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The Efficacy of Spiramycin-based Triple Therapy for First-Line Helicobacter Pylori Eradication

Skender Telaku[1], Edmond Islamaj[2], Arber Veliu[2], Jeton Bytyqi[2], Mimoza Telaku[3], Hajrullah Fejza[1] Fitim Alidema[1*]

[1]*Department of Medical Science, University for Business and Technology - UBT, Pristina, Kosovo;*

[2]*Department of Gastroenterology, University Clinical Center of Kosovo, Pristina, Kosovo;*

[3]*Department of General Medicine, Faculty of Medicine, Tirana, Albania.*

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CORRESPONDING AUTHORS:
Fitim Alidema fitim.alidema@ubt-uni.net;
tel +38349508509
Address: UBT Main Campus, Lipjan, Kosovo

ABSTRACT

Background/ Objectives: To evaluate the efficacy and safety of spiramycin-based triple therapy for first-line Helicobacter pylori eradication.

Materials and Methods: One hundred and twenty-two dyspeptic patients infected with H. pylori, who had not received previous eradication treatment were randomly divided into two groups. The study group of 70 patients received pantoprazole 40 mg twice a day, spiramycin 1,5 M.U.I., and metronidazole 250 mg (film-coated tablet), three times a day for 10 days. Meanwhile, the control group consisting of 52 patients received standard triple therapy with pantoprazole, clarithromycin, and amoxicillin for 14 days. One month after the completion of therapy, H. pylori status was assessed. If the test for H. pylori was negative, it was considered that eradication had been successfully performed.

Results: In the study group, H. pylori was eradicated in 52 patients (74.3%), whereas in the control group, it was eradicated in 45 of them (86.58%). Although eradication was higher in the second group, the difference between the two groups was not statistically significant (p = 0.097). Regarding the side effects of the ordered therapies, 12 (54.5%) patients were sick in the first group, while 10 (45.5%) in the second group. Common adverse effects were nausea, abdominal pain, and diarrhea. Again, there was no statistical difference between these two groups (p = 0.266).

Conclusion: In our study, it was not proven that spiramycin is more effective than clarithromycin in the eradication rate of H. pylori. No significant statistical difference was found between the study group and the control group. Also, in terms of side effects, there is no difference between the two groups.

1.Introduction

Despite the presence of a large number of antibiotics, the degree of eradication of H. pylori is not satisfactory. Resistance of H. pylori to antibiotics has reached high levels globally, causing the eradication rates of H. pylori to decline. This prompts us to always look for new protocols that will eradicate H. pylori in desirable values.

More than half of the world's population is infected with H. pylori, which always causes chronic gastritis, and can progress to more serious complications such as peptic ulcer, gastric adenocarcinoma, and MALT gastric lymphoma. The majority of the patients, except the structural and functional changes as a result of the active chronic inflammation of the gastric mucosa, have no other clinical symptoms. [1]

Kyoto's Consensus Conference 2015, based on the objective pathologic criteria, defined H. pylori gastritis as an infectious disease, regardless of the presence or the absence of the symptoms or clinical complications. In the new International Classification of Disease, 11th Revision, H. pylori gastritis is included as a separate nosological entity. Based on this, all patients infected with H. pylori should be treated, regardless of the presence or the absence of the symptoms. [2]

Studies done with serology or endoscopy showed a high prevalence of Helicobacter pylori in the Albanian population (54%- 92.1%). [3, 4, 5, 6, 7]

Over the last four decades, the prevalence of antibiotic resistance has gradually increased. This increasing resistance of H. pylori to previously effective antibiotics has become a major concern and requires a careful selection of therapies and re-evaluation of therapeutic strategies.[8]

Bacterial resistance is one of the biggest threats to global health. Both the WHO and the European Union Council advise the careful use of antibiotics to avoid the development of bacterial resistance. [9]

In 1952, spiramycin was discovered as a product of Streptomyces *ambofaciens*. Since 1955 it has been used as a preparation for oral administration. The antibacterial action spectrum of spiramycin is quite broad and typical of macrolides. It compasses most of the pathogens involved in respiratory tract infections, including Gram-negative and Gram-positive cocci, Parvobacteriaceae, Legionella spp., Chlamydia spp., Ureaplasma urealyticum, M. pneumoniae, and Listeria monocytogenes, but not Enterobacteriaceae. Spiramycin is active against many bacteria that have acquired resistance to erythromycin and other macrolides. [10, 11, 12]

Since its discovery in 1952, spiramycin has been used in the treatment of various infections in the human body. It has been widely used, especially in the treatment of Toxoplasma gondii in pregnant women.[12]

During the literature review, we saw that the studies related to the role of spiramycin in the eradication of H. pylori are few. Although few, in some studies with adults[13, 14] and children[15,16] spiramycin has been shown to be effective in eradicating H. pylori infection with high eradication rates of 91-95%. Based on these studies, spiramycin is not inferior compared to amoxicillin and oxytetracycline in the eradication of H.pylori.

The first study that was done regarding the in vivo effect of spiramycin in the eradication of H. pylori was done by Berstad et al. (1995). The percentage of eradication of these patients and healing of peptic ulcers was 91.3%. Side effects that limited daily activities were smaller than those that occurred during the administration of oxytetracycline.[16]

The second study published regarding the effect of spiramycin in the eradication of H. pylori is the study by Olafsson et al. (1999). One hundred and eighty-three patients were treated for ten days in 4 different groups. Intention to treat eradication rates were 93.5% for the first group, 91.3% for the second group, 93.6% for the third group and 88.6% for the fourth group. 33% of patients had side effects, and women had more complaints (p=0.0002). So, the eradication rate for the two groups with spiramycin was 91.3% and 88.6%.[17]

There are two studies that should be mentioned that were done regarding the effect of spiramycin in the eradication of H. pylori in children.

The first study aimed to evaluate the effect of spiramycin compared to amoxicillin in the treatment of

H. pylori with triple therapy with metronidazole and lansoprazole. In the first group out of 14 patients, 12 were eradicated (85.7%), while in the second group 8 out of 11 were eradicated (72.7%), there was no difference between these two groups, p>0.5. Limited side effects were observed in one patient with spiramycin (abdominal pain) and in two cases with lansoprazole (mouth dryness). Therapeutic compliance was excellent. [18]

The second study was also conducted by the same authors and aimed to determine metronidazole resistance in bacterial eradication and the improvement of histological gastritis determined by endoscopic and histological examinations. Eradication in the first AML (Amoxicillin, Metronidazole, Lansoprazole) group was 83.3%, it was not significantly different from the second SML (Spiramycin, Metronidazole, Lansoprazole) group 63.6%, p=0.3).21

As we have seen, the success of H. pylori eradication with different combinations of spiramycin in the literature ranges from 63% to 93.6%. Our eradication rate is similar to those results.

The aim of antimicrobial therapy is to eradicate reliably H. pylori infection in the majority (eg, ≥90%) of patients.

Treatment of H. pylori infection remains challenging. Antibiotic resistance is one of the factors that affect the success of H. pylori eradication. Clarithromycin is one of the key factors in the eradication of H. pylori. Recent studies show primary resistance to clarithromycin in Europe at 21.4% (Italy 36.9%, Croatia 34.6%, Greece 30%, and Bulgaria 26.9%). Here we should also mention the resistance to clarithromycin and metronidazole at the same time, which in this study was 9.7%. Resistance to the other three antibiotics was exceptional; 0.2% for amoxicillin, 0.9% for rifampicin, and 0% for tetracycline.[8]

It is not known about the resistance of H. pylori to clarithromycin and other antibiotics in Kosovo. But if we take into consideration the high values of resistance to clarithromycin in Southern European countries that surround Kosovo, we can assume that resistance to clarithromycin in Kosovo is very high, anyhow over 15%. Another thing that should be mentioned is that resistance to clarithromycin is associated with the use of macrolides in the community. For this reason, extreme caution is preferred when prescribing eradication therapy.[8]

Claritomycin is the most expensive drug used in the eradication of H. pylori. Spiramycin is an older drug than clarithromycin, which was discovered in 1984. [17]

Since it is much more affordable than clarithromycin, we used spiramycin which is in the form of a film-coated tablet Spiramycine / metronidazole 1.5 M.U.I. /250 mg GERDA, a new product on the Kosovar market. To our knowledge, this is the only study conducted with this product.

The aim of our study was to evaluate the efficacy of spiramycin and to monitor the occurrence of side effects while receiving H.pylori eradication treatment based on spiramycin.

2.Materials and Methods

This prospective controlled randomized open-label clinical trial is designed to evaluate the efficacy of spiramycin-based triple therapy for first-line H. pylori eradication. This study was approved by the Ethics Committee of the Kosovo Doctors Chamber (07.07.2022, nr. 108/2022) and conducted from July 2022 to January 2023. The sample consists of 122 patients with dyspeptic complaints diagnosed with H. pylori infection in the Gastroenterology Clinic of the University Clinical Center of Kosovo and two private clinics. Diagnosis of H. pylori was based on the presence of Helicobacter pylori stool antigen, positive urea breath test, and positive urease test.

Exclusion criteria: Patients who were previously treated with H. pylori eradication therapy, those who have used PPIs and antibiotics within the last 4 weeks, those with penicillin and PPI allergies, patients with previous gastric surgery, the coexistence of malignancy, renal failure, and pregnant women.

The diagnosis of the H. pylori infection is made if one of these examinations results is positive. For those who underwent endoscopy, two biopsies were taken for the urease test.

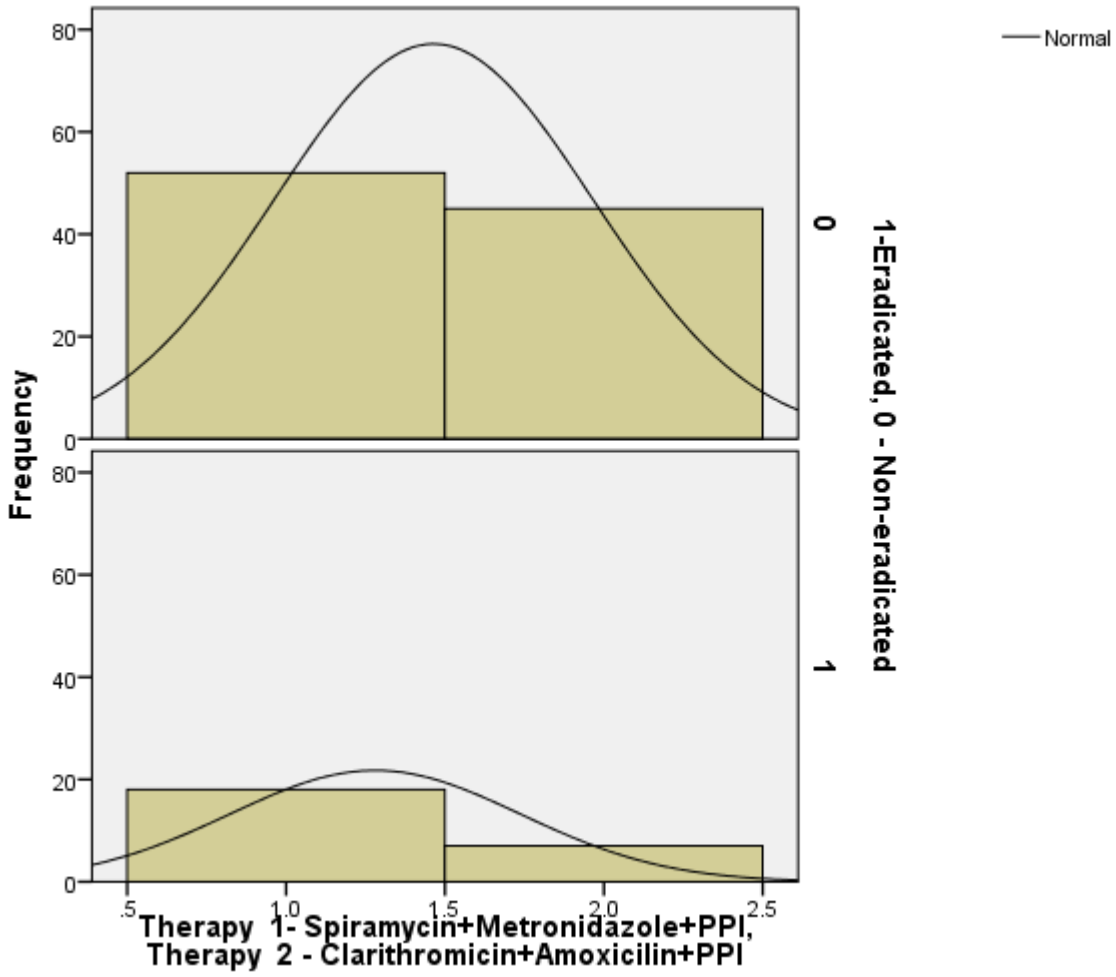

Figure 1 Eradication rate between groups (p= 0.099)

Therapy regimen

The study group, including 70 patients, received pantoprazole 40 mg twice a day, half an hour before meals, for 10 days; spiramycin 1,5 M.U.I. and metronidazole 250 mg in the form of film-coated tablets Spiramycine/Metronidazole GERDA 1.5 M.U.I./250 mg three times daily with food for 10 days. The control group, including 52 patients, received pantoprazole 40 mg twice a day, half an hour before meals, clarithromycin 500 mg twice a day after meals, and amoxicillin 1000 mg twice a day after meals, for 14 days.

In advance, the possible side effects were explained to the patients and their consent to participate in the study was obtained.

After the end of the therapy, the patients did not take any proton pump inhibitor for two weeks and bismuth or any other antibiotic for four weeks. Four to six weeks after the end of the eradication therapy, the success of the therapy has been checked with H. pylori stool antigen, urea breath test, and urease test. In those who underwent endoscopy, two biopsies were taken for a urease test. The negative result of one of these tests was defined as successful eradication.

Statistical Analysis Data was evaluated by the Statistical Package for the Social Sciences (SPSS) 22 computer program. Statistical analyses were carried

Table 1. Demographic characteristics, side effects, and eradication rates of our patients

	Study group	Control group	p
Patients (nr, %)	70 (57.4%)	52 (42.6%)	0.497
Mean age ±SD	41.17±SD 12.565		
Sex (M/F)	M-38(54.3%) F- 32 (45.7%)	27 (51.9%) 25 (48.1%)	0.855
Side effects	12 (54.5%)	10 (45.5%)	0.266
Eradication rate	52 (74.3 %)	45 (85.6%)	0.097

out by T-tests and chi-square tests. P values less than 0.005 were significant.

3.Results

This study included 122 patients with H. pylori infection, 46.72% of them females, with a mean age of 41.17±SD12.565 (18-60). The patients were split into two groups. There were no differences between these groups in terms of gender (p=0.855). The eradication rate in the study group was 74.3%, whereas the control group had an eradication rate of 85.6%. No statistical differences were observed between the two groups, (p=0.099). (Figure 1)

Regarding side effects, in the study group, 12 patients had mild complaints which were nausea, abdominal pain and diarrhea. The most common complaint in the study group was nausea. In the control group, there were 10 patients with mild complaints, with nausea being the most common. Even though the study group had a larger number of patients with complaints there was no statistical difference between the two groups(p=0.266). There were no significant side effects that would force patients to stop the therapy. All patients completed their therapies, (Table 1).

4. Discussion

Our study did not prove that a combination of spiramycin/metronidazole is more effective than clarithromycin-based triple therapy, in the eradication rate of H. pylori. No significant statistical difference was found between the study group and the control group. Also, in terms of side effects, there is no difference between the two groups. In this study, which is the first in our country regarding the efficiency of spiramycin in the eradication of H. pylori, we found a value of 74.3 % in the success rate of the eradication of H. pylori. Based on Graham's scale, it seems that we are dealing with the eradication rate of the category of C or fair (85-89%).[18] At the same time, we saw that the percentage of side effects was low. We did not have any patients who discontinued the therapy due to side effects. The eradication rate of H. pylori with standard triple therapy in Kosovo ranges between 61,3 % and 71%.[19,20]

The study limitations

- H. pylori cultures, antibiotic susceptibility, and drug resistance were not performed,
- Only the presence or absence of side effects was considered, without measuring their severity,
- The small number of patients in the study groups.

5. Conclusion

According to our results, the combination spiramycin/metronidazole is not more effective than clarithromycin-based triple therapy in the eradication rate of H. pylori., since there was not significant statistical difference between the study group and the control group. Also, in terms of side effects, no difference between the two groups was observed. However, the spiramycin/metronidazole combination has an important advantage due to its lower cost. □

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