Original Article

A comparison between standard triple therapy and sequential therapy on eradication of *Helicobacter pylori* in uremic patients: A randomized clinical trial

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Abstract

Background: The prevalence of peptic ulcer disease in hemodialysis dependent patients is higher than the general population. These patients are also more prone to upper gastrointestinal bleeding. The aim of this study was to compare the effects of a standard triple therapy with a sequential therapy on *Helicobacter pylori* eradication in azotemic and hemodialysis patients.

Materials and Methods: Forty nine hemodialysis and azotemic patients, naïve to *H. pylori* treatment, were randomized into two groups to receive either standard triple therapy (pantoprazole 40 mg, amoxicillin 500 mg and clarithromycin 250 mg twice a day for 14 days) or a sequential therapy (pantoprazole 40 mg for 10 days, amoxicillin 500 mg twice a day for the first 5 days and clarithromycin 250 mg + tinidazole 500 mg twice a day just during the second 5 days). *H. pylori* eradication was evaluated by fecal *H. pylori* antigen assessment 8 weeks after the treatment.

Results: Of 49 patients, 45 patients (21 in triple therapy group and 24 in the sequential group) completed the study. Based on intention to treat analysis, *H. pylori* eradication rates were 66.7% (95% confidence interval [CI]: 47.8-85.5%) in standard triple therapy group and 84% (95% CI: 69.6-98.3%) in sequential therapy group ($P = 0.34$). Per-protocol (PP) eradication rates were (95% CI: 76.2%. 6-89.3%) 54 and 87.5% (95% CI: 68.8-95.5%), respectively ($P = 0.32$).

Conclusion: According to Maastricht III consensus report, the results of our study showed that sequential therapy might be a better choice compared with the standard triple therapy in azotemic and hemodialysis patients Iran. We propose to assess the effects of shorter-duration sequential therapy (less than 10 days) for *H. pylori* eradication.

Key Words: Azotemic, *Helicobacter pylori*, hemodialysis, sequential, triple therapy

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INTRODUCTION

World-wide, about 1.1 million people have chronic kidney disease (CKD) receiving hemodialysis. This population is growing at a rate of 0.7% per year due to advances in medical and dialysis techniques.[1] On the other hand, about 50% of the world's population is infected with *Helicobacter pylori*.[2] This rate even

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exceeds 70% in some developing countries.[3] The infection plays an important role in some gastric conditions including peptic ulcer disease, gastric carcinoma and gastric mucosa associated-lymphoid tissue lymphoma, both in a healthy population and in those with chronic renal failure receiving hemodialysis or continuous ambulatory peritoneal dialysis.[4-7]

The studies reporting the prevalence of *H. pylori* in uremic patients are limited[8] and it seems to be equal or lower than the normal population.[7] However, the prevalence of peptic ulcer disease in hemodialysis patients infected with *H. pylori* is higher than the general population.[9] Since gastric mucosa of hemodialysis patients is fragile and anticoagulant therapy is inevitable during hemodialysis, these patients are more prone to upper gastrointestinal bleeding.[10] In order to prevent or to treat peptic ulcer disease in uremic patients, *H. pylori* eradication is recommended as the first line therapy.[11]

According to Mastricht III consensus report, first line therapy for *H. pylori* eradication is a standard triple therapy including a proton-pomp inhibitor (PPI) + clarithromycin + either amoxicillin or metronidazole for 7-14 days.[12] Currently, the same regimen is recommended for hemodialysis patients, administered for 2 weeks.

However, in the general population, the eradication rate using standard triple therapy has fallen to 75-80% from the initial 90%.[13,14] Therefore, this regimen has been questioned and other therapies have been proposed.

Recently, sequential therapies have shown significant success rates in *H. pylori* eradication.[15-18] According to a meta-analysis including 3200 non-hemodialysis patients, sequential therapies were significantly more effective than standard triple therapies in *H. pylori* eradication.[15] We have recently shown 89.1% eradication rate by sequential therapy in non-uremic patients.[19]

In this study, we compared the effects of a standard triple therapy with a clarithromycin-containing sequential therapy on *H. pylori* eradication in azotemic and hemodialysis patients.

MATERIALS AND METHODS

This study was an open label randomized clinical trial performed in Sari, situated in North of Iran from 2010 to 2011. The study protocol was approved by the Hospital Institutional Review Board and Ethics Committee (number: 88-4) and was registered in Iranian registry of clinical trials (number: 138706211241n1). Also, informed consent was obtained from all participants.

Based on findings of previous studies and statistical consultation, our study had to include a minimum of 40 subjects. However, we randomly included 49 patients due to the usual poor compliance of CKD patients, which could result in some loss during the study.

The inclusion criteria were: CKD patients with a serum creatinine level of more than 2 mg/dl or a creatinine clearance (Cl_{cr}) of 15-59 ml/min for at least 3 months and also hemodialysis patients undergoing 2-3 times dialysis per week for at least 3 months. They were all aged >18 years and complained of dyspepsia for at least 1 month and all were positive for *H. pylori* infection using tissue exam or rapid urease test. Also, they were all naïve to *H. pylori* treatment.

The exclusion criteria were history of sensitivity to penicillin or PPIs, non-steroidal anti-inflammatory drug use, taking H2-blockers and/or PPIs and/or antibiotics during the previous 4 weeks, history of upper gastrointestinal surgery, ketoconazole or steroids consumption, alcoholism, pregnancy, having severe heart disease (including myocardial infarction or ejection fraction ≤30), liver disease or malignancy.

Endoscopic procedure and *H. pylori* assessment

All 49 patients had undergone an upper endoscopic examination (using Fujinon EG-250WR5 videogastroscope, Fuji Photo Optical Ltd, Japan). Three biopsies were taken from gastric body and antrum. *H. pylori* infection was confirmed by rapid urease test and histological evaluation of biopsy samples. Biopsies were stained using H and E and wright stains. If at least one of the two tests was positive, the patient was considered positive for *H. pylori* infection.

All patients were randomly enrolled to either of two groups using a computer-generated randomization: 25 patients received standard triple therapy pantoprazole, amoxicillin and clarithromycin (PAC): Pantoprazole 40 mg, amoxicillin 500 mg and clarithromycin 250 mg twice a day for 14 days and 24 patients received sequential therapy pantoprazole, amoxicillin- clarithromycin, tinidazole (PA-CT): Pantoprazole 40 mg twice a day for 10 days, amoxicillin 500 mg twice a day for the first 5 days and clarithromycin 250 mg + tinidazole 500 mg twice a day just during the second 5 days. The dosage of antibiotics was adjusted according to Cl_{cr} in CKD patients. The patients were asked to record any adverse effects of therapy. Compliance to treatment was considered excellent if patient took >80% of medications, good if

70-80% of prescribed drugs were used and moderate or bad if the patient used 60-70% or less than 60% the drugs, respectively. Adverse effects of therapy were considered as mild (not interfering with daily activities), moderate (partially interfering with daily activities) and severe (preventing daily activities).

Due to reported toxic effects of amoxicillin on renal function in CKD patients,[20] we measured creatinine and blood urea nitrogen at the beginning of treatment and also 1 and 4 weeks after therapy in all patients.

Due to the lower specificity of urease breath test in uremic patients,[21] we used fecal *H. pylori* antigen assessment to evaluate *H. pylori* eradication 8 weeks after the treatment. The test was performed by enzyme-linked immune-assay (Instrument: Lab systems Multiskan MS, Washington DC, USA; Kit: Catalog number: 7010, generic assay company, Dahlewitz, Germany) and the cut-off value was 0.1, which had >95% accuracy for detecting *H. pylori* infection.

Mean ± SD and median values were calculated for continuous variables, whereas frequencies were measured for categorical variables. Continuous variables were analyzed using *t*-test and categorical variables were analyzed by Chi-square. Data were analyzed using Statistical Package for the Social Sciences software (version 14) by a statistician who was unaware of the patients' group. In order to calculate intention to treat eradication rate, all participants were included in the analysis, but only those who completed the whole protocol with more than 80% compliance to treatment were included in PER-protocol (PP) analysis. *P* values less than 0.05 were considered statistically significant.

Table 1: Demographic characteristics of the patients at baseline

Variable	Standard group (%)	Sequential group (%)	*P* value
Male/female	10/14 (41.7/58.3)	13/12 (52/48)	0.46
Age (mean±SD) (years)	55.3±18.04	54.54±14.35	0.96
Weight	61.3±13.11	68.93±16.21	0.089
Height	154.48±11.85	159.5±12.27	0.11
History of DM	10 (41.7)	9 (36)	0.68
History of IHD	3 (12.5)	5 (20)	0.47
History of HTN	15 (62.5)	15 (60)	0.85
History of CVA	3 (12.5)	1 (4)	0.27
History of ADPKD	2 (8.3)	1 (4)	0.52
History of dialysis	16 (66.7)	12 (0.48)	0.18
History of GI bleeding	0	2 (8)	0.19
History of retinopathy	2 (8.3)	3 (12)	0.87
History of CABG	1 (4.2)	1 (4)	0.97

DM: Diabetes mellitus, IHD: Ischemic heart disease, HTN: Hypertension, CVA: Cerebro-vascular attack, ADPKD: Autosomal dominant poly-cystic kidney disease, CABG: Coronary artery bypass grafting, GI: Gastrointestinals

RESULTS

Demographic characteristics of the patients at baseline are shown in Table 1 and endoscopic findings are shown in Table 2. Twenty eight patients were hemodialysis dependent: 16 patients in the standard therapy and 12 in sequential therapy groups.

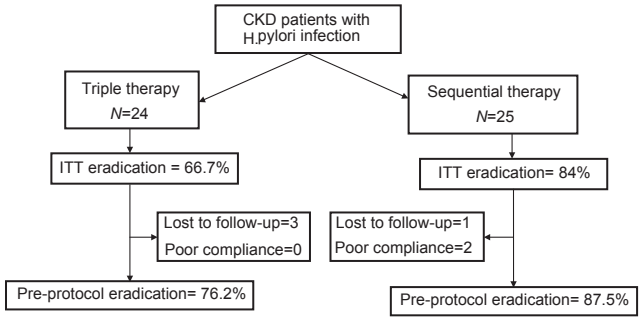
Of 49 patients, 45 (21 in standard therapy group and 24 in sequential therapy group) completed the study.

Four patients of 49 patients were lost to second follow-up and did not perform S/E (three patients in standard therapy group and one in sequential therapy group). Three patients complained of adverse effects: One reported bitter taste due to triple therapy and two reported severe nausea caused by sequential treatment. The latter two patients were dialysis-dependent, one of whom stopped treatment due to side-effects. The remaining patients had more than 80% compliance to treatment.

According to intention to treat analysis, 16 patients (66.7%; 95% confidence interval [CI]: 47.8-85.5%) of the standard therapy group and twenty one (84%; 95% CI: 69.6-98.3%) of sequential therapy group had negative fecal *H. pylori* antigen test after treatment, which did not show a significant difference between the two groups (P = 0.34). PP eradication rates were 76.2% (95% CI: 54.6-89.3%) and 87.5% (95% CI: 68.8-95.5%), respectively (P = 0.32) [Table 3 Flow-chart 1].

Among 28 hemodialysis dependent patients, 26 patients completed the study (15 of 16 patients in standard therapy group and 11 of 12 patients in sequential therapy group). Eradication was achieved in 12 (80%) patients of standard therapy group and 10 (90.9%) patients of sequential therapy group and (P = 0.44).

Among 21 non-hemodialysis dependent patients (8 in standard and 13 in sequential groups), 19 patients



Flow-chart 1: The study design and eradication rates during follow-up

Table 2: Endoscopic findings of the patients in both groups before therapy

Endoscopic findings (%)	Standard group			Sequential group		
	$60>Cl_{cr}\geq30$	$30>Cl_{cr}\geq15$	$Cl_{cr}<15$	$60>Cl_{cr}\geq30$	$30>Cl_{cr}\geq15$	$Cl_{cr}<15$
Gastritis	0 (0.00)	1 (20)	4 (80)	1 (14.30)	4 (57.10)	2 (28.6)
Erosive gastritis	1 (16.70)	2 (33.30)	3 (50)	0 (0.00)	6 (75)	2 (25)
GU	0 (0.00)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	2 (100)
Duodenitis	0 (0.00)	2 (33.30)	4 (66.70)	0 (0.00)	0 (0.00)	2 (100)
Erosive duodenitis	1 (50)	0 (0.00)	1 (50)	0 (0.00)	2 (50)	2 (50)
DU	0 (0.00)	1 (33.30)	2 (66.70)	0 (0.00)	0 (0.00)	1 (100)
Normal	0 (0.00)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	1 (100)
Total	2 (8.30)	6 (25.00)	16 (66.70)	1 (4)	12 (48.00)	12 (48.00)

GU: Gastric ulcer, DU: Duodenal ulcer

Table 3: *Helicobacter pylori* eradication rates in different stages of kidney disease according to ITT in both groups

Drug diet (%)	Dialysis	Stage 4	Stage 3	Total
Standard group	12 of 15 (80)	3 of 4 (75)	1 of 2 (50)	16 of 21 (76.2)
Sequential group	10 of 11 (90.9)	10 of 12 (83.3)	1 of 1 (100)	21 of 24 (87.5)

ITT: Intention to treat

completed the study (six patients (75%) of standard therapy group and 13 patients (100%) of sequential therapy group). Eradication was achieved in four of six patients (66.7%) in standard therapy group and 11 of 13 patients (84.6%) in sequential therapy group ($P = 0.37$).

Totally, 22 hemodialysis dependent patients (84.6%) eradicated *H. pylori* with both regimens while 15 non-hemodialysis dependent patients (78.9%) achieved eradication ($P = 0.62$).

DISCUSSION

According to our results, sequential therapy seems to be more effective than standard triple therapy in CKD patients, although it seems that the patients' compliance with sequential therapy is not as good as with standard regimen.

Upper gastrointestinal symptoms are common in uremic patients.[20] It has been shown that chronic renal failure, either prior to renal transplantation or in patients on hemodialysis, is a predisposing factor for gastro-duodenal mucosal lesions.[20] These gastrointestinal complications can be directly associated with *H. pylori* infection in uremic patients.[9]

Nowadays, eradication of *H. pylori* infection is recommended as the 1st-step in preventing and treating peptic ulcer disease, not only in patients with normal renal function, but also in uremic patients.[20-21] In recent studies, standard triple regimens had disappointing results and only few hemodialysis dependent patients could achieve *H. pylori* eradication.[22]

According to a study by Wang *et al.* on 40 hemodialysis dependent patients, 7 day omeprazole-amoxicillin-clarithromycin (OAC) regimen could eradicate *H. pylori* in 86.8% of cases.[23] In addition, Tsukada *et al.* reported 82.1% eradication rate using the same regimen for 39 hemodialysis patients.[24] Sezer *et al.* showed a high eradication rate (94.1%) among 17 hemodialysis dependent patients using 14-day OAC regimen.[25] However, Itatsu *et al.* reported low eradication rate (72.7%) among 11 hemodialysis patients who had received 7-day lansoprazole-amoxicillin-clarithromycin.[21] On the other hand, Won studied the effects of low-dose OAC on 33 hemodialysis dependent patients and reported an eradication rate of 83.4%.[26]

Since amoxicillin and clarithromycin are primarily eliminated via the renal route, these antibiotics need a dosage adjustment based on Cl_{cr} in patients with renal failure.[27] Toxic effects of amoxicillin on renal function in patients with chronic renal failure have been reported in various studies. The regimen of clarithromycin and lansoprazole without amoxicillin has succeeded only in 33.3% of patients.[20] Furthermore, 36.4% of patients with end-stage renal disease have been reported to have clarithromycin-resistant strains, which is significantly higher than renal disease is limited due to its toxic effects.[28]

Therefore, it seems that common standard regimens in CKD patients have fewer efficacies and more complications than normal populations.

In recent studies, a new regimen is introduced for eradication of *H. pylori* infection in peptic ulcer disease that uses a sequential order of drugs. This regimen has shown significant success rates, exceeding even 90% in the normal population.[29,30] A meta-analysis on 3200 non-hemodialysis patients showed that sequential therapies were significantly more effective than

standard triple therapies for *H. pylori* eradication.[15] Zullo *et al*. evaluated 1049 non-uremic patients with dyspepsia in two groups of standard and sequential regimens. He reported 92% eradication rate by sequential therapy versus 74% by standard therapy.[30] Studies by De Francesco and Hassan showed the same results.[29-31] The highest eradication rates using the sequential regimen has been shown in Italy, but reports from Asia have shown different results. Seyyedmajidi *et al*. compared the effects of a 14-day standard triple therapy with a new sequential therapy (omeprazol and amoxicillin for 14 days, ciprofloxacin just during the 1st week and furazolidone just during the 2nd week) on 39 patients with *H. pylori* infection. The eradication rates were 80% and 78.9% for standard triple therapy and sequential therapy, respectively.[32] In our previous study, *H. pylori* eradication rate in non-uremic patients was 89.1% by sequential therapy.[19]

In the present study, all patients using triple therapy had excellent compliance to treatment without any severe adverse effects leading to discontinuation of therapy. However, two patients (8%) in the sequential therapy group had severe side-effects and one of them discontinued therapy because of severe nausea. Lower doses of antibiotics and the simplicity of treatment might have been two reasons for excellent compliance in the triple therapy group, but the number of antibiotics and the complexity of therapy might have influenced compliance using sequential therapy.

Apart from compliance, antibiotic resistance is another factor influencing *H. pylori* eradication rates. One of the problems in renal failure patients is the probability of higher rates of antibiotic resistance since most of them have previously received different kinds of antibiotics due to impaired immune system. In hemodialysis dependent patients, even using lower doses of antibiotics or PPIs may lead to high plasma concentrations of the drugs. On the other hand, hemodialysis can remove PPIs and antibiotics from the body and therefore, decreasing the plasma level of drugs to lower than expected. Thus, it is essential to set an optimal dosing program to improve eradication rates. In addition, it is better to use antibiotics according to monitored levels of drugs to increase safety.

If we consider *H. pylori* infection as an infectious disease, the ideal regimen is one that can eradicate *H. pylori* infection in more than 95% of cases. Graham classified the efficacy of treatment according to per-protocol success as: (A) Excellent (>95% eradication rate), (B) good (90-95%), (C) fair (85-89%), (D) poor (81-84%) and (F) unacceptable (≤80%).[33] However, in practice, well-tolerated cost-effective regimens with intention-to-treat eradication rates more than 80% are assumed ideal according to Maastricht III consensus report.[12]

According to our results, standard treatment is classified as group F (unacceptable) and sequential treatment as group C (fair) (76.2% vs. 87.5% according to PP analysis, respectively). Although there was no significant difference between the two regimens (P value = 0.346), it seems that the sequential regimen is more effective than standard regimen based on Dr. Graham's classification. In intention-to-treat analysis, the eradication rates were 66.7% and 84%, respectively, which was not significantly different between the two groups (P = 0.34). However, based on Maastricht III consensus report, sequential therapy can be clinically an ideal regimen for eradication of *H. pylori* infection in CKD patients due to achieving more than 80% success rate.

The main limitations of our study were the small number of patients and the unavailability of *H. pylori* culture; therefore, we cannot correlate the results with our regional resistance pattern. Furthermore, we could not assess the variations in plasma concentrations of the drugs after each dialysis course.

CONCLUSION

Based on these results, it seems that sequential therapy might be a better choice compared to the standard regimen for CKD and hemodialysis patients in Iran. Further modifications are needed to improve sequential therapies in uremic and hemodialysis dependent patients to achieve better results in developing countries.

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