

# **The Effect of Creatinine Clearance on *Helicobacter Pylori* Eradication Rate in Patients with Peptic Ulcer Disease**

## **ABSTRACT**

**Title:** The Effect of Creatinine Clearance on *Helicobacter Pylori* Eradication Rate in Patients with Peptic Ulcer Disease

### **Authors:**

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

**Materials & Methods.** In this randomized clinical trial, 150 patients with peptic ulcer disease and *Helicobacter Pylori* (HP) infection were enrolled in this study. Patients were divided into five groups by creatinine clearance (CrCl). For all patients, a 14-day standard regimen as triple therapy was prescribed with 20 mg omeprazole bid, 500 mg clarithromycin bid and 1 gr amoxicillin bid. After 6 weeks of finishing treatment, HP eradication rate were evaluated and compared in different groups with Urea Breath Test (UBT).

**Results.** The mean age of 132 studied patients was  $44.84 \pm 12.20$  years and 51.5% (n=68) of them were female. The results of UBT at 6 weeks after treatment, in 82.6% (n=109) patients were negative and in 17.4% (n=23) also were positive. The differences among 5 study groups were not statistically significant in age, gender and BMI ( $p > 0.05$ ). Also there was no statistically significant difference between HP eradication (UBT at 6 weeks after treatment) in 5 groups ( $p > 0.05$ ).

**Conclusions.** This study showed there is no significance between eradication of HP infection and renal function based on CrCl.

**Key Words.** *Helicobacter Pylori* Eradication, Creatinine Clearance, Peptic Ulcer Disease

## INTRODUCTION

Gastrointestinal complaints are common in patients with renal 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.<sup>1</sup> Over the past decade, progressively HP infection in developed countries has declined, but still are more common in people who have emigrated from endemic areas or who that HP was common in their childhood and were infected at that time.<sup>2</sup>

Several factors, including geographical location, culture, age and socioeconomic factors is involved in HP infection.<sup>2</sup> Although HP infection has declined in resulting to improve health status and anti-bacterial treatments, however, it was observed a gradual rise coincided with the treatment failure rate.<sup>3</sup> Antimicrobial resistance, especially against claritromycin is considered as the main cause of treatment failure of eradication of HP<sup>4</sup> that probably be in the overuse in treatment of upper respiratory tract infections.<sup>5</sup>

HP infection is important in the forming gastrointestinal lesions; on the other hand, high urea levels in the gastric mucosa of patients with renal failure may be causing to HP infection for much of them, because, this bacteria converts urea to ammonia and raises the local pH of the stomach which is needed for the survival of this microorganism.<sup>6</sup> Because of high-potential risk of gastrointestinal mucosal lesions in uremic patients and HP colonization, the screening and eradicating the bacteria is needed for these patients. Bacterial resistance is a great problem in the treatment HP infection, and on the other hand, bismuth compounds is toxic in uremic patients.<sup>7</sup>

Since have not been performed the ever comprehensive study about HP eradication rate in patients with renal failure in Iran and the few available studies only conducted in hemodialysis patients; therefore, in this study, the eradication rate of this bacteria to separation of different groups from normal stage to end-stage kidney disease (hemodialysis) were assessed and the eradication rates in the different groups were compared.

## MATERIALS & METHODS

This randomized clinical trial was conducted after approval from the Research Ethics Committee of Golestan University of Medical Sciences. The patients with peptic ulcer disease who have recently been diagnosed with endoscopy and HP infection in their antral samples were confirmed with rapid urea test (RUT) were selected for the study. Exclusion criteria included pregnancy, catching of cancer or liver failure, a history of taking NSAIDs, PPI, bismuth and antibiotics during the past four weeks, a history of smoking, alcohol and drug allergy. A total of 150 patients who had no exclusion criteria were divided into five groups based on creatinine clearance (CrCl) (Group A: CrCl $\geq$ 90 cc/min; Group B: CrCl=60-89 cc/min; Group C: CrCl=30-59 cc/min; Group D: CrCl<30 cc/min without the need for dialysis; Group E: hemodialysis patients).

Creatinine clearance was measured by 24-hour urine collection and according to the formula [Cr concentrations/Cr urine $\times$ urine volume (cc/min)]. For all patients, the standard 14-day regimen of three drugs, including 20 mg omeprazole, 500 mg clarithromycin and 1000 mg amoxicillin for two times a day were prescribed. In cases where creatinine clearance was below 30 cc/min, the doses of clarithromycin and amoxicillin were to 50 percent. The creatinine clearance in persons from three months before and during the study in the specified group must remain constant. After six weeks of finishing treatment, HP eradication rates in the different groups were evaluated and compared with urea breath test (UBT). The collected data were analyzed using SPSS-18 software and chi-square ( $\chi^2$ ) and Fisher's exact tests.

## RESULTS

18 of 150 patients didn't refer for follow up and excluded. Finally, 132 patients were studied. The mean age of the patients was  $44.84 \pm 12.20$  years and 51.5% (n = 68) of them were female. Body mass index (BMI) in 9.8% of the patients was less than normal and 34.8% was normal, 43.9% overweight and 11.4% of them were also obese. All patients had HP infection and different levels of renal function. 26 patients were in group A with  $\text{CrCl} \geq 90$  cc/min (normal), 27 patients in Group B with  $\text{CrCl} = 60-89$  cc/min, 26 patients in Group C with  $\text{CrCl} = 30-59$  cc/min, 27 patients in group D with  $\text{CrCl} < 30$  cc/min without the need for dialysis and 26 patients in Group E were undergoing hemodialysis. The differences between five study groups were not statistically significant in age, gender and BMI (P values=0.67, 0.98 and 0.26, respectively) (Table 1).

**Table 1.** Demographic data of patients in different study groups

Variable	Study Groups					Total (n=132)	P value
	A (n=26)	B (n=27)	C (n=26)	D (n=27)	E (n=26)		
Age (year)	45.30±12.38	45.74±13.62	45.30±10.95	42.07±10.85	45.84±13.46	44.84±12.20	0.67
Sex (M/F)*	13/13	14/13	12/15	12/14	64/68	68/64	0.98
BMI** (kg/m <sup>2</sup> )	25.23±4.22	25.10±4.13	24.36±4.12	25.56±3.49	24.98±5.10	25.05±4.19	0.26

\*M=Male, F=Female

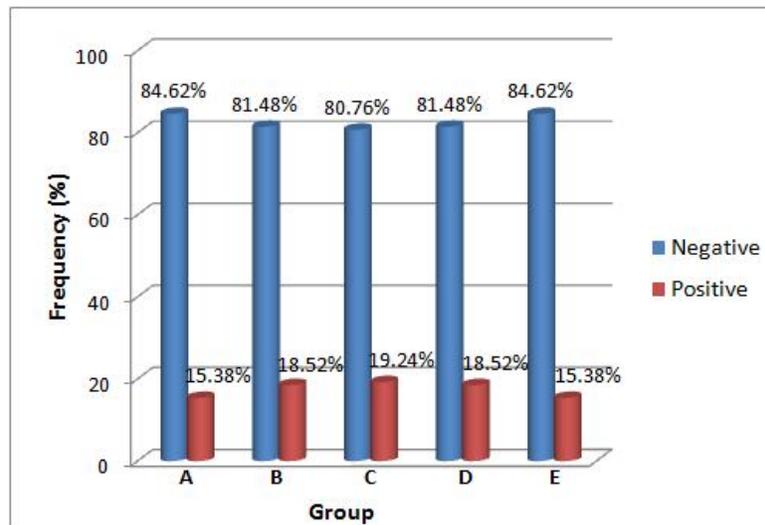
\*\*BMI=Body Mass Index

The Result of UBT at six weeks after treatment in 82.6% (n= 109) of the patients was negative and in 17.4% (n=23) of them also was positive. The results showed no statistically significant difference between the HP eradication rate (according to the result of UBT at six weeks after treatment) in five groups (P=0.99) (Table 2 & Figure 1).

**Table 2.** Results of UBT at six weeks after treatment in different study groups

UBT Result *	Study Groups					Total (n=132)	P value
	A (n= 26)	B (n= 27)	C (n= 26)	D (n= 27)	E (n= 26)		
Negative	22 (84.62%)	22 (81.48%)	21 (80.76%)	22 (81.48%)	22 (84.62%)	109 (82.6%)	0.99
Positive	4 (15.38%)	5 (18.52%)	5 (19.24%)	5 (18.52%)	4 (15.38%)	23 (17.4%)	

\*UBT= Urease Breath Test



**Figure 1.** Results of UBT at six weeks after treatment in different study groups

## DISCUSSION

The findings didn't show a significant correlation between creatinine clearance and eradication of HP infection in studied patients. According to the some factors affecting the disease process can be justified the study results. These findings can be attributed to the prevalence of peptic ulcer and HP infection in different populations. Peptic ulcer in patients with renal failure compared with healthy population are more common, which known to be effective various causes, including increased gastrin and gastric acid secretion, increased parathyroid hormone and decreased mucosal resistance. However, about the prevalence of HP infection is presented different statistics in various studies. Some studies have reported the prevalence of HP infection in patients with renal impairment similar to normal population.<sup>8,9</sup> A study in Iran also showed that the prevalence of HP infection is similar in patients with and without chronic renal failure.<sup>10</sup> While in other studies, the prevalence of HP infection in patients with impaired kidney function is less than the normal population, which the causes are attributed to the protective role of high concentrations of urea or acid-reducing medications and antibiotics.<sup>11,12</sup>

About effects of the factors such as age, sex, race, and BMI on the prevalence of HP infection and response to eradication therapy in patients with kidney failure is not available enough information. In this study, the response to HP eradication therapy among the study groups was not significantly different in 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<sup>13,14</sup> and the rate of colonization with bacteria increase from childhood to the age above 60 years.<sup>15</sup> Also, on gender distribution in some studies, HP infection is more common in males<sup>16,17</sup> and other studies have reported a higher prevalence in females.<sup>18,19</sup>

On the other hand, because of removing bismuth from HP eradication regimens for renal toxicity in this study may be overwhelmed by the response to eradication therapy,<sup>20</sup> while some other studies, the regimens without bismuth have preferred than standard regimen.<sup>21,22</sup> Also, because of substantially increased antibiotic resistance to clarithromycin in particular on HP infection in the world in recent years, this factor is likely to distort the results.<sup>23,24</sup>

In addition to the above factors, the diagnostic accuracy of urea breath test to assess eradication of HP infection is also an important confounding factor in the study. Calvet, et al. in their study found that urea breath test has 75% sensitivity and 60% specificity, but with change in the diagnostic threshold, the sensitivity and specificity increased to 90%.<sup>25</sup> In Peng, et al. study, the sensitivity and specificity of urea breath test for HP were reported 100% and 85.1%, respectively.<sup>26</sup> Kawai, et al. in their study were reported the sensitivity and specificity of urea breath test 97% and 100%, respectively.<sup>27</sup> Despite the many studies done on the accuracy of urea breath test, few studies on the diagnostic accuracy of these test have conducted in patients with renal failure. Lopez, et al. in their study were determined the sensitivity and specificity of the test for diagnosis of HP infection in hemodialysis patients, 94% and 96%, respectively.<sup>28</sup>

On the other hand, Nardone and colleague's study showed the diagnostic accuracy of UBT doesn't decrease in patients with uremia and therefore, it's a useful method for the diagnosis of HP infection.<sup>29</sup> Other researchers found different results in the eradicating HP infection and creatinine clearance using various treatment regimens and methods. In contrast to our findings, the study Itatsu and colleagues showed that low-dose regimen of seven days of lansoprazole, amoxicillin and clarithromycin (LAC) is safe and effective in the treatment of HP infection in hemodialysis patients.<sup>30</sup> Mak, et al. concluded that short-term 3-drug treatment in patients with renal failure is substantially effective.<sup>31</sup> Sheu and colleague's study showed the 3-drug regimen containing clarithromycin, metronidazole without amoxicillin is more effective in patients with

renal failure.<sup>32</sup> The other two studies also were obtained similar results of the above studies.<sup>33, 34</sup> In contrast, the study of Tsukada, et al. showed the 3-drug regimen of omeprazole, amoxicillin and clarithromycin were effective in both hemodialysis patients and normal population and eradication of HP has not significant difference between two groups.<sup>35</sup> Moreover, Seyyedmajidi, et al. obtained similar results in their study and reported the response to HP eradication therapy in patients with kidney failure as the control group<sup>36</sup> that findings of two recent studies were similar to present study.

Although the findings of this study showed no significant difference in response to the eradicating HP infection among patients with kidney failure and a normal population, it can be inferred that uremia is not an effective factor in response to HP eradication therapy. Because hypergastrinemia causes ammonium increase in gastric juice and reducing gastric pH and thereby plays a role in the pathogenesis of peptic ulcer disease, therefore, some studies have suggested that eradication of HP infection by lowering serum gastrin in hemodialysis patients may reduce the incidence of peptic ulcer disease.<sup>37,38</sup>

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, but the 2-year study of Tseng and colleagues showed that relapse rates in patients with ESRD were significantly higher than nonuremic patients.<sup>39</sup> So besides, initial treatment response, relapse rate and the rate of treatment failure due to drug side effects is important in evaluating eradication of HP in uremic patients.

## **CONCLUSION**

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

## **CONFLICT OF INTEREST**

None declared.

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