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Review Article

Experiences with *Helicobacter Pylori* Treatment in Iran

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Abstract

Helicobacter pylori (*H. Pylori*) infection is currently recognized as the major cause of chronic active gastritis, peptic ulcer disease and mucosa associated lymphoid tissue (MALT) lymphoma and carcinoma of the stomach. Eradication of the infection will prevent the recurrence of the majority of such diseases. Different combined treatments have been tried in Iran for eradication of *H. Pylori*, but the optimal eradication needs further evaluation. Herein, we have reviewed the eradication regimens of *H. Pylori* used by Iranian scientists during a 16 year period from 1990 to 2006, regarding the number, the type of drugs used, the duration, eradication rate, and their side effects.

From 26 articles retrieved, 22 drug regimens were evaluated. Triple drug therapy was favored in our country, as it consisted of 63% of the regimens. But it could not achieve an optimal eradication rate. Of eight quadruple drug regimens, two led to an optimal eradication rate, with the highest eradication rate being 92% based on furazolidone quadruple regimen. But this regimen had significant side effects in more than 62% of the patients.

The best first line treatment regimen for eradication of *H. Pylori* in Iran seems to be a type of furazolidone or clarithromycin based quadruple therapy for a minimum duration of two weeks. However, the patients should be monitored for furazolidone side effects. Furthermore, in metronidazole based quadruple therapy drug resistance is a major problem, even with doses of more than 1 gm/day. In patients with treatment failure, medication should be adjusted according to antibiotic sensitivity and newer antibiotic therapies, which is designed as clinical trials.

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Keywords ● *H. pylori* ● eradication ● treatment experiences ● Iran

Introduction

Helicobacter pylori (*H. Pylori*) is a gram negative spiral bacillus causing peptic ulcer disease, low-grade gastric mucosa-associated lymphoid tissue lymphoma (Maltoma), and carcinoma. More than 95% of patients with duodenal ulcer and 80% of patients with gastric ulcer are infected with *H. Pylori*.[1] In addition to acid reduction; eradication of *H Pylori* is the main therapeutic modality for the treatment of peptic ulcer disease. The role of *H. Pylori* eradication in the long term prevention of gastric carcinoma is still unclear. However, recent studies showed that the incidence of gastric carcinoma

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during 8 years follow up was more than 5% in patients with dyspepsia without peptic ulcer, infected with *H. Pylori*.[2]

The incidence rate of *H Pylori* infection in the developed countries may be as low as 30%, while in developing and underdeveloped countries it is more than 80%, and in Iran this rate is 86%.[3] Antibiotic resistance, patient's poor compliance and intolerance to therapeutic regimens are said to be the major problems with eradication of *H. Pylori*.[4] In recent years, resistance to antibiotic therapy have increased, and multiple drug therapies have decrease the patient's compliance.

Triple therapy using a proton pump inhibitor, or ranitidine plus bismuth citrate combined with clarithromycin and amoxicillin or metronidazole was the first-line of *H. Pylori* eradication. Whereas, quadruple therapy with a proton pump inhibitor, bismuth, metronidazole and tetracycline was defined as the second-line eradication treatment for *H. Pylori* infection.[5] McLoughlin and colleagues used a seven-day proton-pump inhibitor-amoxicillin-clarithromycin triple therapy as the first-line therapy for *H. Pylori* infection followed by a ten-day sequential treatment as an alternative first-line therapy. Bismuth-based quadruple therapy was considered as the second-line regimen of choice.[6] Novel triple-therapy regimens containing rifabutin, levofloxacin, or furazolidone seemed to be a useful alternative and a second or third-line therapy.[6]

Decreasing the duration and the number of drugs in the *H. Pylori* eradication regimens were reported to achieve better outcome by increasing the patient's compliance in other countries, but these forms of therapies seem to be less effective in *H. Pylori* infection in our country.[7] An important problem in Iran, as of other developing countries, is the high rate of re-infection after eradication of *H Pylori*. The re-infection rate of three years *H. Pylori* eradication was reported as being 20.4% in Iran,[8] and 34% in Yemen.[9] Evaluation of different studies for eradication of *H. Pylori* in Iran may help to identify the effectiveness of therapeutic regimens and new research studies. It is intended to recommend effective and suitable regimens regarding to their availability and tolerance in eradication of *H. Pylori* with accord to previous experiences of Iranian investigators.

The present work reviews all reports on *H Pylori* eradication performed in Iran and published in national medical journals during 1990-2006 and also cited in Iran-Medex. Likewise, international databases, such as PubMed.com, are used to look into all published researches based on clinical trials performed in this field from Iran. Twenty-eight articles were retrieved from these two databases. These were evaluated in regard to the study design, inclusion and exclusion criteria, the number and the type of medications, the tests used for detection and eradication of *H Pylori*, the rate of eradication, and the side effects of the drugs used in this field.

Although, the comparisons of the results of these papers were very difficult, due to different methods used, different treatments and follow-up protocols, they are categorized according to the composition of each regimen and the number and the type of drugs used. Two investigations included patients with peptic ulcer disease and other studies comprised patients with dyspepsia with or without peptic ulcer. The *H. Pylori* infection was proved by histology and/or urease test and *H. Pylori* eradication was confirmed by urea breath test and/or histological examination of the gastric mucosa and the results were categorized according to the number of drugs used.

Single drug therapy

An eradication rate of 15-36% was reported with single drug therapy such as clarithromycin in a European study. Another study reported bacteriostatic effects in vitro of proton pump inhibitors (PPI), while they did not have any bactericidal effect.[7,10] There was no study showing the use of single drug therapy in Iran and regarding low eradication rate, this type of treatment had no role in *H. Pylori* eradication.

Combination drug therapy

As clearing up *H. Pylori* infection needs multiple antibiotics, the recommended therapeutic protocols tried so far included fewer numbers of drugs, shorter period of treatment, and an eradication rate of usually more than 90% with fewer side effects.

Double drug therapy

Supplementing acid reducing agents such as proton pump inhibitors or histamine H_2 receptor blockers with an anti-microbial agent, increases the eradication rate in addition to earlier disappearance of peptic ulcer symptoms. The most common double drug regimen used during the recent decade was omeprazole with amoxicillin. In these studies, the eradication rate of this regimen was lower (19-35%) than the usual standard therapy.[11,12] However, similar studies performed in Europe, showed that increasing the dose of omeprazole from 20 to 120 mg/day increased the *H. Pylori* eradication rate from 37% to 85%.[13]

In two studies reported from Shiraz, double drug regimen including an acid reducing agent (famotidine, ranitidine, or omeprazole) and an anti-microbial agent without bismuth compounds led to a very low eradication rates less than 50%, but the symptoms were improved in more than 50% of patients.[12,14] The efficacy of omeprazole plus ciprofloxacin regimen for a 7-day period in healing of the duodenal ulcer and eradication of *H. Pylori* showed a healing rate of 88% and an eradication rate of 65%.[15] The eradication rates of double drug regimens, most often including omeprazole and clarithromycin, were reported to be 46-69%.[11] However, this rate was lower in Iran, possibly due to the excessive costs of clarithromycin.[15]

Triple drug therapy

Fourteen papers reported the use of triple drug regimen in their methodology but their *H. pylori* eradication rates were from 17.1% to 88.2% (Table 1). In 12 studies, the therapeutic regimens included an acid reducing agent, mostly PPI, plus two anti-microbial agents. PPI based regimens were accompanied by fewer side effects when compared with other acid reducing agents such as using H2 receptor blockers. Eight studies performed in other countries, as well as in Iran, showed that metronidazole was the most common drug used in combination with amoxicillin or tetracycline.[12,14,16,20,21]

The *H. pylori* eradication rate of metronidazole based triple drug regimen was 80-90%, in western countries, whereas, in Iran this rate was lower, possibly due to increasing rate of drug resistance.[17,20] In a recent study performed in our center, the approximate rates of drug resistant of *H. Pylori* isolates were 70% to metronidazole, 10% to clarithromycin and furazolidone, 20% to amoxicillin, and 5% to tetracycline and ciprofloxacin, whereas, the *H. Pylori* isolated from patients with peptic ulcer disease and dyspepsia were not resistant to amoxicillin plus clavulanic acid (unpublished data). High rate of metronidazole resistance (62.7%) was also reported from other Asian countries too.[18]

The rate of adverse effects, which in some cases were very severe, was more frequent with furazolidone based regimen and usually started from the end of first and early second week. Malekzadeh and colleagues reported that in two groups of patients who were receiving the same doses of omeprazole, furazolidone and tetracycline with the durations of 4 and 7 days, the adverse effects of the drugs was very low and the eradication rate of *H. pylori* in both groups were 17% and 23.8%, respectively.[20] In this study they concluded that in Iran the use of these regimens with durations less than two weeks are ineffective and a minimum of two weeks are needed to have an acceptable outcome.[19] Roughani et al. reported that in the triple therapy consisting of bismuth subcitrate, metronidazole and tetracycline, the eradication rate was 80.7% in metronidazole sensitive strains *H. pylori* and 64% in metronidazole resistant strains.[20] Triple therapy including clarithromycin resulted in an acceptable eradication rate, whereas when the combination of amoxicillin, clarithromycin, and omeprazole used for a duration of 7 and 14 days, the *H. Pylori* eradication rates were about 86% and the intent-to-treat eradication rates were 73.1% and 65% respectively.[21]

Table1: triple and quadruple *H pylor*i eradication regimens used in Iran during past decade

Regimens	Detection Method	Type Of Disease	no of Patients	Eradication Rate (%)		Side Effects (%)	Ref
				Per Protocol	Intention for Treatment		
Triple therapy							
OAC (7 days)	UBT	NUD	45	41	35	4	19
OAC (10 days)	UBT	DU, NUD	--	92	75	--	22
OBC	RUT, HIS	NUD	76	67	--	--	16
ABM	UBT, DU	DU	50	57	54	8	12
OFT (7 days)	UBT	NUD	42	--	24	--	19
BMT	HIS	PUD	43	58	--	--	17
OAT	UBT, HIS	DU	44	48	--	--	12
Quadruple therapy							
OBMT	UBT	DU, NUD, GU	76	76	--	--	16
OBFT	UBT	DU, NUD, GU	--	90	--	--	22
OABM (10 DAYS)	UBT	DU, NUD	90	84	69	--	24
OABC	UBT	DU	63	55	84	--	21
OFBA	UBT	DU	63	90	85	--	21
OAzBM	UBT, HIS	DU, GU, NDU	64	78	74	3	15
OBFA	UBT	DU	90	78	--	--	23
OBAM	UBT, HIS	DU, GU, NDU	63	76	70	4	15

A: Amoxiycillin1000 mg qd, C: Clarithromycin 1gm/d, B: Bismuth sub citrate:240 mg bd, F: Furazolidon:100 mg bd
T: Tetracycline: 100 mg qd, O: Omeprazole: 20mg QD, M: Metronidazol:250 mg q8h, RUT: rapid urease test, HIST: histology, UBT: urea breath test, PUD: peptic ulcer disease, DU: duodenal ulcer, GU: gastric ulcer.
Az: Azithromycin 250mg daily

Table 2: Recommendable treatment regimens for helicobacter pylori eradication in Iran

First line treatment options:
1.Clarithromycin 500 mg bd, Amoxicillin 1000 mg bd, bismuth subcitrate 240 mg bd , omeprazole 20 mg bd for 14 days (A)
2. Tetracycline 500 mg qid, metronidazole 500mg tds, bismuth subcitrate 120 mg qd, omeprazole 20mg bd for 14 days (B)
Second line treat ment options:
1.Regimen A (if clarithromycin has not been used in the first line)
2. Furazolidone 200mg bd, Amoxicillin 1000 mg bd/ or Tetracycline 500 mg qid, Bismuth subcitrate 240 mg bd, omeprazole 20mg bd for 14 days

Quadruple drug therapy

Quadruple drug regimens generally induced better results than triple therapy particularly in metronidazole resistant cases. However, their drawbacks were due to low compliance, high cost, and the number of drugs used in each day. Most of these regimens consisted of H_2 receptor blocker, or a proton pump inhibitor, combined with three antimicrobial agents. The compositions of these regimens were bismuth subcitrate plus amoxicillin, or tetracycline, and metronidazole, or furazolidone, and clarithromycin or azithromycin. In these triple therapies, the highest eradication rate was observed in furazolidone based regimens.

Quadruple regimens based on metronidazole or clarithromycin recommended in other studies had an eradication of 78%.[23] The side effects and the severity of this regimen with furazolidone were higher in metronidazole based regimens. In most reports the duration of treatment were two weeks, but in one study the duration of quadruple therapy was considered as three weeks. In children the quadruple therapy in metronidazole based regimen was compared with triple clarithromycin based regimen for 10 days, but the results were comparable to the standard schedule of two weeks with eradication rate of 75.5%.[24] Performance of anti biogram before treatment for detecting metronidazole sensitivity has shown to increase the *H. Pylori* eradication rate from 15% to 20%.[20] The side effects of the quadruple regimens were nausea, vomiting, dizziness, fatigue, anorexia, abdominal pain and in more severe conditions fever and diarrhea.[20-24]

Although, most studies mentioned in here failed to show correlation between age, gender, duration of the symptoms, or smoking habits, with *H. Pylori* eradication, some study indicated that in patients of more than 42-years-old had better prognostic indication factors for *H. Pylori* eradication.[25] Other factors such as socioeconomic condition and geographical situation were not considered in these studies and there was not a correlation between recurrence of peptic ulcer and the type of drugs used for *H. pylori* eradication. As shown in Tables 1 and 2, the triple and quadruple drug regimens caused an eradication rate equal to, or higher than, optimal levels (75-80%). In a recent report the standard quadruple therapy consisting metronidazole, bismuth, tetracycline and omeprazole was said to be superior to quadruple therapy of consisting furazolidone tetracycline bismuth and levofloxacin-based triple therapy consisting ciprofloxacin bismuth subcitrate.[25]

Eradication of *H. Pylori* has become complicated due to the increasing emergence of drug resistant strains. Metronidazole resistance is very common and the resistance frequency of *H. Pylori* isolates to amoxicillin, clarithromycin and tetracycline have increased exponentially as shown by in vitro studies. In addition to better eradication rates, we should also consider other factors such as localized delivery of drugs to the stomach.[25] In recent reports the newer treatment regimens such levofloxacin or rifabutin based therapies have been used in multiple studies around the world, and should be used in well designed clinical studies in our country.[26]

Conclusion

The best treatment schedule for eradication of *H. Pylori* in Iran is a type of quadruple therapy for a minimum duration of two weeks. Since, clarithromycin and furazolidone based quadruple regimen has the highest eradication rate up to 92%, it can be considered as the first line therapy. Metronidazole based quadruple therapy may be used as an alternative choice of first line therapy. It is also important to not that furazolidone based regimens could induce side effects and are highly contraindicated in patients with G6PD deficiency.

Other aspects for better *H. Pylori* eradication include such as patient's knowledge and compliance, use of correct drug doses, duration and formulation of the antibiotics, as well as bacterial factors, and sensitivity tests should be considered in clinical practice.

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