

Impact of Creatinine Clearance on *Helicobacter Pylori* Eradication Rate in Patients With Peptic Ulcer Disease

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Introduction. Gastrointestinal complaints are common in patients with kidney failure. The aim of this study was to investigate the effect of creatinine clearance on *Helicobacter pylori* (HP) eradication rate in patients with peptic ulcer disease.

Materials and Methods. In this clinical trial, 132 patients with a range of kidney function (normal to end-stage renal disease) and peptic ulcer disease with HP infection were enrolled and divided into 5 groups by their creatinine clearance. For all patients, a 14-day standard regimen of triple therapy for peptic ulcer was started with omeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1 g; twice per day. After 6 weeks, HP eradication rate were evaluated and compared between the groups with urea breath test.

Results. The mean age of the participants was 44.84 ± 12.20 years and 68 (51.5%) were women. The five groups were not significantly different in terms of age, sex distribution, or body mass index. The results of urea breath test at 6 weeks were positive in 23 patients (17.4%). There was no significant difference in HP eradication rate (negative urea breath test) between the five groups.

Conclusions. This study showed no association between the success rate of eradication of HP infection and kidney function.

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INTRODUCTION

Gastrointestinal complaints are common in patients with kidney failure. In hemodialysis patients, pathological changes in the stomach is causing a rise in serum gastrin, *Helicobacter pylori* (HP) infection, and delayed emptying of the stomach.¹ Over the past decade, HP infection has progressively declined in developed countries, but still is more common in people who have immigrated from endemic areas or who had been infected during their childhood when HP had been common.²

Several factors, including geographical location, culture, age, and socioeconomic factors are involved in HP infection.² Although HP infection

has declined as a result of improvement in health status and antibacterial treatments, it was observed that a gradual rise coincided with the treatment failure rate.³ Antimicrobial resistance, especially against clarithromycin is considered the main cause of treatment failure of eradication of HP that probably was due to the overuse in treatment of upper respiratory tract infections.^{4,5}

Helicobacter pylori infection is important in forming gastrointestinal lesions; on the other hand, high urea levels in the gastric mucosa of patients with kidney failure may cause development of HP infection for much of the patients. This bacterium converts urea to ammonia and raises the local pH of the stomach needed for the survival.⁶ Because of

the high potential risk of gastrointestinal mucosal lesions in uremic patients and HP colonization, screening for and eradicating HP is needed for these patients. Bacterial resistance is a great problem in the treatment of HP infection; however, treatment is challenging since for example, bismuth compounds are toxic in uremic patients.⁷

To our knowledge, there has been no comprehensive study about HP eradication rate in patients with kidney failure in Iran, and there are a few available studies only conducted in hemodialysis patients; therefore, we aimed to evaluate the eradication rate of HP in patients with a range of kidney function from normal to end-stage kidney disease.

MATERIALS AND METHODS

This clinical trial was conducted after approval from the Research Ethics Committee of Golestan University of Medical Sciences (Iranian Registry of Clinical Trials No, 2013060913609n1). Esophagogastroduodenoscopy was done for 1200 patients with different degrees of kidney function to evaluate dyspepsia in the endoscopy division of Gorgan 5th Azar Hospital between October 2012 and November 2013. Gastroscopy was done using a videoscope (Olympus GIF-XQ260, Japan). The patients with peptic ulcer disease who had recently been diagnosed with endoscopy and HP infection in their antral samples were confirmed with rapid urea test and were selected for the study. Exclusion criteria included pregnancy; cancer; liver failure; a history of taking nonsteroidal anti-inflammatory drugs, proton pump inhibitors, bismuth, and antibiotics during the past 4 weeks; and a history of smoking, alcohol, and drug allergy. The patients enrolled in this study had not been previously treated for HP infection. All participants signed an informed consent form.

A total of 150 participants were divided into 5 groups based on creatinine clearance: group 1, creatinine clearance of 90 mL/min and higher; group

2, creatinine clearance between 60 mL/min and 89 mL/min; group 3, creatinine clearance between 30 mL/min and 59 mL/min; group 4, creatinine clearance less than 30 mL/min without the need for dialysis; group 4, hemodialysis patients. Creatinine clearance was measured in 24-hour urine collection and calculated as division of serum creatinine concentration by urine creatinine concentration, multiplied by urine volume.

For all of the patients, the standard 14-day regimen of three drugs was started, including 20 mg of omeprazole, 500 mg of clarithromycin, and 1000 mg of amoxicillin, twice a day. In cases where creatinine clearance was below 30 mL/min, the doses of clarithromycin and amoxicillin were reduced by 50%. Creatinine clearance was monitored for 3 months before the start of the study and during the study to ensure that it remained constant. A urea breath test (UBT) was done using a 13C-UBT device (HeliArobe kit, Kibion, Uppsala, Sweden) for eradication assessment 6 weeks after completion of the treatment.

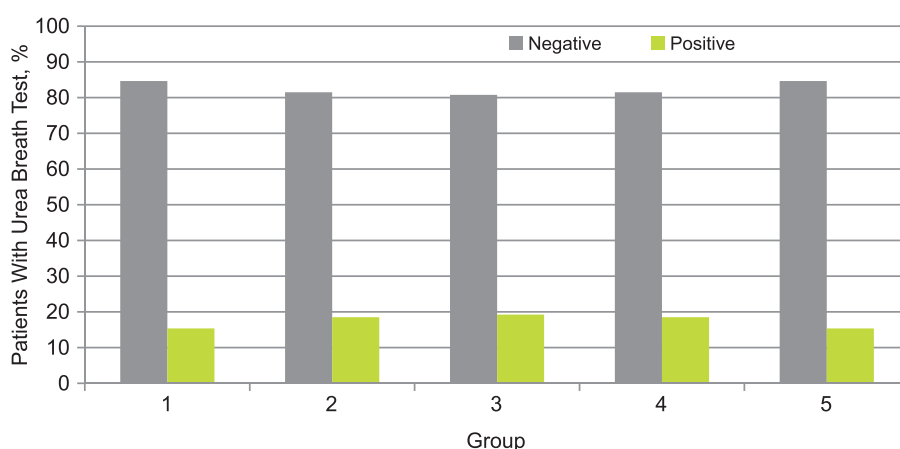
The collected data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, Ill, USA). Comparisons were done using the 1-way analysis of variance test, and the chi-square and Fisher exact tests for continuous and categorical variables, respectively. A *P* value less than .05 was considered significant.

RESULTS

Eighteen patients did not return for follow-up and 132 patients were remained in the analysis. The mean age of the patients was 44.84 ± 12.20 years and 51.5% ($n = 68$) of them were women. Body mass index was less than normal in 9.8% of the patients and normal in 34.8%, while 43.9% were overweight and 11.4% were obese. All of the patients had HP infection and different levels of kidney function. The Table shows the distribution

Demographic Data of Participants

Parameter	Study Groups					All	P
	1	2	3	4	5		
Number of patients	26	27	26	27	26	132	...
Mean age, y	45.30 ± 12.38	45.74 ± 13.62	45.30 ± 10.95	42.07 ± 10.85	45.84 ± 13.46	44.84 ± 12.20	.67
Sex							
Male	13	14	12	12	17	68	
Female	13	13	15	14	9	64	.98
Mean body mass index, kg/m ²	25.23 ± 4.22	25.10 ± 4.13	24.36 ± 4.12	25.56 ± 3.49	24.98 ± 5.10	25.05 ± 4.19	.26



Results of urea breath test 6 weeks after treatment.

of the patients in groups 1 to 5 (normal kidney function to dialysis dependence). The differences between the study groups were not significant in terms of age, sex, and body mass index (Table).

The result of UBT 6 weeks after treatment was negative in 109 (82.6%) patients, while it was positive for 23 (17.4%). There was significant difference between the HP eradication rate (according to the result of UBT at 6 weeks) between the five groups ($P = .99$; Figure).

DISCUSSION

Findings of this study did not show a significant relationship between creatinine clearance and eradication of HP infection in the studied patients. According to some factors affecting the disease process, this can be justified. These findings can be attributed to the prevalence of peptic ulcer and HP infection in different populations. Peptic ulcer is more common in patients with kidney failure compared with healthy population, which could be due to various causes, including increased gastrin and gastric acid secretion, increased parathyroid hormone, and decreased mucosal resistance. However, the prevalence of HP infection is varying between different studies. Some studies have reported the prevalence of HP infection in patients with renal impairment similar to normal population.^{8,9} A study in Iran also showed that the prevalence of HP infection is similar in patients with and without chronic kidney failure.¹⁰ In other studies, the prevalence of HP infection in patients with impaired kidney function is less than in the normal population, which rises the hypothesis of the protective role of high concentrations of urea

or acid-reducing medications and antibiotics.^{11,12}

There is not enough information about the effects of factors such as age, sex, race, and body mass index on the prevalence of HP infection and response to eradication therapy in patients with kidney failure. In this study, the response to HP eradication therapy among the study groups was not associated with these variables. However, based on various studies, in Iran and other countries, the average age of patients with HP infection is between 40 and 60 years,^{13,14} and the rate of colonization with bacteria increases from childhood to the age above 60 years.¹⁵ Also, HP infection is more common in men,^{16,17} while some other studies have reported a higher prevalence in women.^{18,19}

On the other hand, because of removing bismuth from HP eradication regimens for renal toxicity, response to eradication therapy in this study may not be comparable to the expected rates based on other observations,²⁰ while some other studies have reported a better eradication rate with the regimens without bismuth than the standard regimen.^{21,22} Also, the substantially increased antibiotic resistance to clarithromycin in the world in recent years, in particular of the HP infection, is likely to distort the results.^{23,24}

In addition to the above factors, the diagnostic accuracy of UBT to assess eradication of HP infection is also an important confounding factor in the study. Calvet and colleagues found that UBT has a sensitivity of 75% and a specificity of 60%, but with the change in the diagnostic threshold, the sensitivity and specificity increased to 90%.²⁵ In Peng and colleagues' study, the sensitivity and specificity of UBT for HP were reported 100%

and 85.1%, respectively.²⁶ Kawai and colleagues reported a sensitivity and a specificity 97% and 100%, respectively.²⁷ Despite several studies on the accuracy of UBT, few studies have conducted on the diagnostic accuracy of this test in patients with kidney dysfunction. Lopez and colleagues determined a sensitivity and a specificity of 94% and 96%, respectively, for diagnosis of HP infection in hemodialysis patients.²⁸ Nardone and colleague's study showed the diagnostic accuracy of UBT did not decrease in patients with uremia, and therefore, it was a useful method for the diagnosis of HP infection.²⁹

Researchers have reported different results of the eradicating HP infection and creatinine clearance using various treatment regimens and methods. In contrast to our findings, Itatsu and colleagues showed that low-dose regimen of 7 days of lansoprazole, amoxicillin, and clarithromycin was safe and effective in the treatment of HP infection in hemodialysis patients.³⁰ Mak and associates concluded that short-term 3-drug treatment in patients with kidney failure was substantially effective.³¹ Sheu and colleague's study showed the 3-drug regimen containing clarithromycin and metronidazole without amoxicillin was more effective in patients with kidney failure.³² Two other studies also obtained similar results to the above studies.^{33,34} In contrast, the study of Tsukada and coworkers showed the 3-drug regimen of omeprazole, amoxicillin, and clarithromycin were effective in both hemodialysis patients and general population, and eradication of HP was not significantly difference between the two groups.³⁵ Moreover, Seyyedmajidi and colleagues obtained similar results in their study and reported comparable response to HP eradication therapy in patients with kidney failure to the control group.³⁶

Given the findings of this study showed no significant difference in responses to the eradicating HP infection among patients with kidney failure and those with normal kidney function, it can be inferred that uremia is not a factor in response to HP eradication therapy. Since hypergastrinemia causes ammonium increase in gastric juice and reducing gastric pH and thereby plays a role in the pathogenesis of peptic ulcer disease, some studies have suggested that eradication of HP infection by lowering serum gastrin in hemodialysis patients may reduce the incidence of peptic ulcer disease.^{37,38}

Although this study has assessed only an initial response to HP infection in patients with renal impairment compared to normal population and has not evaluated the recurrence rate of peptic ulcer after eradication of HP and adverse effects of regimen, the 2-year study of Tseng and colleagues showed that relapse rates in patients with ESRD were significantly higher than nonuremic patients.³⁹ Additionally, initial treatment response, relapse rate, and the rate of treatment failure due to drug side effects are important in evaluating eradication of HP in uremic patients.

CONCLUSIONS

Our results showed no significant relationship between eradication of HP infection and kidney function. It can be concluded that renal impairment has not a significant effect on the response to eradicating HP infection, and it seems there are not much differences between uremic patients and the general population. However, to confirm our findings, we suggest more widespread research in the future.

CONFLICT OF INTEREST

None declared.

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