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A Comparison between Hybrid Therapy and Standard Triple Therapy for *Helicobacter pylori* Eradication in Patients with Uremia: A Randomized Clinical Trial

Atieh Makhlough[1], Hafez Fakheri[2*], Samaneh Hojati[3], Vahid Hosseini[4], Zohreh Bari[5]

1. Associate Professor, Department of Nephrology, Gut and Liver Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
2. Professor, Department of Gastroenterology, Gut and Liver Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
3. Resident of Internal Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
4. Associate Professor, Department of Gastroenterology, Gut and Liver Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
5. Fellow of Gastroenterology, Mazandaran University of Medical Sciences, Sari, Iran.

* **Corresponding Author:**
Hafez Fakheri, MD
Professor, Department of Gastroenterology, Gut and Liver Research Center, Mazandaran University of Medical Sciences, Sari, Iran
Tel: + 98 11 50670
Fax: +98 11 50671
Email: hafezfakheri@gmail.com
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ABSTRACT

BACKGROUND

The prevalence of peptic ulcer disease in hemodialysis patients is more than the general population. They are also more prone to complications including upper gastrointestinal bleeding. The aim of this study was to compare the efficacy of 14 days hybrid regimen with 14 days triple therapy for *Helicobacter pylori* (*H. pylori*) eradication in hemodialysis patients.

METHODS

Forty hemodialysis patients with naïve *H.pylori* infection were randomized to receive either hybrid regimen (pantoprazole 40 mg + amoxicillin 500 mg, both twice a day during the first 7 days, followed by pantoprazole 40 mg + amoxicillin 500 mg + clarithromycin 500 mg + tinidazole 500 mg, all twice a day, for the second 7 days, or standard triple therapy including pantoprazole 40 mg, clarithromycin 500 mg, and amoxicillin 500 mg, all twice a day for 14 days. *H.pylori* eradication was assessed by fecal *H.pylori* antigen test 8 weeks after the treatment.

RESULTS

All the patients completed the study. According to both intention to treat and per-protocol analyses, *H.pylori* eradication rates were 100% (95% confidence interval (CI): 100) in those who received hybrid therapy and 70% (95% CI: 69.4 – 70.8) in those who were treated by standard triple therapy (p=0.02). Severe adverse effects were not reported by any patient; however, mild adverse effects were more frequent in those who received standard triple therapy (p<0.05).

CONCLUSION

Hybrid regimen could achieve ideal *H.pylori* eradication rates with low rates of adverse effects.

KEYWORDS
Hybrid; Hemodialysis; *Helicobacter pylori*

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INTRODUCTION

Helicobacter pylori (*H.pylori*) is the most common infection worldwide. Almost half of the world's population is infected by the organism.[1] It is associated with peptic ulcer disease (PUD), gastric/duodenal erosions, gastric adenocarcinoma, and gastric lymphoma both in healthy population and patients with uremia.[2-4]

Studies have shown that PUD is more prevalent in *H.pylori* positive hemodialysis patients than the general population.[5] Furthermore, these patients are more prone to gastrointestinal bleeding, partially because of the fragility of gastric mucosa and inevitable use of anticoagulant therapy during hemodialysis.[6] Therefore, *H.pylori* treatment is an important issue in this group of patients.

On the other hand, patients with uremia, especially those with end-stage renal disease (ESRD) have some degrees of immune system dysfunction. Therefore, they have higher rates of infection and antibiotic use. This leads to higher rates of antibiotic resistance in this group of patients.[7] Consequently, the eradication of *H.pylori* may be more difficult in such patients, because antibiotic resistance is the most common cause of failure to eradicate *H.pylori*.[8]

Hybrid regimen is a novel treatment including a proton pump inhibitor (PPI) + amoxicillin during the first 7 days, followed by quadruple regimen of a PPI + amoxicillin + clarithromycin + metronidazole/tinidazole for the second 7 days. The eradication rates achieved by hybrid regimen have been promising in most studies. Also, a recent review article considering *H.pylori* eradication regimens in west Asia has reported hybrid regimen as an ideal regimen for first line *H.pylori* therapy in this geographic region.[9] However, to the best of our knowledge, no study has assessed the effects of hybrid regimen for *H.pylori* eradication in patients with uremia. Therefore, we designed a study to compare the effects of hybrid therapy with standard triple therapy in hemodialysis patients.

MATERIALS AND METHODS

From December 2013 to January 2014, forty hemodialysis patients with naïve *H.pylori* infection entered the study. *H.pylori* infection had been confirmed by both rapid urease test (RUT, Shim anzy, Tehran, Iran) and fecal *H.pylori* antigen test (Dahelwit 93, Germany). The reasons for gastrointestinal evaluation were long-standing dyspepsia, iron deficiency anemia, or being candidate for renal transplantation. Before starting the protocol, written informed consents were obtained from all the patients.

The exclusion criteria were age less than 18 years or above 85 years, any chronic disease that would hinder follow-up (such as liver failure, heart failure, chronic pulmonary disease, or history of malignancy), history of allergic reactions to any of the medications used in this study, history of gastric or esophageal surgery, using antibiotics during the previous week, pregnancy, or breastfeeding.

The patients were randomized into two groups, using computer-generated randomization. Twenty patients received hybrid regimen including: pantoprazole 40 mg + amoxicillin 500 mg both twice a day during the first 7 days, followed by pantoprazole 40 mg + amoxicillin 500 mg + clarithromycin 500 mg + tinidazole 500 mg, all twice a day, for the second 7 days. The remaining 20 patients received standard triple therapy including: pantoprazole 40 mg, clarithromycin 500 mg, and amoxicillin 500 mg, all twice a day for 14 days.

The patients were advised to call the doctor in case of any severe side effects. After treatment, all patients were visited and were asked about the number of remained medications (if any). Compliance to treatment was considered excellent if the patient took more than 90% of the medications, good in case of taking 70-90% of the drugs and poor, if the patient used less than 70% of the prescribed medications.

H.pylori eradication was assessed by fecal *H.pylori* antigen test (Dahelwit 93, Germany) 8 weeks after the treatment. In order to calculate intention to treat eradication rates, all the patients who entered the study were included in the analysis. But in order to calculate per-protocol eradication rates, only data of those who completed the entire protocol with more than 90% compliance to treatment were analyzed.

Data were analyzed using IBM SPSS software for windows (version 16). Chi-square and t tests were used as appropriate. p values less than 0.05 were considered as statistically significant.

RESULTS

All the patients completed the study. Nineteen patients were men (47.5%) and 21 (52.5%) were

women. The mean age was 51.3 ± 16.9 years. Demographic data including age, sex, history of gastrointestinal bleeding, endoscopic findings, the reasons for gastrointestinal evaluation, and the need for *H.pylori* eradication did not show statistically significant difference between the two groups (table 1). The indications for *H.pylori* eradication were: being candidate for renal transplantation, dyspepsia, or gastroduodenal ulcer or erosions.[10]

Six patients in the triple therapy group (30%) reported mild adverse effects (four cases of metallic taste and two cases of malaise). Also, two patients who received hybrid regimen (10%) complained of mild metallic taste ($p<0.05$). However, compliance to treatment was excellent in all patients and no one interrupted treatment because of adverse effects of the treatment.

According to both intention to treat and per-protocol analyses, *H.pylori* eradication rates were 100% (95% CI: 100) in those who received hybrid regimen and 70% (95% CI: 69.41– 70.89) in those who were treated by standard triple therapy ($p=0.02$, figure 1)

Table 1: Demographic characteristics of the patients in both groups

Variable		Hybrid therapy	Triple therapy
Male/ Female		11/9	8/12
Age (years)		51.0 ± 19	51.5 ± 15
History of GIB		1	4
Endoscopic findings	Gastric ulcer	4	10
	Duodenal ulcer	1	3
	Gastric erosion	12	4
	Duodenal erosion	2	2
	Erosive gastro-duode-nopathy	1	1
Indication for gastrointestinal evaluation	Dyspepsia symptoms	4	5
	Iron deficiency anemia	5	6
	Candidate for renal transplan-tation	11	9

GIB: gastrointestinal bleeding

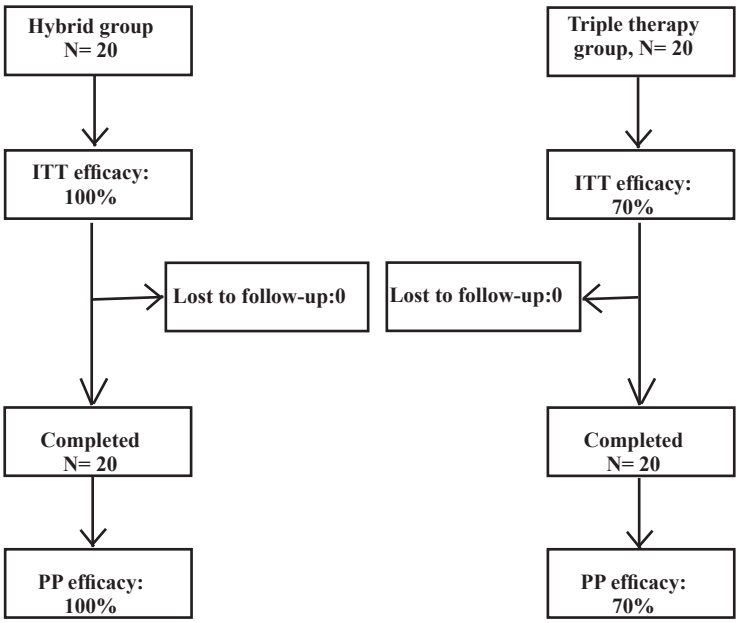
DISCUSSION

Our study showed that hybrid regimen could eradicate *H.pylori* in 100% of patients, but the eradication rate achieved by standard triple therapy was disappointing. Furthermore, the rates of side-effects of treatment were significantly lower in those who received hybrid regimen. However, both regimens were well tolerated and no one interrupted the treatment because of the adverse effects of the prescribed drugs.

If we consider *H.pylori* as an infectious disease, the ideal regimen would be the one that can eradicate *H.pylori* in more than 95% of the cases.[11] Most of previous studies could not achieve optimal eradication rates in hemodialysis patients.

Comparing the results of our study with previous reports, standard triple therapy could not achieve ideal eradication rate. This is in concordance with most previous studies. According to a recent study performed by Makhlough and colleagues, 49 hemodialysis patients were randomized to receive either 14-day clarithromycin-containing triple therapy or sequential regimen. *H.pylori* eradication rates were 76.2% and 87.5% by per-protocol analysis, respectively.[12] According to another study by Wang and co-workers on 40 hemodialysis patients, 7-day omeprazole-amoxicillin-clarithromycin(OAC) regimen could eradicate *H.pylori* in 86.8% of cases.[13] In addition, Tsukada and colleagues reported 82.1% eradication rate using the same regimen for 39 hemodialysis patients.[14] Sezer and others showed a high eradication rate (94.1%) in 17 hemodialysis dependent patients using 14-day OAC regimen.[15] However, Itatsu and colleagues reported low eradication rate (72.7%) among 11 hemodialysis patients who had received 7-day lansoprazole-amoxicillin-clarithromycin.[16] On the other hand, Chang studied the effects of low-dose OAC on 33 hemodialysis patients and reported an eradication rate of 83.4% by per-protocol analysis.[17]

On the other hand, our study showed excellent (100%) *H.pylori* eradication rate by hybrid regimen. Hybrid regimen is a novel *H.pylori* eradication protocol with promising eradication rates.



ITT: intention to treat; PP: per-protocol

Fig. 1: Method of follow-up & treatment efficacy

However, to the best of our knowledge, all related studies have been performed on patients without uremia and no study has been performed on patients with uremia. According to a study performed by De Francesco and coleagues on patients without uremia, hybrid therapy could achieve 82.7% eradication rate by intention to treat analysis.[18] Also, Oh and coworkers reported 81.1% and 85.9% eradication rates by hybrid therapy according to intention to treat and per-protocol analyses, respectively.[19] Zullo and others evaluated the effects of concomitant, sequential and hybrid therapies on 270 patients with non-ulcer dyspepsia. The eradication rates achieved by hybrid therapy were 80% and 85.7% according to intention to treat and per-protocol analyses, respectively.[20] Sardarian and colleagues also performed a study to compare the effects of hybrid therapy versus sequential therapy for *H.pylori* eradication. Two hundred and ninety six patients entered the study. The eradication rates achieved by hybrid therapy were 89.5% and 92.9% by intention to treat and per-protocol analyses, respectively. In the mentioned study, the eradication rate achieved by hybrid therapy was significantly higher than sequential therapy.[21]

Upper gastrointestinal symptoms are common in patients with uremia. It has been shown that chronic renal failure, either prior to renal transplantation or in patients on hemodialysis, is a predisposing factor for gastroduodenal mucosal lesions.[6,22] These gastrointestinal complications can be directly associated with *H.pylori* infection.[5] Also patients with uremia are more prone to complications of PUD than the general population.[6] Furthermore, some studies have reported higher resistance rates to antibiotics in patients with uremia than the general population.[23] Therefore, introducing an *H.pylori* eradication regimen with ideal eradication rates seems to be important in this group of patients and our study reported excellent *H.pylori* eradication rate by hybrid regimen.

Our study has some limitations. One of the main limitations was small number of patients that is because of evaluating a special group of patients (hemodialysis patients). Another important limitation was the unavailability of *H.pylori* culture. However, the strong point of the present study was to evaluate the effects of hybrid regimen in patients with uremia, because to the best of our knowledge, no study has been performed to evaluate the effects of hybrid therapy in hemodialysis patients

In conclusion, hybrid regimen could achieve ideal *H.pylori* eradication rate with low rate of side-effects and excellent compliance to treatment. Further

studies with larger number of patients are suggested.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Egan BJ, Marzio L, O'Connor H, O'Morain C. Treatment of Helicobacter pylori infection. *Helicobacter* 2008;**13** Suppl 1:35-40. DOI:10.1111/j.1523-5378.2008.00639.x.
2. Sugimoto M, Sakai K, Kita M, Imanishi J, Yamaoka Y. Prevalence of Helicobacter pylori infection in long-term hemodialysis patients. *Kidney Int* 2009;**75**:96-103. DOI:10.1038/ki.2008.508.
3. Gioe FP, Cudia B, Romano G, et al. Role and clinical importance of Helicobacter pylori infection in hemodialysis patients. *G Chir* 2008;**29**:81-4.
4. Suzuki H, Saito Y, Hibi T. Helicobacter pylori and Gastric Mucosa-associated Lymphoid Tissue (MALT) Lymphoma: Updated Review of Clinical Outcomes and the Molecular Pathogenesis. *Gut liver* 2009;**3**:81-7. DOI:http://dx.doi.org/10.5009/gnl.2009.3.2.81
5. Khedmat H, Ahmadzad-Asl M, Amini M, Lessan-Pezeshki M, Einollahi B, Pourfarziani V, et al. Gastro-duodenal lesions and Helicobacter pylori infection in uremic patients and renal transplant recipients. *Transplant Proc* 2007;**39**:1003-7. DOI:http://dx.doi.org/10.1016/j.transproceed.2007.03.034.
6. Fabian G, Szigeti N, Kovacs T, Nagy J. An unusual multiplex cause of severe gastrointestinal bleeding in a haemodialysed patient. *Nephrol Dial Transplant* 2000;**15**:1869-71. DOI:10.1093/ndt/15.11.1869.
7. Aydemir S, Boyacioglu S, Gur G, Demirbilek M, Can FK, Korkmaz M, et al. Helicobacter pylori infection in hemodialysis patients: susceptibility to amoxicillin and clarithromycin. *World J Gastroenterol* 2005;**11**:842-5. DOI:10.3748/wjg.v11.i6.842.
8. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010;**59**:1143-53. DOI:10.1136/gut.2009.192757.
9. Fakheri H, Bari Z, Aarabi M, Malekzadeh R. Helicobacter pylori eradication in West Asia: a review. *World J Gastroenterol* 2014;**20**:10355-67. DOI:10.3748/wjg.v20.i30.10355.
10. Knoll G, Cockfield S, Blydt-Hansen T, Baran D, Kiberd B, Landsberg D, et al. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. *CMAJ* 2005;**173**:1181-4. DOI:10.1503/cmaj.051291.
11. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. *Helicobacter* 2007;**12**:275-8. DOI:10.1111/j.1523-5378.2007.00518.x.
12. Makhlough A, Fakheri H, Farkhani AR, Seddighi O, Hossieni SV, Khademloo M, et al. A comparison between standard triple therapy and sequential therapy on eradication of Helicobacter pylori in uremic patients: A randomized clinical trial. *Adv Biomed Res* 2014;**3**:248. DOI:10.4103/2277-9175.146372
13. Wang YL, Sheu BS, Huang JJ, Yang HB. Noninvasive stool antigen assay can effectively screen Helicobacter pylori Infection and assess success of eradication therapy in hemodialysis patients. *Am J Kidney Dis* 2001;**38**:98-103. DOI:http://dx.doi.org/10.1053/ajkd.2001.25200.
14. Tsukada K, Miyazaki T, Katoh H, Masuda N, Ojima H, Fukai Y, et al. Seven-day triple therapy with omeprazole, amoxycillin and clarithromycin for Helicobacter pylori infection in haemodialysis patients. *Scand J Gastroenterol* 2002;**37**:1265-8. DOI:10.1080/003655202761020524.
15. Sezer S, Ibis A, Ozdemir BH, Ozdemir FN, Külah E, Boyacioğlu S, et al. Association of helicobacter pylori infection with nutritional status in hemodialysis patients. *Transplant Proc* 2004;**36**:47-9. DOI:http://dx.doi.org/10.1016/j.transproceed.2003.11.023.
16. Itatsu T, Miwa H, Nagahara A, Kubota M, Miyazaki A, Sato N, et al. Eradication of Helicobacter pylori in hemodialysis patients. *Ren Fail* 2007;**29**:97-102. DOI:10.1080/08860220601039122.
17. Chang WC, Jo YI, Park HS, Jegal J, Park JH, Lee JH, et al. Helicobacter pylori eradication with a 7-day low-dose triple therapy in hemodialysis patients. *Clin Exp Nephrol* 2010;**14**:469-73. DOI:10.1007/s10157-010-0319-7.
18. De Francesco V, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for Helicobacter pylori eradication: a prospective randomized study. *J Med Microbiol* 2014;**63**:748-52. DOI:10.1099/jmm.0.072322-0.
19. Oh DH, Lee DH, Kang KK, Park YS, Shin CM, Kim N, et al. Efficacy of hybrid therapy as first-line regimen for Helicobacter pylori infection compared with sequential therapy. *J Gastroenterol Hepatol* 2014;**29**:1171-6. DOI:10.1111/jgh.12518.
20. Zullo A, Scaccianoce G, De Francesco V, Ruggiero V, D'Ambrosio P, Castorani L, et al. Concomitant, sequential, and hybrid therapy for H. pylori eradication: a pilot study. *Clin Res Hepatol Gastroenterol* 2013;**37**:647-50. DOI:10.1016/j.clinre.2013.04.003.
21. Sardarian H, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for Helicobacter pylori eradication in Iran: a prospective randomized trial. *Helicobacter* 2013;**18**:129-34. DOI:10.1111/hel.12017.
22. Cocchiara G, Romano M, Buscemi G, Maione C, Maniaci S, Romano G. Advantage of eradication therapy for Helicobacter pylori before kidney transplantation in uremic patients. *Transplant Proc* 2007;**39**:3041-3. DOI:http://dx.doi.org/10.1016/j.transproceed.2007.07.095.
23. Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. *Am J Kidney Dis* 2008;**51**:233-41. DOI:10.1053/j.ajkd.2007.10.038.