. However, there were no significant differences in serum follicle-stimulating hormone, luteinizing hormone, and testosterone among groups. The incidence of adverse events was low, and all events were assumed to be unrelated to the treatments administered. **Conclusions:** Although the exact mechanism by which KRG improves spermatogenesis remains unclear, KRG may be a useful agent for the treatment of male infertility. Nevertheless, additional studies to evaluate the optimal dose and duration of treatment are needed.

KEYWORDS *Panax ginseng*, male infertility, spermatogenesis

Assisted reproductive techniques (ART) have become increasingly popular for the management of male infertility. However, curable male factors should be identified and treated to enhance male fertility prior to performing ART because this improves both the chance of natural pregnancy and the success rate of ART by enhancing sperm quality. Only a small number of infertility-related disorders in males are currently treatable, such as hypogonadotropic hypogonadism using gonadotropins, and obstructive azoospermia with reconstructive surgery. In addition, evidence-based medicine has revealed that most empirical treatments are ineffective. Similarly, anti-estrogens, such as tamoxifen and kallikrein, and other agents such as vitamin C, vitamin E, carnitine, and glutathione are either ineffective or are still being evaluated.[1,2]

Korean red ginseng (KRG) is a health-promoting herbal medicine that has long been used to treat various diseases in Korea. Many clinical studies have been performed to elucidate the therapeutic characteristics of ginseng. KRG is effective in many diseases including cancers, hypertension, Alzheimer's disease, diabetes, acquired immune deficiency syndrome, and sexual dysfunction.[3-6] Several studies have also reported that ginseng improves spermatogenesis in animals.[7,8] These effects were probably caused by anti-oxidant and anti-aging actions, as well as modulation of the hypothalamus-pituitary-testis axis.[9-12] In this study, the effects of KRG on semen parameters in male infertility patients were investigated.

METHODS

Patient Selection

Eighty male infertility patients with varicocele were recruited between April 2011 and February 2012. For inclusion in the study, patients should be males, 25–45 years of age, who had complained of infertility for at least 12 months, and had no history of surgical or medical treatments for infertility. Increased retrograde flow in the internal spermatic vein with venous diameter > 3 mm during the

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Valsalva maneuver on scrotal ultrasonography was used as an indicator of varicocele.[13] Varicocele was graded according to the criteria presented by Lyon, et al.[14] Grade Ⅰ, palpable only with the Valsalva maneuver; Grade Ⅱ, palpable without the Valsalva maneuver; Grade Ⅲ, visible from a distance. The exclusion criteria were as follows: (1) a history of vasectomy or obstructive azoospermia; (2) chromosomal abnormalities; (3) hypogonadism or pituitary abnormalities; (4) anatomical abnormality of the genitals; (5) significant hepatopathy (liver enzymes elevated 2–3-fold higher than the normal range); (6) renal insufficiency (serum creatinine level > 2.5 mg/dL); and (7) medical treatment for infertility during the past 4 weeks.

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of Pusan National University Hospital. Written informed consent was obtained from each patient prior to inclusion.

Study Design

This was a randomized, double-blind, placebo-controlled study. The study protocol involved a 1–2-week period to check baseline characteristic data, followed by four 12-week randomly allocated treatment arms (Figure 1). At the initial visit (visit 1), a complete medical history was obtained and a physical examination was performed in all subjects. Semen analysis and hormonal status, including serum total testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), were checked at the screening visit. The subjects were then randomized into four groups: non-varicocelectomy (V)+placebo (P) group (20 cases, placebo capsules); V+P group (20 cases, placebo capsules and varicocelectomy); non-V+KRG group [20 cases, 3 capsules of KRG (500 mg/capsule) daily] and V+KRG group [20 cases, 3 capsules of KRG (500 mg/capsule) daily and varicocelectomy]. Surgical microscope-assisted varicocelectomy using the subinguinal approach was conducted by a single surgeon. Random permuted blocks were used for patient randomization. When treatments were finished in all treatment arms, semen analysis and determination of hormonal levels were performed after 2-week washout period.

KRG and Placebo Capsules

The KRG capsules and placebo were provided by the Korean Ginseng Corporation (Daejeon, Korea). KRG powder was manufactured from roots of a 6-year-old red ginseng, *Panax ginseng* Meyer, harvested in Republic of Korea. KRG was made by steaming fresh ginseng at 90–100 ℃ for 3 h and then drying at 50–80 ℃.

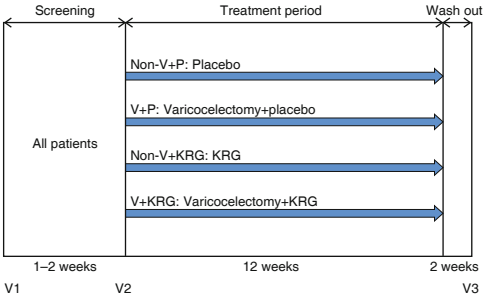

Figure 1. Study Design

KRG powder was prepared from grinded red ginseng (500 mg/capsule). KRG was analyzed by high-performance liquid chromatography. KRG extract contained major ginsenoside-Rb1: 4.26 mg/g, -Rb2: 1.62 mg/g, -Rc: 1.80 mg/g, -Rd: 0.29 mg/g, -Re: 1.71 mg/g, -Rf: 0.67 mg/g, -Rg1: 2.61 mg/g, -Rg2: 0.20 mg/g, -Rg3: 0.13 mg/g, and other minor ginsenosides. During the study period, 3 capsules were taken daily for 12 weeks. The placebo capsules were identical in shape, color, and taste.

Measurements

Semen specimens were collected by masturbation, and an experienced technician performed manual semen analysis for sperm concentration, percent motility, viability, and Kruger/strict morphology using World Health Organization (WHO) methodologies (4th edition). Normal values used here were based on the WHO 2010 reference limits.[15] Serum concentrations of FSH and LH were measured using chemiluminescence assays, and serum total testosterone was quantified by radioimmunoassay. The hormonal status of all patients was recorded at the initial screening visit and post-treatment.

Statistical Analysis

All variables were compared between groups at the end of the 12-week treatment. Data are presented as means ± standard deviation. Within each group, changes from baseline and comparison to non-treatment group (Non-V+P) were assessed by Mann-Whitney U test. One-way analysis of covariance

Table 1. Baseline Patient Characteristics ($\bar{x} \pm s$)

Item	Non-V+P (20 cases)	V+P (19 cases)	Non-V+KRG (20 cases)	V+KRG (18 cases)	*P* value*
Age (years)	33.5 ± 5.9	35.1 ± 6.1	33.3 ± 5.3	34.7 ± 5.4	0.661
Duration of infertility (months)	20.5 ± 7.9	22.1 ± 8.4	23.2 ± 7.7	22.7 ± 9.5	0.224
Sperm concentration (million/mL)	14.0 ± 5.1	13.7 ± 6.1	12.8 ± 6.1	13.4 ± 4.2	0.282
Sperm motility (% motile forms)	24.6 ± 7.3	20.6 ± 7.7	22.2 ± 6.8	20.6 ± 8.4	0.615
Sperm morphology (% normal)	5.1 ± 3.3	5.6 ± 3.7	5.5 ± 3.3	5.31 ± 3.6	0.505
Sperm viability (% viable)	56.3 ± 11.6	55.3 ± 10.6	48.5 ± 12.3	50.2 ± 11.7	0.573
FSH (IU/L)	4.1 ± 1.9	4.5 ± 2.1	4.3 ± 1.6	4.3 ± 1.9	0.852
LH (IU/L)	4.5 ± 1.2	4.6 ± 0.9	4.2 ± 1.9	4.1 ± 1.1	0.275
Testosterone (ng/dL)	481.1 ± 50.5	501.2 ± 52.8	493.4 ± 60.1	488.1 ± 55.3	0.316
Grade Ⅲ (%)	60	65	60	65	0.881

Notes: *Kruskal-Wallis test

Table 2. Changes in Semen Parameters after Treatment ($\bar{x} \pm s$)

Group	Case	Time	Concentration (million/mL)	Motility (% motile forms)	Morphology (% normal)	Viability (% viable)
Non-V+P	20	Pre-treatment	14.0 ± 5.1	24.6 ± 7.3	5.1 ± 3.3	56.3 ± 11.6
		Post- treatment	1.3 ± 1.6	–0.1 ± 0.5	–0.1 ± 0.1	–1.0 ± 0.1
V+P	19	Pre-treatment	13.7 ± 6.1	20.6 ± 7.7	5.6 ± 3.7	55.3 ± 10.6
		Post- treatment	7.5 ± 3.4$^{**\triangle\triangle}$	19.4 ± 7.7$^{**\triangle\triangle}$	1.9 ± 0.3$^{**\triangle\triangle}$	20.1 ± 6.2$^{**\triangle\triangle}$
Non-V+KRG	20	Pre-treatment	12.8 ± 6.1	22.2 ± 6.8	5.5 ± 3.3	48.5 ± 12.3
		Post- treatment	3.2 ± 2.6$^{*\triangle}$	11.8 ± 7.3$^{**\triangle\triangle}$	1.2 ± 0.3$^{**\triangle\triangle}$	8.8 ± 4.2$^{*\triangle}$
V+KRG	18	Pre-treatment	13.4 ± 4.2	20.6 ± 8.4	5.31 ± 3.6	50.2 ± 11.7
		Post- treatment	8.1 ± 4.3$^{**\triangle\triangle}$	24.2 ± 8.1$^{**\triangle\triangle}$	2.8 ± 0.5$^{**\triangle\triangle}$	27.7 ± 7.5$^{**\triangle\triangle}$

Notes: $^{*}P<0.05$, $^{**}P<0.01$, compare with pre-treatment (by ANCOVA); $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$, compare with the non-V+P group (by Mann-Whitney U Test)

(ANCOVA) was used to evaluate treatment effects of KRG. In addition, two-way analysis of variance (ANOVA) was performed to evaluate the interaction of varicocelectomy and KRG. Statistical analyses were performed using SPSS® for Windows ver. 15.0 (SPSS Inc., Chicago, IL). In all analyses, $P<0.05$ was taken to indicate statistical significance.

RESULTS

General Condition

Of the total of 80 subjects, 3 withdrew during screening because they refused varicocelectomy. Seventy-seven subjects (20 in the non-V+P group, 19 in V+P group, 20 in the non-V+KRG group, and 18 in the V+KRG group) completed the study. There were no differences in the mean age or duration of infertility among groups. There were also no differences in baseline semen parameters, including sperm concentration, motility, morphology, viability, hormone levels, and grade of varicocele (Table 1). After the 12-week trial, data from the 77 participants were compared and analyzed.

Changes in Semen Parameters after Treatment

The changes in serum parameters at the end of the study period are shown in Table 2. The V+P, non-V+KRG, and V+KRG groups showed significantly improvements of semen parameters at the end of study. These improvements were also significant comparing with the Non-V+P group. The changes in sperm concentration, motility, morphology and viability from baseline to end of study differed significantly across the 4 arms by one-way ANCOVA. There was no significant varicocelectomy-KRG interaction in change of sperm concentration, motility, morphology and viability by two-way ANOVA (P=0.73, 0.78, 0.68 and 0.80, respectively); the varicocelectomy and KRG main effect were statistically significant.

Changes in Hormonal Parameters after Treatment

There were no significant differences in serum FSH, LH, or testosterone between groups (Table 3). Although the non-V+KRG group and V+KRG group showed slight increases in serum testosterone levels, these changes were not significant.

Table 3. Changes in Hormonal Parameters after Treatment ($\bar{x} \pm s$)

Group	Case	FSH (IU/L)	LH (IU/L)	Testosterone (ng/dL)
Non-V+P	20	0.1 ± 0.1	–0.2 ± 0.2	9.6 ± 10.1
V+P	19	0.2 ± 0.1	–0.1 ± 0.2	5.6 ± 9.8
Non-V+KRG	20	0.1 ± 0.2	0.2 ± 0.2	20.5 ± 14.5
V+KRG	18	0.2 ± 0.2	–0.2 ± 0.2	19.3 ± 12.5

Adverse Effects

Adverse events were mild and resolved spontaneously by the end of the trial. The reported events consisted of two allergic reactions, two common colds, two headaches, and one case of mild nausea. Most of the events were assumed to be unrelated to the trial.

DISCUSSION

Many empirical treatments have been used to improve the quality and concentration of sperm, although good results have not been achieved. As gonadal sex steroid hormones have important roles in spermatogenesis and gonadotropin treatments have been effective in some cases of hypogonadism-related male infertility, hormonal or anti-hormonal therapies have been widely used in cases of idiopathic male infertility. However, success rates have been unsatisfactory.[16] Meta-analyses of published controlled studies regarding androgen and anti-estrogen treatments did not show sufficient evidence that these treatments can improve sperm quality and increase the likelihood of pregnancy.[1] In addition, empirical medications, such as kallikrein and antioxidative agents, including vitamins C and E, carnitine, and glutathione, have either been shown to be ineffective or are still being evaluated.[1,2] Many groups have attempted to identify effective medical treatments for male infertility and the present study was performed to evaluate the efficacy of KRG in male infertility.

Several *in vitro* studies have suggested that ginseng enhances spermatogenesis, although the mechanism by which this occurs remains unclear. *In vivo*, KRG induces spermatogenesis in rats by activating cAMP-responsive element modulator (CREM).[17] The administration of ginsenoside-Rb1 increased the release of LH from the hemi-anterior pituitary glands of male rats in a dose-dependent manner.[9] KRG improved sperm motility and survival in guinea pigs exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin by protecting the blood-testis barrier.[8] In addition, KRG improved spermatogenesis by inducing the expression of glial cell-derived neurotropic factor (GDNF), an important growth factor that facilitates communication between sertoli cells and spermatogonia.[18] Furthermore, KRG exerts an anti-aging effect by up-regulating C21-steroid hormone metabolism via Cyp11a1 in senescent rat testes.[19] Consistent with these observations, rats treated with cultured wild *Panax ginseng* root showed some improvement in sperm number and testis morphology after exposure to tetrachlorodibenzo-p-dioxin.[5] Jang, et al[20] reported that sperm motility and progressiveness were significantly decreased in mice treated with ethanol, whereas the administration of red ginseng extract minimized the negative effects of ethanol toxicity. Some *in vitro* studies using human samples have also been performed. Ginsenoside Rb2 promoted sperm progression, and ginsenoside Rc enhanced both sperm motility and progression.[10] Ginsenoside Rb2 also promoted human sperm capacitation and acrosome reactions through the nitric oxide/cGMP pathway.[11] These *in vitro* studies suggested that KRG has potential for the medical treatment of male infertility. However, there have been few controlled human clinical studies to evaluate the effects of KRG on spermatogenesis in male infertility patients.

In this study, the patients in the KRG-treated groups with or without varicocelectomy showed significantly improved semen parameters in terms of sperm concentration, viability, motility, and morphology. These observations were consistent with the findings of previous *in vitro* studies.[7,8,10,18-20] Although the effects were more prominent in patients who also underwent varicocelectomy, KRG monotherapy also showed significant improvement in semen parameters. These results suggested that KRG could be considered as an adjuvant medical treatment for varicocele-related male infertility or as an empirical treatment for idiopathic male infertility. However, we detected no changes in hormone levels. In contrast, Salvati, et al[12] reported increases in plasma total testosterone levels in patients treated with *Panax ginseng*. Tsai, et al[9] also reported that the administration of ginsenoside Rb1 increased LH secretion in rats. Therefore additional studies are necessary to better understand the effects of KRG on hormone-related male fertility.

The present study population consisted of

patients with varicocele, which is well known to be the main cause of male infertility because it impairs spermatogenesis via several pathophysiological mechanisms.[13] Current research suggests that oxidative stress plays a major role in the pathophysiology of varicocele-induced male infertility, although the mechanisms underlying these effects have not been evaluated in detail.[1,21] Therefore, we hypothesized that patients with varicocele were appropriate for this study because the ability of KRG to scavenge oxygen radicals is well known *in vitro*[22,23] and in other systems.[10-12]

Panax ginseng contains various pharmacologically active ingredients, including ginsenosides, polyacetylenes, polyphenolic compounds, and acidic polysaccharides.[24] The most important and well understood of these active ingredients are ginsenosides, a diverse group of triterpenoid saponins. Approximately 150 ginsenosides have been identified to date.[25] However, the diverse array of effects of *Panax ginseng* cannot be mediated by ginsenosides alone. As it is difficult to elucidate the *in vivo* pharmacological action or mode of action of each individual ginsenoside; it is generally accepted that ginsenosides and other active ingredients act in concert.[8]

There have been few studies of the optimal dose of KRG. However, a dose of 1.5 g of KRG root powder per day was used in the present study, consistent with the doses ranging from 0.8 to 6 g per day in published clinical studies using KRG.[26] There have also been no comparative studies regarding prescribed doses and real concentrations of KRG in humans. As such, the optimal plasma concentrations of ginseng after oral ingestion that are required to improve spermatogenesis remain unclear. This lack of additional pharmacokinetic data regarding the optimal dose of KRG represents a limitation of this study.

The incidence of adverse events in this study was low, and all events were assumed to be unrelated to the trial; all symptoms had resolved by the end of the trial. Reports of adverse events with red ginseng are rare, and those that have been reported were mild.[27] Nevertheless, the possibility of adverse events caused by high doses of ginseng should be considered, and so future studies to assess the optimal doses are critical.

Several limitations of this study should be noted. Although we identified significant improvements in semen parameters after KRG treatment, we did not evaluate additional parameters, such as the levels of reactive oxygen species in seminal plasma, the sperm DNA fragmentation index, seminal plasma total antioxidant capacity, and pathological changes in the testes. Further studies to assess these parameters would enhance our understanding of the mechanism of action of KRG. In addition, we assessed only varicocele-related infertility patients. This could restrict the applicability of our results to idiopathic male infertility. Finally, the number of patients and the treatment duration were not sufficient to elucidate the effects of KRG on spermatogenesis.

In summary, we demonstrated that treatment with KRG for 12 weeks improved sperm concentration, motility, morphology, and viability. Although the exact mechanisms by which KRG enhanced spermatogenesis are yet to be elucidated, KRG may be a useful agent for the treatment of male infertility. Future studies to establish the optimal treatment dose and duration of treatment for male infertility are needed.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Park HJ was responsible for the concepts and design of this study. Choe S and Park NC participated in the literature research, clinical studies and data acquisition. Park HJ, Choe S and Park NC participated in the data analysis and statistical analysis. Park HJ and Park NC participated in the literature research, manuscript preparation and manuscript editing.

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