Comparison of Furazolidone Versus Clarithromycin for Eradication of Helicobacter Pylori Infection: A Randomized Multicenter Clinical Trial

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Background and study aims: to evaluate efficacy of Furazolidone versus clarithromycin in quadruple therapy for eradication of Helicobacter Pylori (HP) infection .

Patients and Method: During a period of six months, all of the cases with HP infection in 3 referral tertiary centers included. The participants randomly allocate to receive either clarithromycin or Furazolidone base quadruple regimen. For all of the participants pantoprazole continued for 4 more weeks and after 1 to 2 weeks of off therapy, they underwent Urea Breath Test to prove eradication.

Results: Overall 386 patients included (165 male (42%), average age 44.2y). They diagnosed as non-ulcer dyspepsia (311 cases), peptic ulcer disease (34 cases) and intestinal metaplasia (45 cases). The participants randomly allocated to groups A & B to receive either clarithromycin or Furazolidone. In groups A and B, 80.9% & 82.1% of participants achieved eradication respectively (P = 0.819). During study, there was not any major complication but 3.1% of participants in each group reported minor side effects including bitter taste, Gastrointestinal (GI) upset, headache and or vertigo. In sub group analysis, the eradication rate of clarithromycin among patients with non-ulcer dyspepsia, peptic ulcer disease (PUD) and intestinal metaplasia were 80%, 100% & 55.6% respectively. These figures in group B (Furazolidone) were 80.7%, 100% & 85.7% respectively (P= 0.906, 0 & 0.162). Overall, there was no significant difference in success rate between clarithromycin and Furazolidone but in cases with intestinal metaplasia, the positive results with Furazolidone was more (85.7% vs. 55.6%).

Conclusion: In areas with high rate of resistance to clarithromycin, Furazolidone could be a potential candidate in HP eradication regimen and in cases with intestinal metaplasia; Furazolidone could be even more efficient than clarithromycin.

INTRODUCTION

Helicobacter pylori (HP) which infect almost half of the world population is the main offender in creation of disorders such as gastritis and peptic ulcer disease and has known as a major risk factor of gastric cancer **[1, 2, 3, 4]**. Though the rate of HP infection has decreased in developed countries, its prevalence is still increasing in developing communities probably because of poor socioeconomic level and life style **[2, 5, 6, 7, 8, 9].**

In recent decades, a large number of associations with nongastric diseases and HP infection have been reported beside gastric problems that further emphasize on importance of HP detection and eradication **[10, 11, 12]**.

On the other hand, Prevalence of H. pylori antibiotic resistance is increasing worldwide, a main factor that affecting efficacy of current therapeutic regimens **[13]**. Antibiotic

resistance in Helicobacter pylori is the major cause of eradication failure and an ever-changing issue. Primary H. pylori susceptibility patterns are becoming less predictable and currently, high (≥20%) clarithromycin resistance rates have been observed in the developed countries **[14]**. The resistance rate is even more in developing countries and is the main reason for eradication failure **[15, 16, 17]**. This emerging pattern of resistant, necessitate evaluating different therapeutic regimens for clinical purposes **[18]**. In this regard, a potential substitute could be Furazolidone based regimen as a well-established and inexpensive antibiotic, which is also shown to be a potentially good alternative to metronidazole, especially in areas where metronidazole resistance is common **[19, 20, 21]**. In this randomized multi centric clinical trial, we evaluated efficacy of Furazolidone versus clarithromycin as quadruple therapy for eradication of HP infection.

METHODS

During a 6 months period, all of the cases who had attended outpatient clinics of 3 referral tertiary centers with complain of dyspepsia and their HP infection diagnosed based on tissue biopsy specimen included and allocate randomly into groups A & B. Participants in group A treated with clarithromycin base quadruple regimen (Pantoprazole 40 mg bid, Clarithromycin 500mg BID, amoxicillin 1gr BID & Bismuth sub salicylate 240mg BID) and those in group B received Furazolidone base quadruple regimen (Pantoprazole 40mg BID, Furazolidone 100mg BID, Amoxicillin 1gr BID & Bismuth sub salicylate 240mg BID) for 2 weeks. Then all of the cases prescribed pantoprazole 40mg BID for 4 more weeks and after 1 to 2 weeks of off therapy (week 7 or 8), they underwent Urea Breath Test (UBT) to prove eradication. Then the rate of eradication and complication between 2 groups determined and compared.

Exclusion criteria include severe heart failure, chronic renal failure, pulmonary insufficiency, advanced chronic liver diseases including viral hepatitis, active malignancy in last 3 years, history of surgery on upper GI tract, consumption of antibiotics recent 4 weeks or HP eradication in last six months, uncontrolled diabetes mellitus, any organ transplantation, past history of allergy to any of the medications used in HP eradication regimen, any history of esophageal varices, pregnancy or breast feeding for women and warfarin or clopidogrel consumption.

Inclusion criteria include confirmation of HP infection by endoscopic biopsy, age range between 18 to 75 year old with clinical and endoscopic diagnosis of Peptic Ulcer disease (PUD), non-ulcer dyspepsia or intestinal metaplasia.

All statistical analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Program version 19 for windows. The differences with P values < 0.05 were considered as significant.

RESULTS

During study period, overall 386 patients included (165 male (42%), average age 44.2y, age range 18 - 75). Based on their endoscopic findings and pathology report they classified as non-ulcer dyspepsia (311 cases), peptic ulcer disease (30 cases) and intestinal metaplasia (45 cases). The demographic characters of participants mentioned in table 1. The participants randomly allocated to groups A & B to receive either clarithromycin or Furazolidone base HP quadruple therapeutic regimen. At the end of intervention, all of them evaluated by UBT to confirm eradication. At the end of intervention, 65 cases in group A and 89 cases in group B did not returned for their follow up and they omitted in per protocol analysis (PP) but supposed as eradication failure in intention to treat (ITT) analysis (figure 1).

In groups A and B, 80.9% & 82.1% of participants achieved eradication respectively (univariable P = 0.819, multi variable P= 0.691, per protocol analysis (PP)). In intention to treat (ITT) analysis, these figures were 79% in group A and 80.5% in group B respectively (P= 0.81). During study, there was not any major complication but 3.1% of participants in each group reported minor side effects including bitter taste, GI upset, headache and or vertigo.

In sub group analysis, the eradication rate of clarithromycin among patients with non-ulcer dyspepsia, PUD and intestinal metaplasia were 80%, 100% & 55.6% respectively. These figures in group B (Furazolidone) were 80.7%, 100% & 85.7% respectively (P= 0.906, 0 & 0.162; table 2). Overall, there was no significant difference in

success eradication rate between clarithromycin and Furazolidone in any of the clinical categories but among those with intestinal metaplasia, the positive results with Furazolidone was more efficient (85.7% vs. 55.6%).

Table (1): Demographic characters of participants based on clinical diagnosis .

Clinical diagnosis	Number	Average Age (y)	Male/Female
Non-ulcer dyspepsia	311	43.1	125/186
Peptic Ulcer disease	34	44.02	22/12
Intestinal metaplasia	45	51.6	18/27
Overall	390	46.24	165/225

Table (2): Subgroup analysis of eradication rate by clarithromycin and Furazolidone (C: clarithromycin, F: Furazolidone, PUD: peptic ulcer disease).

Clinical diagnosis	Therapeutic regimen	Eradication rate	Failure rate	P value
Non ulcer dyspepsia	C	84 (80%)	21 (20%)	0.906
	F	71 (80.7%)	17(19.3%)	
PUD	C	17(100%)	0 (0%)	-
	F	4(100%)	0(0%)	
Intestinal Metaplasia	C	5(55.6%)	4(44.4%)	0.162
	F	12(85.7%)	2(14.3%	

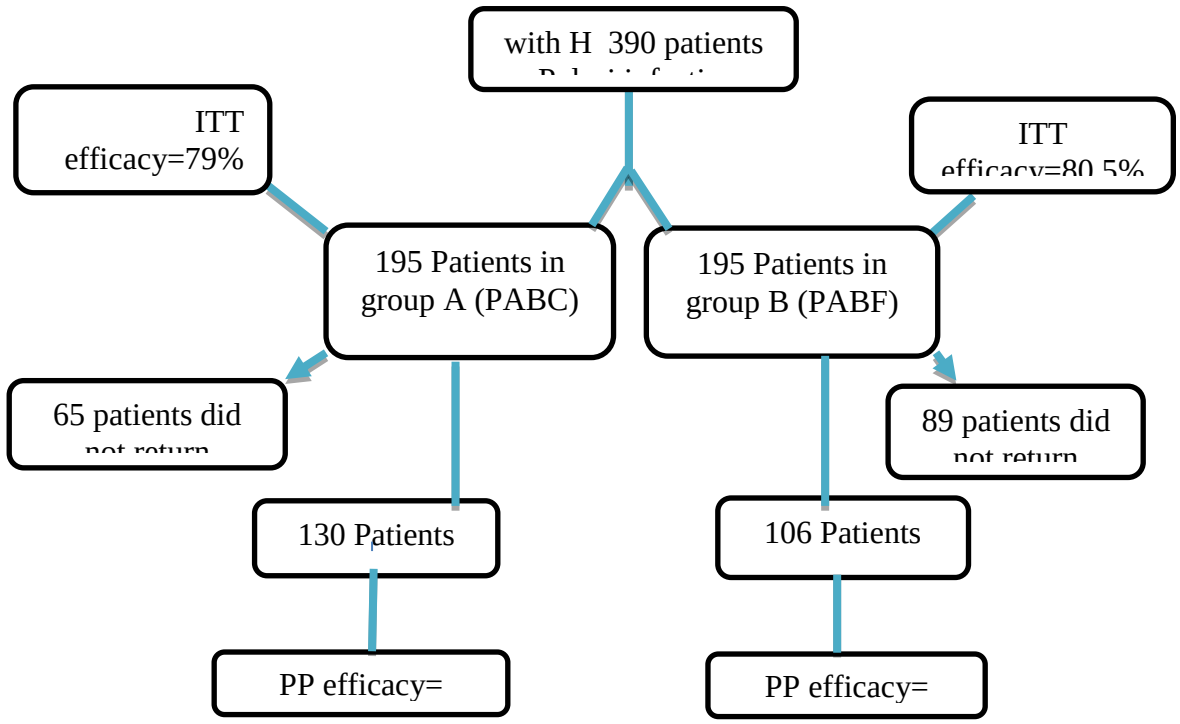

Figure (1): Flow chart of study (ITT: intention to treat; PP: per protocol; PABC: pantoprazole, amoxicillin, bismuth, clarithromycin; PABF: pantoprazole, amoxicillin, bismuth, Furazolidone).

DISCUSSION

Potential complications of H. pylori infection emphasize on importance of effective eradication of this bacterium and in this regard, antibiotic resistance is a great challenge **[22]**. Considering ever changing pattern of bacterial resistance, the success rate of eradication declined from more than 80% in early 90s to even less than 50% in recent years **[13, 23]**, which is an issue that highlights the importance of seeking for new therapeutic regimens **[24]**.

An optimal anti-HP regimen is defined as one that reliably produces cure rate of 90% or greater

and an acceptable therapy should reach the cure rate around 85% to 89% **[25]**. Clarithromycin is one of the most commonly used medications in eradicating HP worldwide with variable success rates; however, increasing HP resistant to Clarithromycin has caused concerns about its efficacy during clinical practice **[13, 15]**. The resistance rate of H. pylori against clarithromycin in Ahvaz city has been reported to be 24%, which cause this region to consider as a high resistance rate **[26]**.

Based on this resistance pattern, the current study designed to evaluate efficacy of Furazolidone as a potential substitute for clarithromycin in clinical practice. Previously multiple trials with various doses and different regimens have shown that Furazolidone is tolerable and could be efficient for this propose **[27, 28]**. However, most of them have been single center with fewer participants.

In study of Fakheri et al in 2007, quadruple regimens containing Furazolidone and Clarithromycin compared and there was not any significant difference in eradication rate. They reported success eradication of 84%, 85% in ITT analysis, respectively, and 90% for both in PP analysis **[28]** which are comparable to the results of current study. In 2009, Bahari reported eradication rate of 97.9% by Furazolidone from South east of Iran **[29]**. Another study from china showed that Furazolidone-containing regimen achieves satisfactory eradication rate of 90.22% in ITT analysis (95% CI: 84.0–96.4) and 93.26% in PP analysis (95% CI: 87.9–98.6)**[30]**. These results are differ from others who showed that Furazolidone regimen achieved relatively poor results with PP ranging from 56% to 85.7% in Iran **[31]** and also higher than results of our study. The difference could be related to geographic distribution, culture, population variations and or patients' compliance.

The findings of current study (80.9% for clarithromycin and 82.1% for Furazolidone in PP analysis) were in contrast to a similar study by Rahmani et al. who reported the clarithromycin-quadruple efficacy to be higher than Furazolidone-based quadruple therapy (53.3% vs. 38.3%) **[32]**. This difference could be explained by high rate of complications and side effects in that study (Headache 61.7%, nausea 46.7%, vomiting 15%, diarrhea 53.3%) which could result in sub optimal compliance and subsequently decreased success rate. In clinical practice, the main concern about prescribing Furazolidone in its side effects and fear of poor compliance **[33]** but in current study, rate of complication was not different between Furazolidone and clarithromycin (3.1% in each group). Although it is presumable that some of the cases who did not returned for follow up also suffer from medications side effects.

One of the distinctive features of current study is participation of patients with different clinical diagnosis and sub group analysis. Among cases who suffer from non-ulcer dyspepsia or those who diagnosed with PUD, the eradication rate between 2 therapeutic regimens was comparable and equal but in case of intestinal metaplasia, the story differs and Furazolidone was superior to clarithromycin (85.7% vs. 55.6%, P= 0.162). Intestinal metaplasia is a well-known gastric cancer risk factor **[34, 35]** and if superiority of Furazolidone is proved in future studies, it can be a great harvest for better regimen selection in such cases. Though the number of cases with intestinal metaplasia was not too much and it worth to evaluate in future clinical trials.

One of the limitations of current study is high rate of drop out of participants (65 cases in group A and 89 cases in group B) which could be partly due to potential side effects of therapeutic regimens. These cases consider as therapeutic failure if ITT analysis.

CONCLUSION

In areas with high rate of resistance to clarithromycin, Furazolidone could be a potential candidate and clarithromycin substitute in HP eradication regimen and in cases with intestinal metaplasia; Furazolidone could be even more efficient and better choice than clarithromycin..

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Ethical considerations

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, so this study approved by ethical committee of Ahvaz Jundishapur University of Medical Sciences in October 2018 (IR. AJUMS. REC. 1397.070) and registered in Iranian randomized clinical trial registration as IRCT 20171203037734N1. Before participation, the method of study explained for all of the participants and they requested to sign a consent form. They were in touch with clinician by phone call and requested to report any potential complication or side effect.

Funding and conflict of interest

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The authors declare to have any conflict of interest.

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