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□원 저□

Effect of Korean Red Ginseng on Sleep : A Randomized, Placebo-Controlled Trial

고려 홍삼이 수면의 질에 미치는 영향 : 무작위 위약-대조군 연구

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초 록

목 적 : 인삼은 한국을 비롯한 아시아 국가에서 전통적으로 불면증의 치료에 사용되어 왔으며 쥐를 이용한 동물실험에서 수면을 촉진시키는 효과가 있다는 연구 결과가 있어왔다. 하지만 이러한 효과를 입증할 만한 임상 실험은 거의 이루어지지 않았다. 이에 본 연구에서는 고려 홍삼이 수면에 미치는 영향을 알아보고자 한다.

방 법 : 건강한 성인 남성 20명을 대상으로 하였으며 이들은 무작위로 홍삼군과 위약군에 배정되어 2주간의 실험이 진행되었다. 홍삼군의 경우 하루 4,500 mg의 홍삼을 섭취하였다. 실험 시작시점과 2주 후인 종료시점에 수면다원검사를 시행하여 두 군간의 변수의 변화를 비교하였다.

결 과 : 총 15명의 대상자, 즉 홍삼군 8명과 위약군 7명이 수면다원검사를 시행 받았으며 홍삼군이 위약군 보다 실험 종료 시점에서 3단계 수면이 증가한(p=0.087) 반면에 2단계 수면이 감소하는(p=0.071) 경향을 나타냈다.

결 론 : 본 연구 결과는 고려 홍삼이 깊은 잠은 증가시키고 얕은 잠은 감소시키는 경향이 있음을 보여준다. 이는 통계적으로 유의한 결과는 아니지만 홍삼이 수면의 질을 향상시키는 데 효과적임을 짐작하게 한다. 그러나, 보다 많은 대상군과 충분한 홍삼 용량으로 보다 긴 기간 동안 진행되는 연구를 통해 고려 홍삼의 수면에 대한 효과를 확인할 필요가 있다.

중심 단어 : 고려 홍삼 · 수면 · NREM · 수면다원검사.

INTRODUCTION

Panax ginseng, the herbal root of *Panax ginseng* C. A. Meyer and also known as Asian or Korean ginseng, has been used for thousands of years in Korea as a traditional medicine to promote health and treat illness. Although there are various forms of ginseng processed differently for use, white ginseng and red ginseng are used most widely. White ginseng is air-dried, while red ginseng is produced by steaming and drying. It has been reported that red ginseng is pharmacologically more active than white ginseng (Baek et al. 1996). The different biological activities of red and white ginsengs may result from production of different chemical constituents during the steaming process (Baek et al. 1996). Korean red ginseng is known to have broad efficacious effects against hypertension, diabetes, pain and cancer, and to counteract weakness (Baek et al. 1996).

Ginseng has a complex profile of activity including antioxidant, anti-inflammatory, anti-apoptotic and immune-stimulatory properties (Xiang et al. 2008). With these properties,

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ginseng has effects of stabilizing and balancing the whole physiology. Researchers have found that the active components in ginseng include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, vitamin, minor elements and enzymes (Xiang et al. 2008). Ginsenosides or ginseng saponins are the major active ingredients in ginseng and more than 40 different ginsenosides have been identified (Baek et al. 1996). The ginsenoside content of ginseng varies depending on the Panax species, the plant age, the parts of the plant, the preservation method, the season of harvest and the extraction method. Ginsenosides are found only in Panax species, many of which exist in very small amounts, and are believed to be responsible for most of the actions of ginseng. Ginsenosides act through diverse mechanisms and it is suggested that each ginsenoside seem to have its own specific tissue-dependent effects (Murphy and Lee, 2002).

Although many mechanisms and its components remain unknown, ginseng has long been clinically used for treatment of insomnia (Xiang et al. 2008). Although the efficacy in humans is not clearly established, it has been shown in previous studies that ginseng exerts a stabilizing effect on sleep-waking disturbances in rats. Rhee et al. (1990) showed that ginseng can actually normalize the sleep-waking disturbances caused by sleep deprivation in rats. In freely behaving rats after continued 1-week intake of Panax ginseng, the amount of wakefulness and slow wave sleep (SWS) during the 12-h light period slightly but significantly decreased and increased, respectively. They concluded that the health-improving effect of Panax ginseng may be, at least in part, related to its sleep-modulatory, both sleep-enhancing and sleep-stabilizing, activity. Lee et al. (1990) reported the amount of wakefulness and SWS significantly fluctuated during 48h food deprivation and subsequent recovery periods in freely behaving male rats while such fluctuations were significantly less prominent in age-matched male rats chronically treated with Panax ginseng.

The purpose of this study was to investigate the effect of Korean red ginseng on change of sleep architecture in humans.

METHODS

1. Participants

A total of 20 healthy young male volunteers aged 19 to 25 years were studied. They were recruited through on-line and off-line advertisement. They were selected based on review of preliminary sleep questionnaires and sleep diaries followed by an interview with a board-certified psychiatrist. All subjects had regular sleep and wake habits and had neither psychiatric disorders nor cognitive problems. For assessment of subjective sleep quality, the subjects completed Pittsburgh Sleep Quality Index (PSQI), Athens Insomnia Scale (AIS) and Epworth Sleepiness Scale (ESS) in addition to sleep questionnaires and sleep diaries. During 2 weeks of trial, they were advised to maintain their usual sleep-wake habits and were instructed to refrain from medications and excessive alcohol. During this period, 3 of the participants wanted to be dropped out of the trial and 2 others were excluded being suspected of a sleep disorder after first polysomnographic recording. As a result, only 15 participants were included. All volunteers signed informed consent prior to entering the study.

2. Procedure

The subjects were randomly assigned to red ginseng or placebo group and were administered red ginseng or placebo accordingly for 2 weeks. The total daily dose of ginseng was 4,500 mg ; 1,500 mg were administered 3 times a day. The polysomnographic recordings were made at baseline and at 2 weeks after. The effects of red ginseng and placebo on sleep were assessed by comparing the changes in polysomnographic variables between the two groups. The polysomnographic recordings were performed using an Embla S7000 and Somnologica 4 (Medcare, Iceland) system. Electroencephalographic (EEG) leads, electrooculogram (EOG) leads and chin electromyogram (EMG) were placed according to standardized procedures. Airflow from nasal and oral breathing, chest and abdominal respiratory effort, sound of breathing and oxygen saturation were measured. Bilateral electromyogram leads were placed on the anterior tibialis muscle to monitor leg movements. Electroencephalograms (EEG) were positioned based on the international 10−20 system. The polysomnographic recordings were interpreted according to American Academy of Sleep Medicine manual (Iber 2007).

3. Statistical Analysis

For comparison of demographic variables between the two groups, the independent t-test was performed using SPSS for Windows. Inter-group comparisons of changes in polysomnographic variables were assessed by means of repeated measure analysis of variance (ANOVA). All statistical analyses were two-tailed, and the level of statistical significance was set at $p<0.05$.

RESULTS

A total of 15 subjects, 8 from red ginseng group and 7 from

placebo group, were included to undergo polysomnographic procedures. There were no significant differences between red ginseng and placebo groups in demographic variables (Table 1) except for height (p=0.010), as well as subjective sleep quality as measured by PSQI (p=1.000), AIS 8 (p=0.232), AIS 5 (p=0.232) and ESS (p=0.637). The changes of total sleep time, sleep latency and sleep efficiency between the red ginseng and placebo group were not significantly different. The red ginseng group showed increased stage 3 sleep (p=0.087) and decreased stage 2 sleep (p=0.071) from the baseline compared with the placebo group. However, this increase in deep sleep was not statistically significant (Table 2). Although not statistically significant, the total sleep time decreased in red ginseng group.

DISCUSSION

We have found that Korean red ginseng tends to increase deep sleep and decrease shallow sleep. This result is in line with the belief that ginseng is effective in sleep and prove further that it has sleep stabilizing effect. Although efficacy in animals does not necessarily equate with efficacy in humans, our result is in line, at least in part, with previous findings that Korean red ginseng increased total and NREM sleep in rats (Ma et al. 2008).

The exact mechanism of ginseng is still unknown, but there has been a previous report that the anxiolytic effects of ginseng appear to be related to the GABA-benzodiazepine-chloride channel receptor complex. Park et al. (2005) reported that ginsenosides interact with the ligand-bindings of the $GABA_A$ and $GABA_B$ receptors and induce sedative effects at higher doses and anxiolytic-like effects at lower doses. Active maintenance of slow wave sleep (SWS) is dependent on increased GABA release that continuously suppresses activity in the various wake-promoting regions of the brain.

Korean red ginseng also has an important role as a mo-

Table 1. Comparison of demographic variables between red ginseng and placebo groups

Variables	Red Ginseng	Placebo	*t*	*p*-value
Age (yr)	23.50 (1.20)	23.43 (2.07)	0.083	0.935
Height (cm)	177.75 (4.62)	171.43 (3.26)	3.016	0.010
Weight (kg)	71.11 (10.85)	66.86 (8.28)	0.843	0.414
BMI (kg/m^2)	22.46 (2.91)	23.13 (3.20)	−0.426	0.677
Neck circumference (cm)				
Sitting position	36.01 (1.69)	35.19 (1.66)	0.951	0.359
Supine position	35.53 (1.88)	35.47 (0.99)	0.067	0.947
Waist circumference (cm)	80.91 (6.83)	82.60 (7.00)	−0.47	0.645

Data are given as mean (standard deviation). BMI : Body mass index

Table 2. Differences in changes of polysomnography variables between red ginseng and placebo group

Variables of polysomnography	Red ginseng		Placebo		F	P
	Baseline	2 weeks	Baseline	2 weeks		
Time in bed (min)	437.0 (25.3)	421.8 (57.2)	457.5 (17.0)	456.9 (14.5)	2.89	0.113
Total sleep time (min)	406.3 (33.0)	377.8 (55.3)	414.4 (34.4)	432.2 (18.4)	3.63	0.079
S1 sleep stage (%)	17.0 (6.3)	17.9 (8.4)	15.9 (4.1)	14.4 (3.5)	0.70	0.417
S2 sleep stage (%)	44.2 (4.2)	42.9 (3.9)	46.1 (6.8)	48.0 (5.4)	3.88	0.071
S3 sleep stage (%)	6.8 (2.3)	7.3 (2.6)	9.3 (3.3)	8.9 (2.5)	3.44	0.087
S4 sleep stage (%)	11.4 (5.5)	13.2 (6.3)	9.0 (5.7)	8.4 (5.5)	1.87	0.195
REM sleep stage (%)	20.6 (5.5)	19.7 (1.6)	18.8 (7.9)	20.3 (7.7)	0.02	0.886
Wake after sleep onset (min)	17.6 (12.4)	30.2 (28.7)	30.2 (28.7)	14.9 (11.3)	0.10	0.755
Sleep efficiency (%)	93.0 (6.5)	90.0 (9.5)	90.0 (9.5)	90.3 (11.7)	0.12	0.730
Sleep latency (min)	13.2 (18.3)	10.3 (11.0)	12.9 (8.9)	9.8 (3.1)	0.01	0.924
REM latency (min)	88.7 (27.9)	101.6 (42.7)	77.9 (18.3)	94.1 (60.6)	0.27	0.613
Total wake time (min)	30.8 (29.0)	44.0 (43.6)	43.1 (26.6)	24.7 (11.9)	0.09	0.775
Apnea hypopnea index (per hour)	3.9 (3.0)	4.3 (4.0)	1.7 (1.1)	4.3 (5.6)	0.44	0.518
Flow limitation arousalindex (per hour)	0.9 (1.4)	0.5 (0.4)	2.0 (2.5)	1.8 (1.7)	2.71	0.124
Periodic limb movement during sleep (per hour)	5.6 (7.6)	6.2 (9.5)	4.7 (7.7)	1.3 (2.2)	0.70	0.418
Periodic limb movement during waking (per hour)	9.5 (20.8)	9.4 (21.8)	28.9 (23.2)	27.8 (41.5)	1.92	0.189
Total arousal index (per hour)	17.5 (7.0)	17.6 (6.9)	15.8 (3.6)	15.9 (4.2)	0.40	0.539

Data are given as mean (standard deviation)

dulator to maintain homeostasis of autonomic-endocrine systems (Kaneko and Nakanishi 2004). Ginseng is also known as an adaptogen, a substance which helps the body to resist the adverse influences of physical, chemical and biological factors, and helps the restoration of homeostasis (Ma et al. 2008). It is generally accepted that HPA axis functions to ensure the body adaptation and is one of the most important systems closely related to stress and there are some reports on inhibitory effects of ginseng on stress-induced increase of corticosterone level (Ma et al. 2007).

Another possible mechanism is through immune system. Cytokines, especially interleukin-1 β and TNF- α, are well characterized as being involved in NREM sleep regulation (Kryger et al. 2005). The homeostatic influence is believed to be due to some structure or substance that accumulates 'need to sleep' during prolonged wakefulness. When these substances reach a critical level, our metabolic process responds by slowing down wake-promoting neuronal activities, thus lowering the rate of production until the substances return to basal levels. This homeostatic process is the primary factor necessary to initiate sleep. The substances believed to be involved in sleep initiation include adenosine, gamma-aminobutyric acid (GABA), glycine, prostaglandin D2 (PGD2), interleukin-1 β and tumor necrosis factor (TNF) (Datta and Maclean 2007). Non-rapid eye movement (NREM) and REM sleep probably have separate homeostatic systems. NREM sleep is typically replenished first and it is NREM sleep to which above-mentioned sleep-promoting substances are specifically related. Administration of either IL-1 β or TNF- α promotes NREM sleep. The pathways in which IL-1 and TNF promote sleep include several steps. Interleukin-1 and TNF stimulate nuclear factor kappa B (NF κ B). Nuclear factor kappa B, in turn, induces nitric oxide synthase (NOS) to produce nitric oxide. Nitric oxide (NO) production in basal forebrain is needed to produce sleep. Previous research had found that ginseng stimulates NO synthesis through promoting NOS production and thus might have sleep-producing effect (Gillis 1997). Since the process by which IL-1 and TNF induce sleep consists of multiple steps, the sleep-promoting effect of ginseng through NO stimulation might involve direct action on NOS or indirect actions affecting IL-1 and TNF production. As our current knowledge of the molecular steps by which IL-1 and TNF induce sleep is still limited, the process by which ginseng is involved in sleep regulation and immune function is remained to be explored. Further studies examining effect of ginseng administration on changes of levels of IL-1 and TNF might be a one way to explore this.

Some controversial reports indicated that sleep disorders were most commonly experienced adverse events of ginseng (Ma et al. 2008). This might be due to uncontrolled open research designs, so the evidence from clinical trials did not evaluate well the ginseng efficacy, and even made contradictory conclusions. Besides, the actions of ginseng are less evident in non-stressed human subjects (Gillis 1997). It should be noted that herbal medicine on pathological states are usually better, but are not obvious or can be even adverse on physiological states. Further, the effect on chronic adminis-tration might be different from that of acute one (Kitaoka et al. 2009).

The efficacy of red ginseng in human sleep is not clearly established. Our study is of significance in that it is one of the first clinical trials to explore the effect of ginseng on sleep. However, there are some limitations to our study. The sample size was too small and the trial was too short of duration. The dosage of ginseng might have been inadequate also. The recommended daily dose of ginseng in human beings is 1.5 to 3.0 g/day (Jin et al. 2007). However, in previous studies with rats, the dosage of ginseng varied greatly ranging from as low as 10 mg/kg/day to as high as 500 mg/kg/day (Ma et al. 2008 ; Jin et al. 2007 ; Min et al. 2003 ; Kim et al. 2009). In a clinical trial, Heo et al. (2008) have used ginseng up to 9.0 g/day. From this, it might be inferred that the dosage we used in this study was too low to reach statistically significant results but only showed a trend toward increased deep sleep. Quite contrary to what is expected, the total sleep time decreased in red ginseng group. This decrease might be due to improved quality of sleep but it should be confirmed with further studies with larger sample size.

In conclusion, the result of current study suggests that Korean red ginseng tends to increase deep sleep and decrease shallow sleep. Further studies, well-designed clinical trials with higher ginseng dosage, larger sample size and longer trial duration should be conducted to confirm the sleep stabilizing and balancing effects of Korean red ginseng.

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■ ABSTRACT

Effect of Korean Red Ginseng on Sleep : A Randomized, Placebo-Controlled Trial

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Objectives: Ginseng has a long history of being used in insomnia treatment and there is some evidence from animal studies of its sleep-enhancing property. From this, it can be assumed that ginseng has sleep-promoting effect in humans. The purpose of this study was to investigate the effect of Korean red ginseng on change of sleep architecture in humans.

Methods: A total of 20 healthy young males with regular sleep and wake habits and without any psychiatric nor cognitive problems were selected based on review of sleep questionnaires and sleep diaries they completed followed by an interview with a board-certified psychiatrist. The subjects were randomly assigned to red ginseng or placebo for 2 weeks of trial. The total daily dose of ginseng was 4,500 mg. The polysomnographic recordings were made at baseline and at 2 weeks after. The effects of red ginseng and placebo on sleep were assessed by comparing the changes in polysomnographic variables between the two groups.

Results: A total of 15 subjects, 8 from red ginseng group and 7 from placebo group, were included to undergo polysomnographic procedures. The red ginseng group showed tendencies to increase stage 3 sleep (p=0.087) and to decrease stage 2 sleep (p=0.071) from the baseline compared with the placebo group.

Conclusion: Korean red ginseng tends to increase deep sleep and decrease shallow sleep. Our result is in line, at least in part, with previous findings that Korean red ginseng increased total and NREM sleep in rats. Further studies with higher ginseng dosage, larger sample size and longer trial duration should be conducted to confirm the sleep stabilizing and balancing effects of Korean red ginseng.

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Key words: Korean red ginseng · Sleep · NREM · Polysomnography.