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Relationship between *Helicobacter pylori* and Rosacea : It May Be a Myth.

Although it is debatable whether *Helicobacter pylori* may play a role in the pathogenesis of rosacea, some authors suggested that the treatment of *H. pylori* might have a beneficial effect. The aim of this investigation was to compare the prevalence of *H. pylori* between rosacea patients and controls, and to evaluate an effect of *H. pylori* eradication on rosecea by a 2-week triple therapy that was composed of amoxicillin, clarithromycin and omeprazole. *H. pylori* was detected by using gastroscopic biopsy with Warthin- Starry stain. Forty-two (84%) of 50 patients with rosacea and 39 (78%) of 50 controls had *H. pylori*, showing no significant difference in prevalence. The cure rates of *H. pylori* in rosacea patients and controls were 80% (16/20) and 85% (17/20), respectively. There was no significant decrease in the intensity of erythema in active treatment and placebo groups both during and after the treatment. Temporary improvement in papulopustules exclusively during the treatment (within 2 weeks) could be independent of *H. pylori* eradication. Overall, no significant reduction in the number of papulopustules was observed in active treatment and placebo groups after the treatment (in 2 months). Taken together, our study found no significant lessening of rosacea lesions by treating *H. pylori* infection, which conclusively does not concur with a view that *H. pylori* may be related to rosacea.

Key Words: *Helicobacter pylori; Acne Rosacea; Prevalence; Therapy; Gastroscopic Biopsy*

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INTRODUCTION

Rosacea is one of the common skin diseases. It is characteristic of telangiectatic erythema and/or papulopustular eruptions on central face of adults (1). Its cause is not clearly known, but genetic predisposition, gastrointestinal disturbances, *Demodex folliculorum* mites, topical steroids and psychogenic factors particularly contribute to this disorder (2, 3). Rosacea responds to antibiotics, metronidazole or retinoids that can be administered orally or topically (2, 4). Inasmuch as rosacea tends to be cosmetically annoying and difficult to treat, it has brought much attention to dermatologists.

An association of *Helicobacter pylori* with rosacea was originally issued by Rebora et al. in 1994 (5). *H. pylori* is a spiral shaped, motile, gram-negative bacterium that produces urease and resides on the gastric mucosa. Several techniques including culture, serology by enzyme-linked immunosorbent assay, urea breath test, histologic staining, immunohistochemistry and polymerase chain reaction represent the useful methods for identifying *H. pylori*, which have variable sensitivity and specificity (6, 7). In conjunction with possible etiologic role of *H. pylori* in rosacea (5, 8-12), eradication of the organism in the gastrointestinal tract has been expected to have a concurrent effect on rosacea (13-15). In contrast, some previous studies have demonstrated a lack of relationship between *H. pylori* and rosacea (16-21). Thus, it is necessary to clarify the etiology and seek the adequate treatment of rosacea.

Accordingly, we investigated the prevalence of *H. pylori* infection by performing gastroscopic biopsy, the eradication rate of *H. pylori* by conducting triple therapy, and thereafter the scores of severity in erythema and papulopustules of rosacea by using Duluth Rosacea Scoring Instrument (DRSI) (22) between cohorts and between follow-ups.

MATERIALS AND METHODS

Patients

From March 1999 to February 2000, 50 rosacea patients (21 males and 29 females, age range 31-50 years) and age- and sex-matched 50 healthy people (23 males

and 27 females, age range 32-49 years) were selected and enrolled for this study at Department of Dermatology. Candidates with history of taking medications or applying topical agents for rosacea within the past 2 months were excluded from the study. All participants were Koreans and lived in Kangwon province. They signed an informed consent document before entering the investigation. This study was a double-blind, randomized and placebo-controlled trial. Rosacea was diagnosed by typical clinical findings.

Detection of *H. pylori*

A gastric endoscopy was performed in all recruited subjects (n=100) by one endoscopist. Four gastroscopic biopsy specimens were obtained from gastric mucosa (two sites at the antrum and two sites at the anterior and posterior walls of mid-body) and were sent to Department of Pathology where they were stained with Warthin-Starry method, identifying *H. pylori* as positive with black staining. Sixty days after the trial, a gastroscopic biopsy was repeated in *H. pylori*-positive rosacea patients (n=42) and controls (n=39), who received either active medications or placebo, to determine if *H. pylori* was eradicated. The sensitivity (90%) and specificity (95%) of this diagnostic technique were estimated to be reliable to apply to the study (7).

Treatment protocol

Twenty *H. pylori*-positive and 8 *H. pylori*-negative rosacea patients assigned to the active treatment group were given triple regimen consisting of amoxicillin 500 mg 2 times a day, clarithromycin 500 mg 2 times a day and omeprazole 40 mg a day, orally for 2 weeks. On the other hand, 20 *H. pylori*-positive rosacea patients assigned to the placebo group were given 3 formulations resembling active drugs for 2 weeks.

Efficacy measurement

Efficacy measurement for the intensity of telangiectatic erythema and the number of papulopustules in rosacea patients receiving either active medications or placebo were made by one dermatologist at the beginning (baseline, day 0), at the completion of treatment (first follow-up, day 14) and at the end of the trial (second follow-up, day 60) using the score for DRSI (22).

Statistical analysis

The data were analysed by SPSS 8.0 for Windows (SPSS, Inc; 1997, Chicago, IL, U.S.A.). Values were calculated using χ^2 test with Pearson correlation coefficient or the Mann-Whitney/Wilcoxon rank sum test. p values were of comparisons between cohorts and between follow-ups. p value of less than 0.05 was considered significant.

RESULTS

Fifty patients with rosacea and 50 controls were comparable in terms of age (39.2±8.3 versus 42.3±7.8, M ±SD) and sex (58% versus 54% women, respectively). Forty-two (84%) of 50 rosacea patients were positive for *H. pylori* by gastroscopic biopsy examination, while 39 (78%) of 50 controls were positive (Table 1).

The eradication of *H. pylori* was noted in 16 (80%) of 20 rosacea patients and 17 (85%) of 20 controls at the end of the trial, respectively, to whom active drugs were given (Table 2). Each one of placebo-given 20 rosacea patients and 19 controls was negative for *H. pylori* at the follow-up examination. Of those who took the active drugs, 2 persons were unable to complete the study because of adverse reactions such as nausea and headache.

The intensity of erythema demonstrated no significant difference between the baseline and the follow-ups in both active treatment and placebo groups. For the number of papulopustules, a significant decrease was observed between the baseline and the first follow-up in active treatment group of *H. pylori*-positive rosacea patients, but not between the baseline and the second follow-up. The number of papulopustules was not significantly decreased between the baseline and the follow-ups in placebo group. At the first follow-up, there was a significant decrease in the number of papulopustules between active treatment and placebo groups, but not between *H. pylori*-positive and -negative rosacea patients in active treat-

Table 1. Prevalence of *H. pylori* infection

Group	Patients n=50	Controls n=50	p value
Hp[+]	42 (84)	39 (78)	>0.05

Hp, gastroscopic biopsy at the baseline; [+], positive for *H. pylori*; (%)

Table 2. Cure rate of *H. pylori* infection*

Group	Patients n=20	Controls n=20	p value
Hp[-]	16 (80)	17 (85)	>0.05

**H. pylori*-positive subjects on active drugs; Hp, gastroscopic biopsy at the end of the trial; [-], negative for *H. pylori*; (%)

Table 3. Effect of treatment on severity of rosacea lesions*

Group	Active treatment†		Placebo
Hp‡	[+] n=20	[-] n=8	[+] n=20
Intensity of erythema			
Baseline	5.1±1.3	5.1±1.9	5.3±1.3
1st follow-up§	4.5±1.8	4.8±2.3	5.0±1.6
2nd follow-up§	4.9±1.8	5.0±2.7	4.5±1.5
No. of papulopustules			
Baseline	12.7±5.1‖	13.0±5.5	13.6±4.9
1st follow-up§	8.3±4.2‖,¶	10.1±4.0	12.9±5.2¶
2nd follow-up§	9.9±6.1	10.9±5.9	10.8±5.7

*Scores by the Duluth Rosacea Scoring Instrument; Data denote mean±standard deviation.
†Amoxicillin 500 mg bid, clarithromycin 500 mg bid and omeprazole 40 mg qd, for 2 weeks
‡Gastroscopic biopsy with Warthin-Starry stain at the baseline; [+/-], positive/negative
§Two weeks and two months from the baseline, respectively
‖, p=0.005; ¶, p=0.002; otherwise, p>0.05 between-group and -follow-up by Student t test

ment group. At both the baseline and the second follow-up, there was no significant difference in the number of papulopustules between active treatment and placebo groups. The sample size of those (n=4) who failed in active treatment was not significant to compare with. In short, except for the reduction in the number of papulopustules at the first follow-up in active treatment group, no statistically significant improvement on the signs of rosacea was noticed (Table 3).

DISCUSSION

Caution should be taken when interpreting the prevalence of *H. pylori*, which generally increases with age and varies in regions, ranging from 22.6% to 76% (8-11, 16, 17). Interestingly, regardless of the diverse prevalence of *H. pylori* among countries, which means higher in Asia and part of Europe than in North America (10, 12, 14-17, 23), prevalence of rosacea is almost equally distributed worldwide. According to the recent sources from The Korean *H. pylori* Study Group, 66.9% of Korean adults (n=3394) who were more than 16 years old showed seropositivity, and so did 76.2% of those (n=993) in the age range of 31 to 50 (23). Similarly, our data covering the age range of 31 to 50 showed the presence of *H. pylori* infection in 78%, which was examined by gastroscopic biopsy with Warthin-Starry stain. Among *H. pylori*-detecting tests, we chose biopsy with special stain method because of not only its good sensitivity and excellent specificity but also additional advantage of being informed of gastric mucosal condition in connection with *H. pylori* infection (6, 7). Our study should have been double-checked with another method, for instance, immunohistochemistry or culture to reduce the probable false positive reactions.

Rebora et al. (5) in Italy attempted to relate the microbe *H. pylori* to rosacea on the basis that 84% of rosacea patients was positive for *H. pylori* infection, compared with 50% positivity of general population. Other researchers in the United States (8, 11), Germany (10), Ukraine (12), Poland (14) and Turkey (15) have likewise reported favorable results in support of such an association. Conversely, Sharma et al. (16) and Jones et al. (17) in the United States failed to show any difference in the prevalence of *H. pylori* between rosacea patients and controls. Our study revealed no statistically significant difference in the prevalence of *H. pylori* between the two groups (Table 1).

Double or triple regimen therapies have commonly been used for the treatment of *H. pylori*. They comprised amoxicillin, metronidazole, bismuth compounds, omeprazole, tetracycline, clarithromycin, etc, whose formulas could be adjustable (13-15, 18, 24). Our cure rate (80%) was close to that of others using the same regimen, though their dosages and durations differed (13, 14, 17, 24), and cure rate in rosacea patients was similar to that in controls (Table 2). Two (about 5%) of 39 subjects in placebo group were negative for *H. pylori*, which possibly indicated false negative reactions, but self-healed *H. pylori* infection could not be ruled out.

Szlachcic et al. (14) and Utas et al. (15) focused on a significant decrease in the severity of rosacea after the treatment of *H. pylori* infection. Still, Bamford et al. (18, 19), Grilli (20) and Hirschmann (21) strongly criticized the methodology and data analysis of Utas et al.'s article, from which they could not infer anything about the role of *H. pylori* in rosacea. Bamford et al. (18) demonstrated that although antibiotic treatment for *H. pylori* was successful, eradication of *H. pylori* did little more than placebo for rosacea. Since the alleviation of papulopustular lesions continued only within the 2-week period of treat-

ment (Table 3), action mechanisms of our therapeutic regimen could be explained as being independent of *H. pylori* eradication. This finding was in agreement with what Hirschmann stated (21). Furthermore, some topical formulas alone containing antibiotics, metronidazole or retinoids are shown to be promising in the management of rosacea (1, 2, 4), implying that they may have rather local than systemic efficiency on rosacea. It seems remarkable that the active treatment hardly weakened rosacea lesions in 2 months, nor did placebo (Table 3). This feature appears to be unique in that it does not concur with the assumption that placebo effect known as 'remembered wellness' may play a role in the treatment of rosacea (18). Besides, erythema was not nearly influenced even during the treatment with systemic medications (Table 3), insinuating rosacea could be in part attributed to autoimmune pathogenesis or vascular impairment (25).

Two of 4 rocasea patients who failed in active treatment showed no change in lesions and the other two showed slight improvement in papulopustules during the treatment. If the number of subjects studied can be multiplied, the number of treatment-failing subjects will be increased to meet the statistical significance. To fulfill the larger scale design, multi-center trial may be recommended.

In summary, it is reasonable to conclude that this study did not provide any evidences to endorse the hypothesis that *H. pylori* might be involved in the pathogenesis of rosacea.

REFERENCES

1. Plewig G, Jansen T. *Rosacea. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, Fitzpatrick TB, eds. Dermatology in General Medicine. New York: McGraw-Hill Companies, Inc, 1999; 785-94.*
2. Wilkin JK. *Rosacea: pathophysiology and treatment. Arch Dermatol 1994; 130: 359-62.*
3. Bonnar E, Eustace P, Powell FC. *The Demodex mite population in rosacea. J Am Acad Dermatol 1993; 28: 443-8.*
4. Bleicher PA, Charles JH, Sober AJ. *Topical metronidazole therapy for rosacea. Arch Dermatol 1987; 123: 609-14.*
5. Rebora A, Drago F, Picciotto A. *Helicobacter pylori in patients with rosacea [letter]. Am J Gastroenterol 1994; 89: 1603-4.*
6. Befrits R, Granstorm M, Rylander M, Rubio C. *Helicobacter pylori in 205 consecutive endoscopy patients. Scand J Infect Dis 1993; 25: 185-91.*
7. Ashton-Key M, Diss TC, Isaacson PG. *Detection of Helicobacter pylori in gastric biopsy and resection specimens. J Clin Pathol 1996; 49: 107-11.*
8. Schneider MA, Skinner RB, Rosenberg EW, Noah PW, Smith L, Zwarum A. *Serologic determination of Hp in rosacea patients and controls [abstract]. Clin Res 1992; 4: 831A.*
9. Rebora A, Drago F, Parodi A. *May Helicobacter pylori be important for dermatologists? Dermatology 1995; 191: 6-8.*
10. Jansen T, Plewig G. *Rosacea and Helicobacter pylori. Hautarzt 1995; 46: 675.*
11. Parish LC, Witkowski JA. *Acne rosacea and Helicobacter pylori betrothed [comments]. Int J Dermatol 1995; 34: 236-7.*
12. Abrahamovych LY. *Clinical and morphofunctional state of the esophagogastroduodenal system in patients with rosacea: etiological, pathogenic and therapeutic aspects. Lik Sprava 1996; 10: 84-5.*
13. Kolibasova K, Tothova I, Baumgartner J, Filo V. *Eradication of Helicobacter pylori as the only successful treatment in rosacea [letter]. Arch Dermatol 1996; 132: 1393.*
14. Szlachcic A, Sliwowski Z, Karczewska E, Bielanski W, Pytko-Polonczyk J, Konturek SJ. *Helicobacter pylori and its eradication in rosacea. J Physiol Pharmacol 1999; 50: 777-86.*
15. Utas S, Ozbakir O, Turasan A, Utas C. *Helicobacter pylori eradication treatment reduces the severity of rosacea. J Am Acad Dermatol 1999; 40: 433-5.*
16. Sharma VK, Lynn A, Kaminski M, Vasudeva R, Howden CW. *A study of the prevalence of Helicobacter pylori infection and other markers of upper gastrointestinal tract disease in patients with rosacea. Am J Gastroenterol 1998; 93: 220-2.*
17. Jones MP, Knable AL Jr, White MJ, Durning SJ. *Helicobacter pylori in rosacea: lack of an association [letter]. Arch Dermatol 1998; 134: 511.*
18. Bamford JTM, Tilden RL, Blankush JL, Gangeness DE. *Effect of treatment of Helicobacter pylori infection on rosacea. Arch Dermatol 1999; 135: 659-63.*
19. Bamford JTM, Tilden RL, Gangeness DE. *Does Helicobacter pylori eradication treatment reduce the severity of rosacea? [letter] J Am Acad Dermatol 2000; 42: 535-6.*
20. Grilli R. *Helicobacter pylori: related to rosacea? [letter]. J Am Acad Dermatol 2000; 42: 536-7.*
21. Hirschmann JV. *Does Helicobacter pylori have a role in the pathogenesis of rosacea? [letter]. J Am Acad Dermatol 2000; 42: 537-9.*
22. Bamford JTM. *Interobserver variation in the assessment of rosacea [correspondence]. Arch Dermatol 1998; 134: 508.*
23. Kim HY. *Epidemiologic study on the prevalence of Helicobacter pylori in Korea. The 5th Korean H. pylori Study Group Conference; 1999 June 19; Seoul, Korea, 1999; 23-6.*
24. Laine L, Suchower L, Frantz J, Connors A, Neil G. *Twice-daily, 10-day triple therapy with omeprazole, amoxicillin, and clarithromycin for Helicobacter pylori eradication in duodenal ulcer diseases: results of three multicenter, double-blind, United States trials. Am J Gastroenterol 1998; 93: 2106-12.*
25. Wedi B, Kapp A. *Helicobacter pylori infection and skin diseases. J Physiol Pharmacol 1999; 50: 753-76.*