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Original article

Levofloxacin-based triple therapy versus bismuth-based quadruple therapy as a second line treatment for the eradication of H. pylori infection

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SUMMARY

INTRODUCTION: Levofloxacin-based triple therapy has been suggested as an alternative second line treatment to bismuth-based quadruple therapy for persistent Helicobacter pylori (H. pylori) infection. AIM: To compare levofloxacin-based triple therapy (levofloxacin + amoxicillin + PPI) to bismuth-based quadruple therapy (bismuth + tetracycline + metronidazole + PPI) as a second line treatment for the eradication of H. pylori. METHODS: In our study we included 77 patients who failed to eradicate H. pylori following 7-10 days of previous treatment with PPI plus amoxicillin plus clarithromycin. All patients were randomly assigned either to levofloxaxin triple (levofloxacin 500mg bid+amoxicillin 1gr bid + lansoprazole 30mg bid) therapy (Group A, N=39) or to classical bismuth based quadruple regimen (bismuth 120 mg X 4 + tetracycline 500mg tid + metronidazole 500mg tid + lansoprazole 30mg bid) (N=38, Group B). Both groups were treated for 10 days. Eradication of H. pylori was assessed by 13C-urea breath test 4-6 weeks after therapy. RESULTS: The H. pylori eradication rates on the intention to treat analysis (ITT) were 37/39 (94.87%) in Group A and 30/38 (78.9%) in group B (P<0.05). The per protocol eradication rates were 97.3% and 85.7% respectively (NS). Side effects were significantly higher in the quadruple regimen (3 patients discontinued treatment due to side effects versus none in the levofloxacin regimen). CONCLUSION: A 10-day course of levofloxacin triple therapy appeared to be more effective and better tolerated than a 10-day bismuth-based quadruple therapy in the treatment of persistent H. pylori infection.

Key Words: Helicobacter Pylori (H. pylori), H.pylori Eradication therapy, First-line therapy, second-line therapy, levofloxacin based therapies, quadruple therapy

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INTRODUCTION

Helicobacter pylori infection is the main cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. Despite more than 20 years experience in treating H. pylori infection, the ideal regimen is still to be found. All recommended therapeutic regimens have to achieve H. pylori eradication rates higher than 80% on an intention to treat basis.[1-3]

The first-line therapy to eradicate H. pylori is currently recommended as one week of triple therapy, combining proton pump inhibitors (PPIs) with two antibiotics[2,3]. The rates of eradication vary widely, however, ranging from 70% to 95% in regimens using PPI plus amoxicillin and clarythromycin.[4-6] Treatment failure usually occurs because of poor patient compliance or antimicrobial resistance to clarithromycin.[2,6,7] Accordingly, those patients in whom 1-week PPI-based triple therapy fails need an effective rescue regimen, such as quadruple therapy. However, the efficacy of quadruple therapy in eradication of persistent H. pylori infection is optimally only around 60-80%.[8-10] The complex drug regimen and the side-effects of quadruple therapy may lead to poor compliance of patients and thus decrease its efficacy. Moreover, patients who have failed triple therapy with clarithromycin may have persistent

H. pylori infection with acquired clarithromycin resistance.[10] Therefore another regimen containing a new antimicrobial agent is necessary to eradicate the clarithromycin resistant H. pylori strains.

Levofloxacin-based triple therapy has been suggested as an alternative second-line therapy, but also as third-line therapy and even as first line therapy to eradicate H. pylori.

In this study we included patients who failed 1-week PPI-based triple therapy, including clarithromycin and amoxicillin. Patients received 10-days triple therapy using 1000mg levofloxacin, 2gr amoxicillin and 60 mg lansoprazole daily or the classical bismuth based quadruple therapy again for 10 days.

MATERIALS AND METHODS

Patients and Study Design

A total of 79 dyspeptic patients with H.pylori infection, confirmed by positive histology and rapid urease test (CLO-test), were enrolled. All of them had been given 7-10 days PPI-based triple therapy (amoxicillin 1g, clarithromycin 500mg and lansoprazole 30mg, twice daily) to eradicate H. pylori, but the treatment failed as 4-6 weeks after the completion of triple therapy the patients were still positive for H. pylori using urea breath test (C-UBT).

After obtaining informed consent, each enrolled patient was randomly assigned to one of the two rescue regimens. These included amoxicillin 1gr bid, levofloxacin 500mg bid and lansoprazole 30mg (Group A, N=39), or bismuth 120 mg X 4 + tetracycline 500mg tid + metronidazole 500mg tid + lansoprazole 30mg bid) (Group B, N=38). After therapy all patients avoided use of PPI, bismuth salts, and antibiotics until the follow-up UBT.

Eradication of H. pylori was assessed by 13C-urea breath test 4-6 weeks after therapy. All the enrolled patients were tested for H. pylori eradication rate in intention to treat (ITT) analysis. Patients who stopped taking the medication due to severe adverse effects, poor compliance, or loss to follow-up were excluded from the per-protocol (PP) analysis.

Statistics

The students's t-test, Pearson's chi-squared test, and Fisher's exact test were used to determine the parametric difference and nonparametric proportions between the two study groups. All tests of significance were two-tailed with a p value less than 0.05.

RESULTS

A total of 79 patients were randomly divided into two study groups. There was no difference in demographic characteristics and endoscopic diagnosis between the two groups (table 1).

The H. pylori eradication rates on the intention to treat analysis (ITT) were 37/39 (94.87%) in Group A and 30/38 (78.9%) in group B ($P<0.05$). The per protocol eradication rates were 97.3% and 85.7% respectively (NS). (Table 2, Figure 1, Figure 2)

Side-effects occurred significantly more frequently in the quadruple regimen (Group B) and three patients in this study group had to stop therapy due to severe adverse events (Table 3)

DISCUSSION

The choice of a second- line treatment depends mainly on which treatment was used initially, as it would appear that retreatment with the same regimen is not recommended.[11] If a clarithromycin-based regimen was used. a metronidazole-based treatment (or at least clarithromycin-free regimen) should be used afterwards and vice-versa. This recommendation is based on the observation that acquired bacterial resistance to metronidazole or clarithromycin results primarily from the previous treatment failure, and therefore rescue therapies should avoid these antibiotics and use different combinations.

As previously mentioned, after failure of a combination of a PPI-based triple regimen, the use of quadruple therapy has been generally recommended as the optimal

Table 1. Demographic characteristics in the two study groups

Group Variables	Group A (N=39)	Group B (N=38)
Mean age (years)	43.4	44.1
Male/Female	19/20	20/18
Endoscopic diagnosis		
DU/NUD	17/22	15/23
Smoking	21/39	23/38

Table 2. Eradication rates of H.pylori infection in the two study groups.

Eradication rate % (n), (95% confidence interval)	PP analysis	ITT analysis
Group A	97.3 (37/38)	94.7 (37/39)
	(86.2-99.9)	(83.0-99.4)
Group B	85.7 (30/35)	78.9 (30/38)
	(69.7-95.1)	(62.7-90.4)

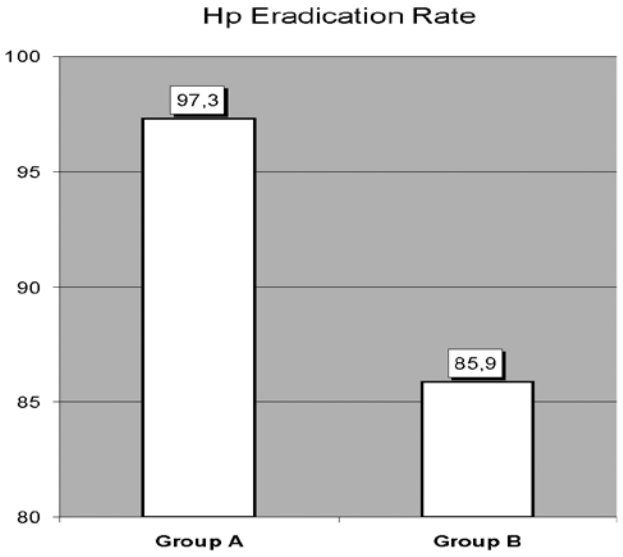

Figure 1. Eradication rate of H.pylori (Per Protocol analysis)

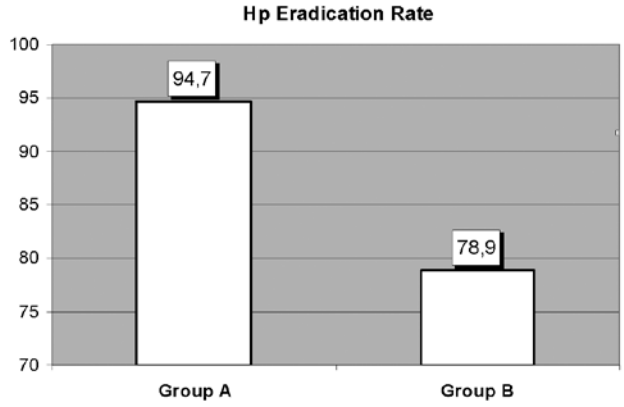

Figure 2. Eradication rate of H.pylori (Intention to Treat Analysis*)

second-line therapy on the basis of relatively good results reported by several studies. However, this quadruple regimen requires the administration of 4 drugs with a complex scheme and is associated with a relatively high incidence of adverse effects[12]. In addition the quadruple regimen still fails to eradicate h.pylori in approximately 20-30% of the patients. All these failed cases constitute a therapeutic dilemma, as patients who failed to achieve cure with two consecutive treatments including clarithromycin and metronidazole will usually develop double resistance.

Table 3. Side-effects in the two study groups

Group Variables	*Group A (N=39)*	*Group B (N=38)*
Side effects (n)		
Nausea	*4*	*7*
Vomiting	*2*	*4*
Constipation	*1*	*3*
Diarrhoea	*3*	*6*
Metallic taste	*3*	*8*
Dark stools	*0*	*14*
Total events	*13*	*42*

Levofloxacin is a fluoroquinolone antibiotic agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens. Recently, some studies have evaluated the efficacy of levofloxacin-based therapies in the eradication of H.pylori infection. These regimens could prove to be a valid alternative to standard therapies not only as first- line therapies but more interestingly as second-line regimens.[13-17] In this respect, levofloxacin-based second-line therapies represent an encouraging strategy for eradication failures, as some studies have shown that levofloxacin has a remarkable activity against H.pylori[18] and that primary resistance to this antibiotic is (still) relatively infrequent (as compared with clarithromycin or metronidazole.[19-21] A previous in vitro study also showed synergistic effect of quinolone antimicrobial agents and PPIs on strains of H.pylori.[22] In another study it has been shown that levofloxacin retains its in vitro activity in resistant H.pylori strains to clarithromycin and metronidazole.[20] These in vitro favourable effects have been confirmed in vivo. A combination of a PPI, amoxicillin and levofloxacin as first-line regimen, has been associated with high eradication rates (of about 90%).[20,23-25] Subsequently this regimen was also used to treat patients who failed to achieve cure with a first line regimen[26]. The majority of these studies also reported favourable results with H. pylori eradication rates ranging from 60-94%. A more recent metanalysis of levofloxacin-based rescue therapies showed (combined with amoxicillin and a PPI in most studies) rates of 80%, which represent a relatively high eradication rate[16]. In the same review higher eradication rates were found with 10-day as compared to 7-day regimens, with the levofloxacin-amoxicillin-PPI combination in particular, suggesting that the longer duration regimen should be chosen.

Another two meta-analyses have also suggested that levofloxacin-based regimens as second line treatment are more effective than the generally recommended quadruple therapy.[15,16] This suggestion is in accordance with the findings of our study, in which the levofloxacin-based regimen proved more effective compared to the standard bismuth-based quadruple regimen. In one of these studies[16] higher H.pylori eradication rates were found with levofloxacin-based triple regimens compared to quadruple combinations (81% vs 70%), but with borderline statistical significance.

In this review studies with great differences in methodology were included and when only high-quality studies were considered, the advantage of levofloxacin regimens increased significantly (88% vs 64%), which also achieved statistical significance[16]. These findings are also consistent with our results in which we found a significant difference in favour of the levofloxacin-based therapy over the quadruple therapy (94.8 vs 78.9%).

It is well-known that the quadruple bismuth-based regimen requires the administration of a complex scheme,[12] which results in significant reduction of patient's compliance. On the contrary the levofloxacin-based therapy represents a promising alternative to quadruple therapy, with the advantage of simplicity. In addition the quadruple regimen is associated with a relatively high incidence of adverse events. In contrast levofloxacin is generally well tolerated and most adverse effects associated with its use are transient and mild to moderate in severity.[4]. The occasional cases of tendinitis and tendon rupture that have been reported in the literature with levofloxacin therapy,[14,27] represent a very low risk as the accumulative data of more than 15 million prescriptions in the US indicated a rate of less than 4 per million prescriptions.[38]

Unfortunately, it has been shown that resistance to quinolones is easily acquired, and in countries with high consumption of these drugs, the resistance rate is increasing and is already relatively high.[28,33,39-41] It is very important to emphasize that the presence of levofloxacin resistance significantly reduces the eradication rate following therapy with this antibiotic. Therefore, many authors have suggested that levofloxacin-based regimens has to be reserved for rescue treatment to avoid the development of resistance.

In conclusion, in our study levofloxacin-based therapy proved more effective and with less side-effects than the standard bismuth-based quadruple therapy, and our results are in accordance with the results reported in the literature. Great concern has to be shown regarding the risk of development of resistance to levofloxacin, which may arise as the result of unnecessary and irrational antibiotic prescription. This resistance phenomenon could lead to significant reduction in the efficacy of the levofloxacin-based regimens.

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