Research Article

Reappraisal of the Effect of Helicobacter pylori Eradication Treatment on Rosacea in Iraqi Patients

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ABSTRACT

Background: Rosacea is a chronic inflammatory skin disease where Helicobacter pylori being involved in its etiopathogenesis is still controversial.

Aim: To evaluate whether H. pylori eradication treatment will improve the clinical features of rosacea in Iraqi patients.

Patients and Methods: a prospective study includes 56 patients with papulopustular rosacea subtype underwent urea breath test and if the test was positive, they were treated for 2 weeks with H pylori eradication kit. Patients were evaluated at baseline, 30 and 60 days follow up periods using the standard grading system of rosacea plus the numerical count of the lesions.

Results: The mean age±SD was 46.7±5.1 years, 96.3% were female. Urea breath test was positive in 44(77.8%). After treatment with H pylori eradication therapy, the mean total score of the standard grading system of rosacea was significantly reduced from 12.4±4.02 at baseline to 7.7±2.71and 6.8±2.6 at day 30 and day 60 follow-ups respectively (p <.005). Lesions count was significantly reduced at day 60 compared to baseline (53±23 versus 5.1±6.4, p<0.005), 45(83%) patients were scored excellent, while only 2(3.7%) responded poorly.

Conclusion: our results support the link between H pylori and rosacea especially in the papulopustular subtype, and a substantial number of patients were improved after eradication of H pylori infection.

Keywords: Helicobacter, pylori, eradication, rosacea

INTRODUCTION

Rosacea is a chronic inflammatory skin disorder that affects mostly on the central part of the face, representing approximately 1% of all skin disorders that have been diagnosed by dermatologists (Buechner SA,2005). Caucasians are more commonly affected by rosacea (Craige H, and Cohen J,2005) especially women between the ages 30 and 60, and almost three times as much as men. Rosacea is classified into five major clinical subtypes, erythrotelangiectatic, characterized by flushing and persistent facial erythema; papulopustular (PPR) with red central face coupled with erythematous multiple papules and pustules; glandular; phymatous, and Ocular (TüzünY et al, 2014). The exact etiology is still not well understood but factors implicated in the pathogenesis of rosacea are endocrinological, pharmacological, immunological, climatical, dietary habits, free radicals, ultraviolet radiation, microbial agents (Crawford GH et al, 2014, Del Rosso JQ , 2013, Lazaridou E et al, 2011) inheritance(Yazici AC et al, 2006) inherent

cutaneous vascular abnormalities(Wilkin JK, 1994) pilosebaceous unit abnormalities,(Marks R, and Harcourt-Webster JN 1969) and matrix degeneration(Gomaa AH et al, 2007). Demodex folliculorum, the small intestinal bacterial overgrowth (SIBO) and Helicobacter pylori (H pylori) are the most investigated but also debated regarding their etio-pathogenesis. H. pylori are gram-negative bacteria which comprise a large number of different strains. Several studies have been conducted to evaluate the relationship between H. pylori infection and rosacea, however, there is still debate around this issue. (Lazaridou E et al, 2017). We aimed to demonstrate whether H pylori eradication in patients with PPR with evidence of H pylori infection will have any therapeutic advantages on signs and symptoms of rosacea.

PATIENTS AND METHODS

A prospective clinical study was conducted at the Department of Dermatology, Basrah Teaching Hospital, Basrah, Southern of Iraq from January

2019 to April 2020. Patients with a papulopustular subtype of rosacea were assigned and screened for evidence of H pylori infection using a C13-urea breath test using 13C-UBT – B.S.I.A. Ltd, Brentford, Middlesex, UK, and those who yielded positive results were included in this trial. Participants who agreed to take part were informed about the protocol of the study and they signed an informed consent. The study was approved by the Ethical Committee of Basrah College of Medicine (Approval No: 030408081-2019).

At the baseline visit, a detailed history was reviewed in all participants including onset and duration of symptoms with special emphasis on gastrointestinal complaints. Clinical evaluation was performed to assess the type and the severity of rosacea based on the report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. In this report, the diagnosis of PPR was depend on its characteristic primary and secondary clinical features and includes constant erythema over the face especially over the center of the face with either papules or pustules or both." Mild" rosacea was defined by presence of few to several papules and pustules, with no plaques, while " moderate" rosacea includes several to many papules and pustules, without plaques. "Severe" rosacea is considered when there is extensive papules and pustules, with or without plaques (Wilkin J et al, 2004). The main exclusion criteria were patients with a history of allergic reactions to one of the following drugs: clarithromycin, tinidazole, and lansoprazole, those on oral or topical rosacea treatments for the last 2 months, pregnant and lactating women. Urea breath testing was performed on eligible participants and those with positive results were given oral H pylori eradication pack which consists of clarithromycin tablet 250 mg, tinidazole tablet 500mg, and lansoprazole tablet 30 mg administered orally before meal twice per day for 14 days. At baseline visit and during follow up periods (day 0,30, and 60) the response to treatment was assessed using the following parameters:

1- Standard grading system of rosacea: each of the primary signs and symptoms of rosacea were graded into absent, mild, moderate, and severe and scored from 0 to 3, while secondary features were graded as absent (zero scores) or present (one score)(Wilkin J et al, 2004)

2- By count the number of inflammatory lesions(papules, pustules, nodules) at the baseline and each follow-up visits, we measured the percentage of numerical reduction of the inflammatory lesions, and compared it with the baseline values. Then we graded the response to treatment for each patient according to the percentage of the total reduction in inflammatory lesion counts into the excellent response (≥80%reduction), good(60-79%), moderate(40-59%), and poor response (<40%)(Dhaher SA and Alhamdi D, 2018).

3- To ensure the eradication of H pylori, a urea breath test (UBT) was repeated on day 30 for those patients with a positive test at baseline assessment.

Data were analyzed using IBM SPSS statistics version 22. Descriptive data were shown in mean and SD (standard deviation) and qualitative data are presented as frequency and percent (%). Chi-square test and z-test were used to detect the statistical significance among different variables.

RESULTS

Fifty-six patients with PPR were evaluated during the study period, and their demographic characterizations were summarized in table 1. Of them, 44(77.8%) patients had positive UBT results, while 12(22.2%) had a negative test and the difference was statistically significant(p<0.005). Even more, dyspepsia symptom was found in 39(72.2%) patients, while 15(27.8%) patients without dyspepsia and the difference was statistically significant(p<0.005). Although not statistically significant difference, patients with positive UBT reported dyspepsia more frequently than those patients with negative UBT, 24(62%) versus 6(50%). After the initiation of H pylori eradication treatment, the mean total score of the standard grading system of rosacea was significantly reduced from 12.4±4.02 (95%CI: 11.22-13.58) at baseline to 7.7±2.71(95% CI:6.9-8.5) and 6.8±2.6(95% CI: 6.04-7.56) at day 30 and day 60 follow-ups respectively (p <.005). Even more, in comparison with baseline, each component of primary and secondary signs and symptoms of rosacea showed significant improvement at the end of the trial except for telangiectasia (table 2). At the same time, the mean of total number inflammatory lesions was significantly reduced at day 60 of the trial compared to baseline (53±23 versus 5.1±6.4, p<0.005) with 90%, 97%, 75% clearance of the papular, pustular, and plaque lesions respectively (table 3, figures 1,2,3 and 4). Results of scoring the patient's response showed that 36(82%) of patients achieved an excellent response to treatment while only 2(4.5%) were responded poorly to treatment (Table 4).

The cure rate from H pylori with the eradication protocol was high as 42(95.4%) patients showed

negative UBT at day 30 and 2(4.6%) patients remained positive.

Table 1: Demographic features of the patients (No:54 participants)

Variable	No. and percentage
Age (years)	Mean±SD (Range): 46.7±5.1 years (31-65 years)
Sex	Male 3 (3.7%) Female 53(96.3%)
Duration(years)	Mean±SD (Range): 3.6±2.4 years(3 months-9 years)
Dyspepsic symptom	40(72.2%)
Severity: mild Moderate Severe	17(30.4 %) 20 (35.7%) 19 (33.9%)

Table 2: Standard grading system of rosacea at baseline, day 30, and day 60 follow up (No:44 participants). *

Variable	Baseline	Day 30	Day 60	P value †
Flushing	2.1±0.5	1.9±0.4	1.8±0.7	<0.005
Non-transient erythema	3±0.52	2.5±0.71	2.2±0.6	
Papules and pustules	2.3±0.9	1.05±0.4	0.8±0.5	<0.005
Telangiectasia	1.6±0.3	1.5±0.7	1.5±0.6	
Burning or stinging	1.8±0.1	1.05±0.3	0.7±0.5	<0.005
Dry appearance	1.2±0.6	0.7±0.4	0.5±0.32	<0.005
Odema	0.8±0.2	0.4±06	0	<0.005
Total score	12.4±4.02	8.7±2.71	7.8±2.6	<0.005

* negative variables were removed from the graded system. † p value < 0.005 was statistically significant difference.

Table 3: The mean ± SD with percentage of clearance of inflammatory lesions at baseline, day 30, day 60 follow up period.

Visit	Papules mean±SD	Pustules mean±SD	Plaques mean±SD	Total No.
Baseline	30±11	21±7	2±1.5	53±23
Day 30	15±2.3 (50%)	8±5.3 (61.9%)	1±8.5 (50%)	24±16.1 (54.7%)
Day 60	3±5.7 (90%)	0.6±0.4 (97%)	0.5±0.3(75%)	5.1±6.4 (90.3%)
P value	<0.005	<0.005	<0.005	<0.005

Table 4: classification of PPR patients according to scoring of the percentage of clearance of the inflammatory lesions.

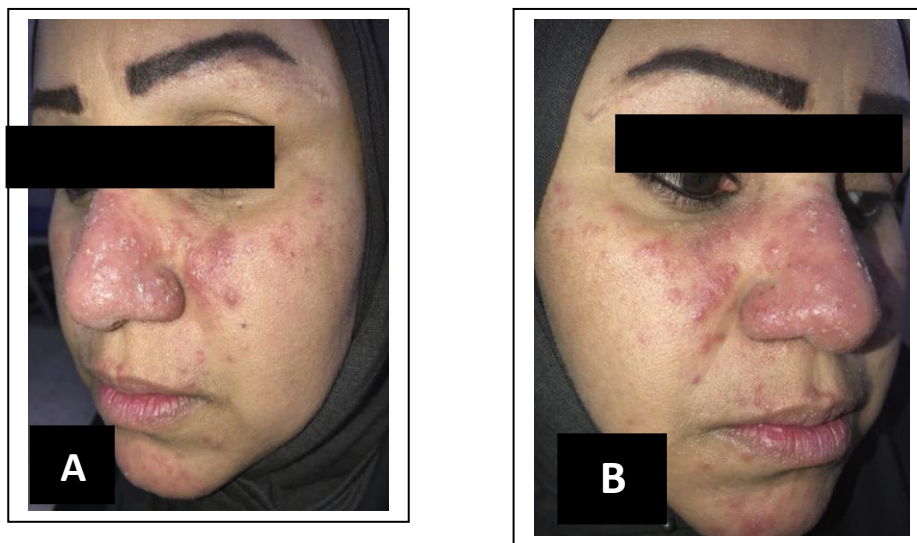| Score	Number (%) of PPR patients
Excellent: ≥ 80% clearance	36 (82%)
Good : 60%-79% clearance	4 (9%)
Moderate: 40%-59% clearance	2 (4.5%)
Poor :< 40% clearance	2 (4.5%)

Fig.1: patient with papulopustular rosacea at baseline showing classical signs of rosacea(A left side, B right side) before treatment.
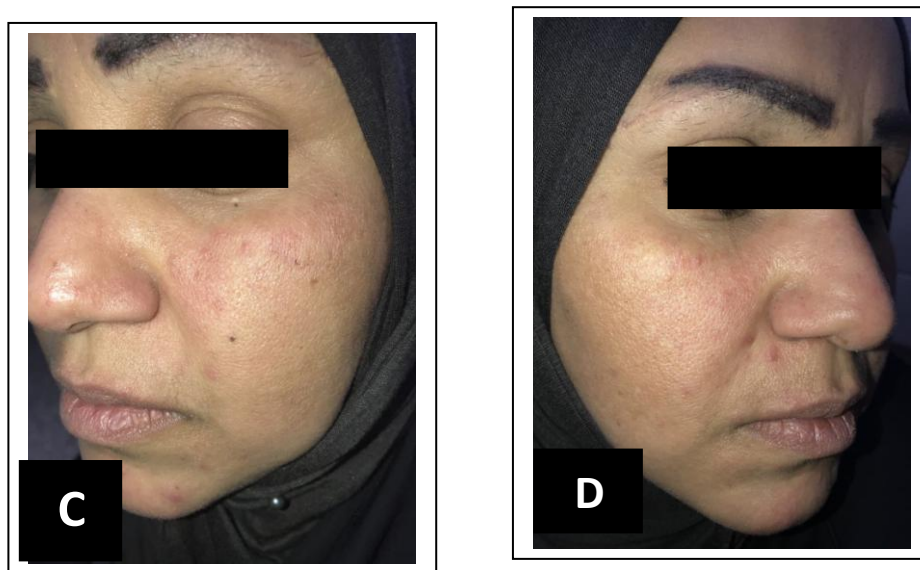

Fig.2: C and D of same patient in figure 1 at day 60 follow-up period showing remarkable clearance of the inflammatory lesions after 2 weeks of H pylori eradication treatment.
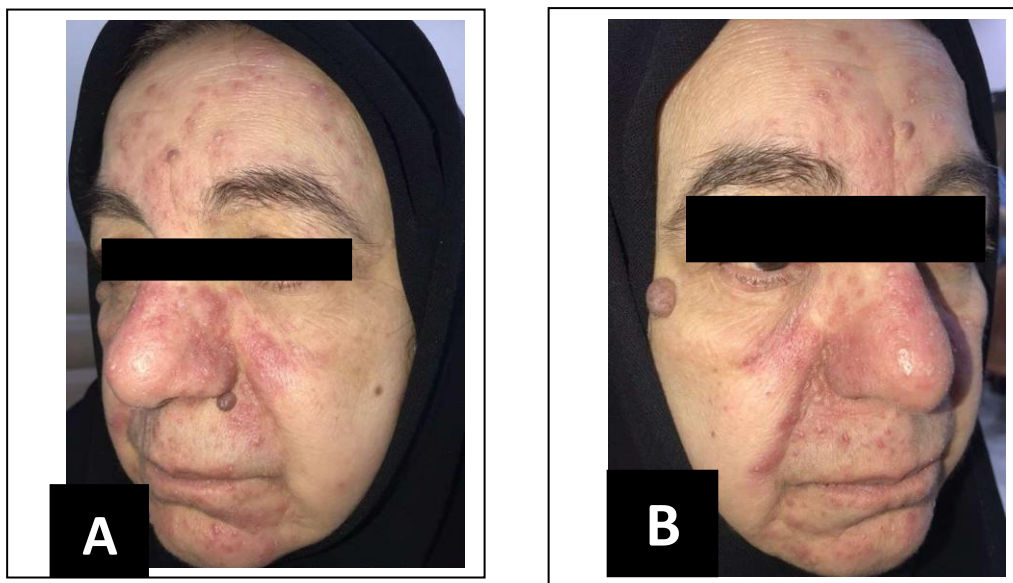
Fig.3: 62 year old lady with rosacea on both sides of the face with positive urea breath test before starting eradication treatment.
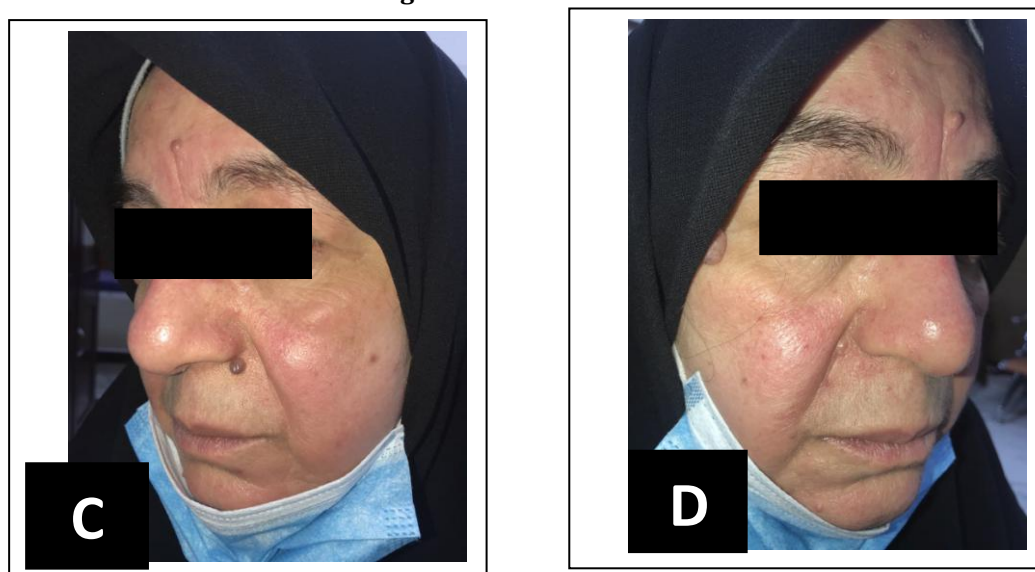

Fig.4: same patient of figure 3 at day 60 after 2 weeks treatment with H pylori eradication showing complete disappearance of all inflammatory lesions

DISCUSSION

The results of our study confirm the high prevalence of H pylori infection of gastrium in PPR patients as 77.8% of patients had positive UBT. Although several laboratory methods are used to detect H. pylori infection, the carbon urea breath test is the most accurate and reliable(Stenstrom B et al, 2008). The test extremely accurate (95% sensitivity and specificity) and the best method to detect the presence of active H. pylori infection. It also ideal for monitoring therapeutic outcomes and confirmation of cure(Best LM et al, 2018). To date, many peers reviewed studies were carried out to address the correlation between H pylori and rosacea but with debatable conclusions. In a case-control study, Szlachcic A. reported H pylori

prevalence in 88% of rosacea(Szlachcic A, 2002), while Argenziano et al. detected anti H pylori antibodies in 81% of patient with rosacea (Argenziano G et al, 2003). On the other hand, many studies were failed to find any connection between rosacea and H pylori gastric infection (Schneider MA et al, 1992, Son SW et al,1999, Herr H and You CH, 2000, Bonamigo RR et al, 2000). Despite these controversies and based on our findings, we support the hypothesis of a high prevalence of H pylori infection in rosacea patients. The pathogenetic influence of H pylori in rosacea is well discussed in the literature, and It is proposed that the bacterium produces specific cytotoxins which lead to the release of histamine prostaglandins, leukotrienes, cytokines, and other inflammatory mediators from an altered innate immune response which leads to higher levels of ROS (Reactive Oxygen Species)(Yamasaki K et al, 2009, Bakar O et al, 2007), whereas in treated rosacea, the aforementioned level is lower(Peus D et al, 1999). In the present study, we demonstrated that successful clearance of rosacea symptoms was found in 83% of patients 60 days after the initiation of eradication therapy, and in all of them, UBT became negative. While the pustules responded earlier, all inflammatory lesions were significantly reduced in comparison to baseline within 30 days after treatment and this response was maintained to escalate during the second month of the follow-up period. Our findings are consistent with the results of another studies (El-Khalawany et al 2012, Saleh P et al,2014) which concluded that elimination of the bacterium resulted in remarkable improvement in signs and symptoms of rosacea, especially papulopustular subtype.

According to the results of our study, we can speculate that the achieved clinical improvement in signs or symptoms of rosacea is most likely attributed to successful eradication of H pylori in these patients, although, some authors disputed that such improvement is due to a non-specific direct benefit from the use of antibiotics, a possibility which cannot be completely ruled out in our patients, rather than eradication of the bacteria, especially when some of the antibiotics like tetracyclines and metronidazole are known for their anti-inflammatory properties in rosacea(Pradhan S et al, 2016, De Francesco V et al, 2017). However, in our study, the finding that negative UBT was observed in majority of responsive patients after a relatively short duration of antibiotic activity and the clinical improvement was maintained during 60 days course of the trial without signs of clinical relapse in favor that the response was linked to H pylori

eradication. Among the macrolides group of antibiotics, clarithromycin can be considered to have no or little anti-inflammatory potential (Lebel M, 1993, Berg H et al,2003) while only topical tinidazole has proven anti-inflammatory property in an animal model (. Nishimuta, K and Ito Y, 2003), but its beneficial effect in rosacea has yet to be identified.

In conclusion, our study indicates that patients with a papulopustular subtype of rosacea demonstrated a high prevalence of H pylori gastric infection and there was a remarkable clinical improvement after successful eradication of the bacteria, and this may help to unveil the controversy about the connection of H pylori and rosacea. However, further evidence from a well-controlled clinical trial is needed to prove or disprove our findings taken into consideration other subtypes and multifactorial pathogenesis of rosacea.

SOURCE OF FUNDING

CONFLICT OF INTEREST
Nothing to disclose

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