

Efficacy of Korean Red Ginseng Supplementation on Eradication Rate and Gastric Volatile Sulfur Compound Levels after *Helicobacter pylori* Eradication Therapy

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This clinical study was performed to evaluate whether supplementation of proton pump inhibitor (PPI)-based triple therapy with Korean red ginseng can enhance *Helicobacter pylori* (*H. pylori*) eradication and reduce levels of halitosis-associated volatile sulfur compounds (VSCs) in the stomach. Seventy-six patients were randomized into an eradication regimen-only group ($n=45$) or an eradication regimen plus 10 weeks of Korean red ginseng supplementation group ($n=31$). The eradication regimen consisted of PPI b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d. for seven days. Korean red ginseng supplementation commenced on the last day of the eradication regimen. ¹³C-urea breath test and halimeter measurements were performed prior to protocol repetition. By intention-to-treat analysis, the *H. pylori* eradication rate in the Korean red ginseng group (77.4%, 24 of 31) was higher than that in the control group (45.0%, 26 of 45). However, by per protocol analysis, the eradication rate in the Korean red ginseng group was significantly higher than that in the control group (92.3%, 24/26 vs. 69.4%, 26/38; $p<0.05$). *H. pylori* infection was significantly associated with increased VSC levels. However, VSC levels decreased significantly in the Korean red ginseng group ($p<0.05$). In conclusion, supplementation of triple therapy with Korean red ginseng increased the *H. pylori* eradication rate and led to significant reductions in VSC levels, suggesting the usefulness of this substance in combating *H. pylori* infection.

Keywords: *Helicobacter pylori*, Korean red ginseng, Eradication, Halimeter, Supplementation, Chronic atrophic gastritis

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is found in 70% to 90% of the population in developing countries and in 25% to 50% in developed countries, and thus poses significant public health risks [1]. *H. pylori* are known to play a major role in the pathogenesis of chronic and atrophic gastritis, gastric and duodenal ulcers, and gastric malignancies, including adenocarcinoma and mucosa-associated lymphoma tissue lympho-

ma [2,3]. Consequently, a great deal of emphasis has been placed on its eradication, as this would reduce the prevalence of a variety of conditions, possibly including gastric carcinomas [4,5]. According to the Maastricht consensus, the first-line therapy for *H. pylori* eradication is a combination of a proton pump inhibitor (PPI) or ranitidine bismuth citrate and clarithromycin plus either amoxicillin or metronidazole [6,7]. With these first-

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line therapies the eradication rate ranges from 75% to 98% with the median at *circa* 80%. Therefore, around 20% of patients are expected to be unresponsive to treatment, a proportion that may be higher in locations with a high prevalence of resistant *H. pylori* strains, such as Korea and Japan [8]. The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, bismuth salt, and a PPI. However, the efficacy of these regimens is limited by poor compliance, treatment duration, number and dose of prescribed drugs, and bacterial resistance to antibiotics [9].

Although bacterial resistance and poor patient compliance are believed to be the primary factors, the exact reasons for treatment failure remain unclear. Occurrence of mild but unpleasant side effects such as diarrhea, nausea, vomiting, and abdominal bloating and pain may cause the patient to interrupt the regimen, thus leading to increased bacterial resistance [10]. Therefore, gastroenterologists and microbiologists continue to search for new therapies due to the increasing prevalence of *H. pylori* infection and the physiological and pharmacoeconomic burden of the second-line therapy. To increase eradication rates of first-line therapy, several clinical trials involving extending treatment duration to more than one week, use of higher doses of per protocol (PP), and/or new antibiotics such as quinolones, use of quadruple therapy, or addition of probiotics, vitamin C, bovine lactoferrin, ginseng, wine, garlic, honey, and cranberry have been carried out [11-15].

Previous studies have suggested that Korean red ginseng 1) inhibits *H. pylori* colonization, 2) exhibits anti-oxidative and antiinflammatory effects during *H. pylori* infection, 3) provides efficient restorative action, 4) inhibits expression of genes associated with generation of volatile sulfur compounds (VSCs), and 5) increases eradication rates in addition to attenuating *H. pylori*-associated halitosis [16-19]. Here, we investigated the effects of supplementation of triple therapy with Korean red ginseng on both *H. pylori* eradication rates and *H. pylori*-associated halitosis.

MATERIALS AND METHODS

Patient recruitment

Individuals with dyspepsia and indigestion (76 total; 35 male, 41 female), with a mean age of 51.6±14.5 years (range, 41 to 70 years), were recruited into the study after providing informed consent. All subjects showed chronic atrophic gastritis on the antrum or corpus. Urea breath test (UBT), rapid urease test, and

Warthin silver staining of biopsied gastric mucosa were performed to characterize patients as *H. pylori*-associated chronic atrophic gastritis-positive or negative. Halitosis, a fetid breath odor, was objectively documented by halimeter test; a reading of >100 ppb was taken as halitosis-positive [20-22]. Individuals taking antibiotics, proton pump inhibitors, H₂ receptor antagonists, nonsteroidal anti-inflammatory drugs, or antihistaminic drugs, were excluded from the study. Furthermore, based on data from the General Health Check Program (Gil Medical Center, Incheon), which included a dental check, blood tests including peripheral blood test, systemic biochemical tests including renal, hepatic, and lipid tests, a serological test for hepatitis, tests for cancer biomarkers, and GI endoscopy including gastroscopy and colonoscopy), individuals with fundamental systemic illnesses, including diabetes, tuberculosis, renal insufficiency, liver disease, *etc.*, or dental problems, were excluded from the study. The study protocol was approved by the institutional review board of Gachon University Gil Medical Center (Institutional Review Board [IRB], March 2009). Subjects (76 total) were randomized into an eradication regimen-only group (eradication alone group, *n*=45) or eradication regimen plus 10 weeks of Korean red ginseng-supplemented group (eradication plus Korean red ginseng group, *n*=31). Korean red ginseng was administered in capsules (300 mg/capsule) provided by the Korea Ginseng Corporation (Jeongkwangjang red ginseng powder; Daejeon, Korea). A total of 2.7 g of Korean red ginseng capsules were given per day, each dose consisting of three capsules, *t.i.d.*, for 10 weeks following cessation of the eradication regimen. The eradication regimen consisted of pantoprazole (40 mg *b.i.d.*; Amore-Pacific Pharma, Seoul, Korea), clarithromycin (500 mg *b.i.d.*; Korea Pharma, Icheon, Korea), and amoxicillin (1 g *b.i.d.*; Chongkeundang Pharma, Seoul, Korea) for seven days. Korean red ginseng (900 mg *t.i.d.*) supplementation commenced on the last day of triple therapy. ¹³C-urea breath tests and halimeter measurements were performed both immediately before and 12 weeks after commencement of treatment.

Urea breath test

UBT was performed both immediately before and after cessation of treatment (10 weeks after eradication regimen and at least one week after cessation of Korean red ginseng). ¹³C-labeled urea (100 mg) was produced by Otsuka Pharmaceutical Co (Tokushima, Japan). UBT was defined as positive when Δ¹³CO₂ was above 2.5 (‰) at 20 minutes after ingestion of ¹³C-urea.

Measurement of VSCs

The halimeter (Model RH-17K; Interscan Co., Chatsworth, CA, USA) was adjusted to zero in ambient air prior to obtaining measurements. Subjects were asked to breathe through the nose, with the mouth closed, for one minute. A straw attached to the halimeter was then inserted into the mouth and air was withdrawn for analysis. Concentrations were determined in triplicate and the mean values were calculated. Therefore, the data reflected the mean level of VSCs originating from the gastric lumen or stomal area. As individuals with poor oral hygiene or those with dental caries were excluded, mean VSC levels and subjective visual analogue scaled levels of halitosis represented were recorded as "levels of halitosis." VSC levels in the breath were recorded as ppb of sulfide equivalents. Concentrations were determined in triplicate and the mean values were calculated. Measurement of VSCs was usually performed in the morning under fasting conditions to avoid the influence of ingested foods.

Gas chromatography for VSC concentrations in gastric juice

Separation and calibration of VSCs were performed by gas chromatography (GC; Agilent 6890N, Agilent Technologies, Wilmington, DE, USA) using a flame photometric detector specific for sulfur compounds. We found that 60°C was the ideal temperature for evaporating gastric juices for GC analysis. Peak areas and retention times were recorded using ChemStation software (3365 ChemStation revision A09; Agilent Technologies). Gastric juice was heated at 60°C to evaporate gas, 500 mL of which was entrapped in a syringe for gas chromatography/flame photometric detection (FPD) analysis. Gastric juices (5 mL) were aspirated during endoscopy using an aspiration tube inserted into the biopsy channel (Olympus, Tokyo, Japan) and stored at -70°C until required. To our knowledge, this is the first report of the measurement of VSC levels in aspirated gastric juice. This was made possible by the development of the FPD-based protocol [9].

Statistical analysis

For intention-to-treat (ITT) analysis, all patients enrolled in the study were included. However, for PP analysis, those who dropped out due to either taking less than 80% of any of the prescribed drugs or adverse events did not undergo final ¹³C-UBT or halimeter breath tests. Eradication rates were compared by χ^2 test. These data were compared with those obtained from the

t-test and $p < 0.05$ was considered significant.

RESULTS

Patient population

A total of 76 patients were enrolled from the GI endoscopy center and out-patient department of Gachon University Gil Medical Center after IRB approval. Of these, 45 were included in the eradication alone group and 31 were included in the eradication plus Korean red ginseng group, assigned randomly based on patient registration number. All of these patients showed *H. pylori*-associated chronic atrophic gastritis (CAG). Baseline characteristics were similar in the two groups: mean age, male: female ratio, proportion of smokers and alcohol drinkers and CAG in the corpus or antrum. Of the 45 subjects in the eradication-only group, seven were excluded from PP analysis due to discontinued therapy (four subjects), lack of follow-up (two subjects), and non-compliance in one subject, who adhered to the study protocol for only three days. Of the 31 subjects in the eradication plus Korean red ginseng group, five were excluded from PP analysis due to lack of follow-up (four subjects) and discontinuation of therapy by one subject, who stopped taking Korean red ginseng due to dyspeptic symptoms. The loss of follow-up in four subjects in the Korean red ginseng group may have been attributable to a change in clinical trial nurse (Fig. 1).

H. pylori eradication rates

According to ITT analysis, eradication rates were 77.4% (24 of 31) in the Korean red ginseng group, compared to 51.0% (26 of 45) in the eradication-only group; this difference was not significant. However, PP analysis suggested that successful eradication of *H. pylori* was achieved in 24 of 26 patients (92.3%) in the Korean red ginseng group, which was significantly higher than that in the eradication-only group (26 of 38, 69.4%; $p < 0.05$) (Fig. 2a). No subjects in the Korean red ginseng group were non-compliant, whereas one subject in the eradication-only group adhered to the protocol for only three days. One subject stopped taking Korean red ginseng supplementation due to epigastric pain and bloating, whereas four subjects in the eradication-only group discontinued medication due to diarrhea ($n=2$), dizziness and nausea in ($n=1$) and bitterness and epigastric soreness ($n=1$). Four subjects in the Korean red ginseng group and one in the eradication-only group were lost to follow-up; we speculated that this was due to a change in medical staff (the clinical trial nurse) after the

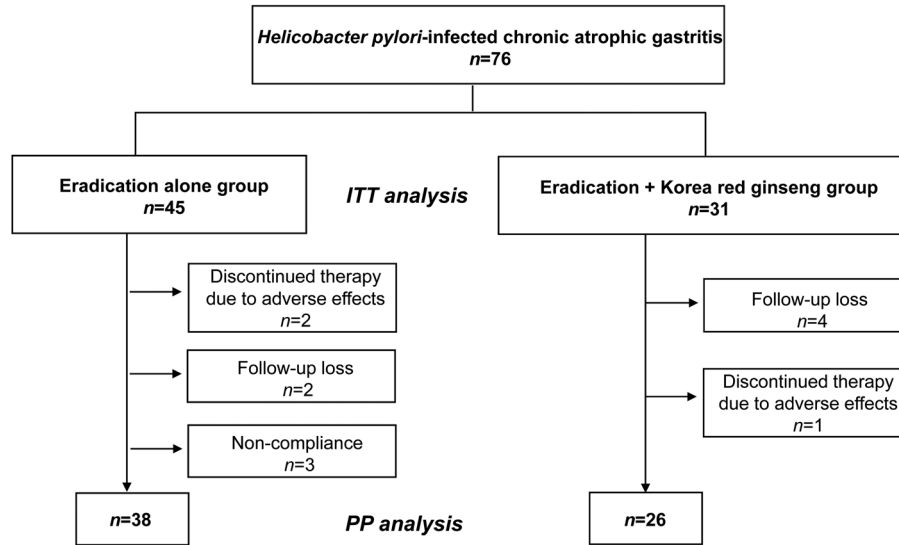


Fig. 1. Flow diagram of the study, including intention-to-treat (ITT) and per protocol (PP) analyses.

trial had begun.

As we have previously reported eradication rates [18,19] (albeit at differing time points than the data presented here), these data (Fig. 2a upper and middle panels) are presented together with those of the study described here (Fig. 2a lower panel). Although the eradication plus Korean red ginseng regime resulted in higher eradication rates than the eradication-only regime in each trial, statistical significance was not achieved, most likely due to the small number of subjects in each trial. However, when these data were combined (Fig. 2b), supplementation with 10 weeks of Korean red ginseng (Jeongkwangjang red ginseng capsule, 2.7 g/day; Korea Ginseng Cooperation) significantly augmented eradication rates (eradication-only group 75/102, 73.5% vs. eradication plus Korean red ginseng group 82/90, 91.1%; $p<0.005$).

***H. pylori* infection and VSC levels**

Data from a previous study [23] suggested that breath VSC levels indicated the presence of erosive or mucosal injury in patients with functional dyspepsia. Thus, to determine the effects of *H. pylori* infection on VSC levels, we recruited 55 subjects with functional dyspepsia. VSC levels were also determined in individuals (110) with mild chronic superficial gastritis (CSG) by endoscopy, and whose *H. pylori* status had been determined by rapid urease test, UBT, and Warthin silver staining were negative.

A total of 55 subjects (21 male and 34 female, mean age 34.3 ± 10.2 years; range, 21 to 51 years) were included in the study. VSC levels were significantly different

between *H. pylori*-positive CSG patients and those who were *H. pylori*-negative (Fig. 3a). This suggests that *H. pylori* infection is associated with increased VSC levels. Furthermore, data obtained by GC/FPD suggested that H_2S was present in the gastric juice of individuals with confirmed *H. pylori* infection (Fig. 3b).

Attenuation of *H. pylori*-associated halimeter ppb levels with the supplementation of Korean red ginseng

Supplementation with Korean red ginseng significantly decreased the mean levels of VSCs as compared to triple therapy alone ($p<0.05$, Fig. 4a). Although the eradication regimen alone decreased the mean levels of halimeter ppb, the difference was not significant. These data suggested that supplementation with Korean red ginseng resulted in health benefits other than enhancement of *H. pylori* eradication. Although there is no clear definition of which VSC levels are diagnostic of halitosis, concentrations lower than 100 ppb are generally acknowledged as denoting no halitosis [21-23]. When we analyzed how many patients were ppb<100 according to group, the number of patients in the Korean red ginseng group was higher than that in the eradication alone group in these goals, but the difference was not statistically significant (Fig. 4b). All subjects who received Korean red ginseng supplementation showed a decrease in VSC level of >30%, compared with only 52.9% of those who did not ($p<0.05$, Fig. 4c). Taken together, these data suggest that supplementation with Korean red ginseng led to a significant reduction in *H.*

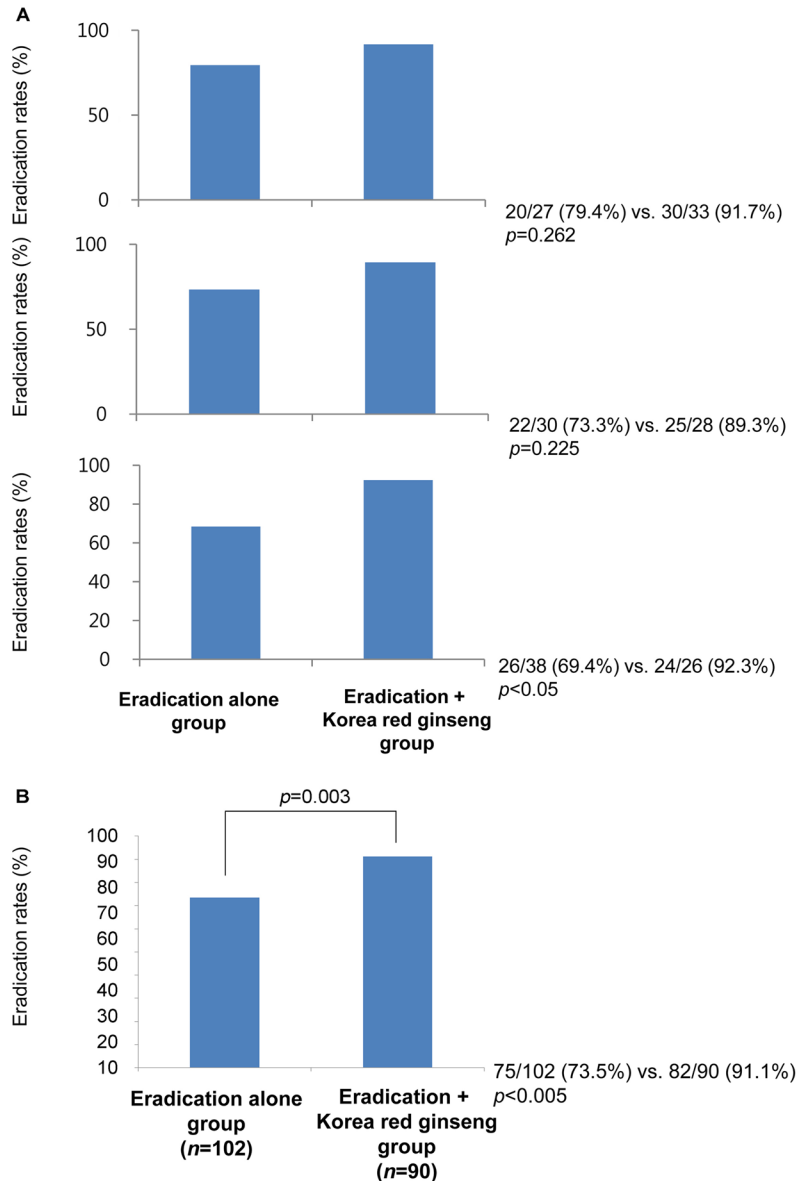


Fig. 2. Eradication rates by patient group: eradication alone and eradication plus Korean red ginseng. (a) Eradication rates in three previous clinical trials. We previously conducted three clinical studies [18,19]. The first [18] was composed of 60 subjects (27 received only eradication therapy and 33 received eradication therapy plus 10 weeks of Korean red ginseng), the main objective of which trial was to measure the change of pathological scores according to group; eradication rate was obtained only as involved parameter (upper panel). The second [19] was composed of 58 subjects (30 and 28 received eradication therapy only and eradication therapy plus Korean red ginseng, respectively). The objective of this trial was to document the efficacy of Korean red ginseng on halitosis, but eradication rates were also additionally recorded (middle panel). The lower figure shows the results of the current trial. (b) Cumulative results of eradication rates according to group. When data from these three trials was combined, the eradication rate in the Korean red ginseng group was significantly higher than that in the eradication-only group ($p=0.0003$).

pylori-associated VSC levels.

DISCUSSION

Supplementation of triple therapy with Korean red ginseng increased *H. pylori* eradication rates and significantly reduced VSC levels in gastric juice. This is especially significant because *H. pylori* eradication alone

has been shown to be insufficient to induce remission of chronic atrophic gastritis or precancerous lesions, or to inhibit gastric carcinogenesis [24-26]. Therefore, we inferred that supplementation of traditional therapies with Korean red ginseng would enhance treatment of *H. pylori* infection, especially in locations with a high incidence of *H. pylori*-associated gastric malignancy. The prevalence of *H. pylori* infection is believed to

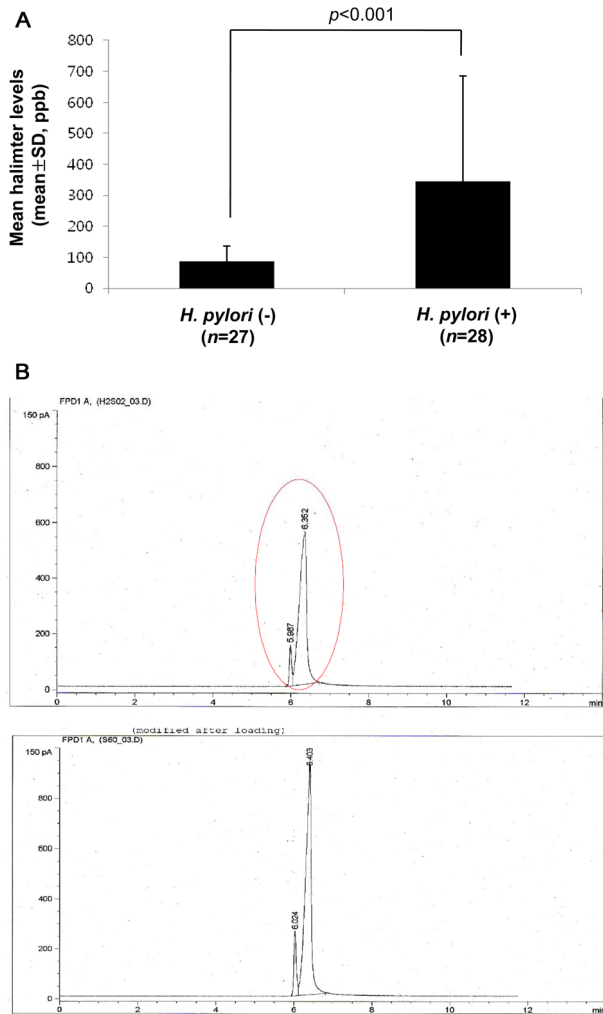


Fig. 3. (a) Mean volatile sulfur compound (VSC) levels in *Helicobacter pylori* (*H. pylori*) infected and uninfected subjects. Mean VSC levels of *H. pylori* (+) patients were significantly greater than those of *H. pylori* (-) patients. (b) Gas chromatographic analysis. Typical chromatograms of headspace air for standard H₂S gas (upper) and for gas evaporated from gastric juice (lower). The longitudinal axis represents the response of the flame photometric detector.

decrease as socioeconomic status improves [27]. However, the prevalence rates of *H. pylori* infection and associated gastric cancer remain high in Korea and Japan. Two studies of asymptomatic Korean adults performed in 1998 and 2005 suggested *H. pylori* prevalence rates of 66.9% and 59.5%, respectively [28,29]. Gastrointestinal symptoms and pathologies develop in 10% to 15% of the infected population and *H. pylori* is recognized as one of the etiological agents of peptic ulcers and a risk factor for the development of gastric adenocarcinoma and lymphoma. Since the World Health Organization classified *H. pylori* as a class 1 carcinogen in 1994, much research on its relationship with gastric

cancer has been carried out and many clinical trials have sought to prevent carcinogenesis by eradicating *H. pylori* infection. However, lack of subject compliance and absence of a truly effective anti-*H. pylori* therapeutic regimen have hindered these efforts.

The ideal regimen for treating *H. pylori* infection remains elusive. Non-antibiotic therapies, including phytochemical compounds, probiotics, and antioxidants, have been investigated as potential alternatives or more efficacious options for treatment of *H. pylori* infection [30]. The rationale for these efforts arises from the fact that *H. pylori* antibiotic resistance, particularly to commonly used agents such as clarithromycin and metronidazole, is a major cause of treatment failure. Therefore, appropriate alternatives to antibiotic use must be considered.

Several *in vitro* and *in vivo* non-human trials of alternative anti-*H. pylori* therapies utilizing a variety of substances, including ginseng, wine, garlic, propolis, cranberry, green tea, probiotic, and antioxidants, have been performed. Garlic, capsaicin, cinnamon, probiotics, some Chinese herbal medicines, lactoferrin, and antioxidants (including vitamin C) have been used in human trials, most of which aimed to assess the efficacy of the substances as supplements after cessation of the eradication regimen [31-36]. Some improvements in rates of eradication and side effects were documented. Kim *et al.* [37] conducted a randomized, open-label study to assess whether PPI-based one-week triple therapy with adjunctive probiotic administration increased *H. pylori* eradication rates and reduced adverse effects. Addition of probiotics to triple therapy did not reduce the side effects of triple therapy, but it increased the eradication rate (78.7% eradication therapy alone vs. 87.5% eradication therapy plus probiotics). Sachdeva and Nagpal [38] performed a meta-analysis to document the effects of fermented milk-based probiotic preparations on *H. pylori* eradication, and concluded that probiotics improved *H. pylori* eradication rates by approximately 5% to 15%, whereas the effect on adverse outcomes was unclear. Detailed clinical trials dealing with *H. pylori* eradication vitamin C and lactoferrin showed similar results to those of the probiotics studies, leading to the conclusion that supplementation with lactoferrin or vitamin C or vitamin E could be effective in increasing *H. pylori* eradication rates and may be appropriate for patients in whom first-line therapies have failed [38-39]. However, other meta-analyses have not supported the efficacy of supplementary therapy. For example, Chuang *et al.* [40] and other many investigators [41] have

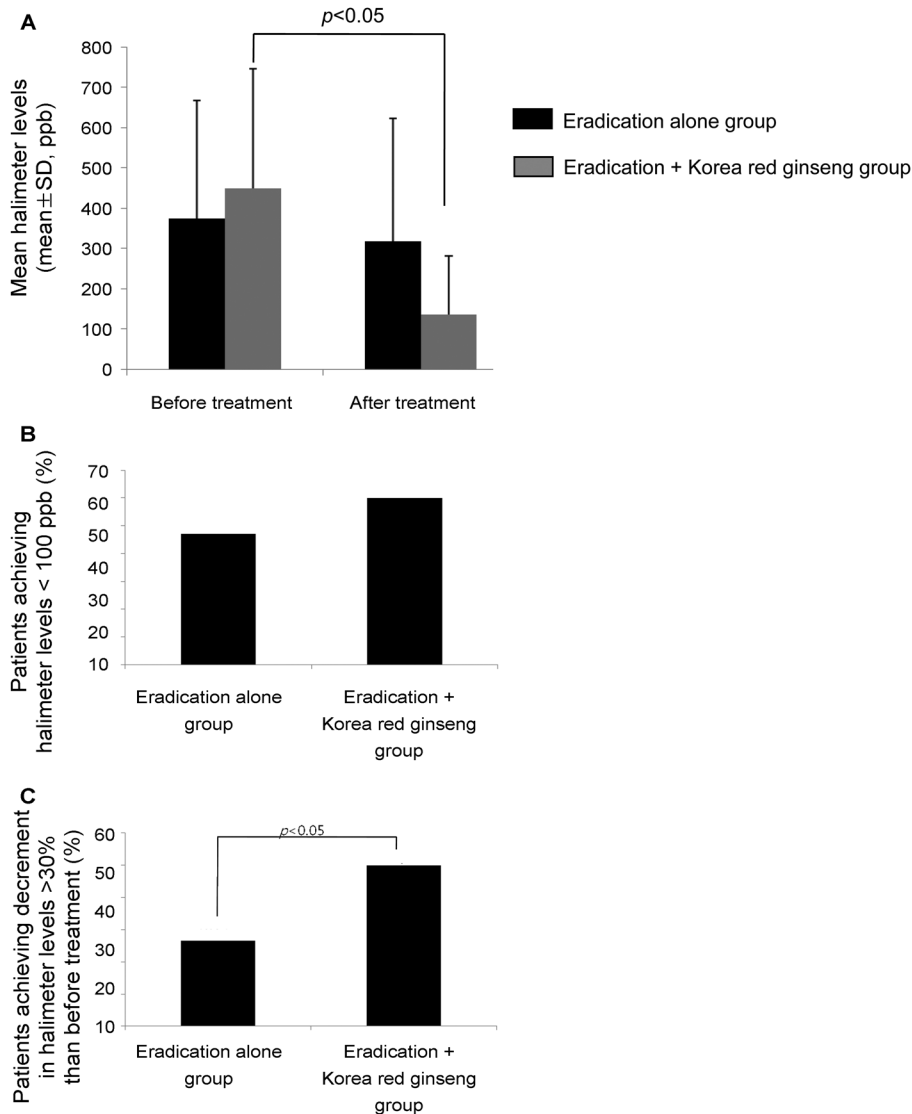


Fig. 4. (a) Comparison of volatile sulfur compound (VSC) levels before and after eradication therapy. Irrespective of group, mean VSC levels were decreased compared to those before treatment. Furthermore, VSC levels were significantly decreased in subjects treated with the eradication regimen plus Korean red ginseng. (b) Proportion of subjects with VSC levels <100 ppb. VSC levels were below 100 ppb in around 60% of subjects treated with the eradication regimen plus Korean red ginseng, as compared to 47% of those who received eradication therapy only. These results suggest that eradication of *Helicobacter pylori* can result in a reduction in halitosis, irrespective of treatment strategy, as reported previously [19]. (c) Proportion of subjects with a decrease in VSC level >30% compared to before treatment. All patients in the eradication plus Korean red ginseng group showed a decrease in VSC level >30% compared to before treatment.

reported that in patients infected with metronidazole-susceptible *H. pylori*, adding vitamins may even reduce the eradication rate of triple therapy. Regular intake of dietary or dairy products may constitute a low-cost and safe alternative to *H. pylori* treatment, but large-scale or prospective clinical trials are necessary to demonstrate efficacy. The data presented here justify further and larger-scale investigation of the efficacy of Korean red ginseng as a supplement to triple therapy. A possible link between *H. pylori* infection and hali-

tosis was first reported by Tiomny *et al.* [42] who followed-up three couples in which either one or both had halitosis. After receiving the eradication regimen, a significant improvement in halitosis was observed. Indeed, halitosis disappeared when *H. pylori* was eradicated. Thereafter, Ierardi *et al.* [43] reported improvement of halitosis with eradication of *H. pylori* in 19 of 30 subjects, whereas in 11 of 30, in whom *H. pylori* positivity persisted, halitosis parameters were unchanged. Since these reports, further studies have documented improve-

ment of halitosis with eradication of *H. pylori* [44,45]. Lee et al. [46] first reported production of VSCs by *H. pylori*. The results of the present study added further support to the hypothesis that *H. pylori* infection is associated with increased levels of VSCs in patients with functional dyspepsia. However, as shown in Figs. 4b and 4c, *H. pylori* infection is not the only cause of halitosis. Thus, Korean red ginseng supplementation may be useful in the treatment of *H. pylori*-associated halitosis [47].

Taken together with previous studies, which suggested that VSC levels were correlated with mucosal inflammation and *H. pylori* infection [23], we concluded that administration of Korean red ginseng after first-line therapy was effective not only in enhancing eradication of *H. pylori* but also in reducing VSC levels in gastric juice.

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