




Outcome of 14-Day Sequential and Levofloxacin-Based Triple Regimen as the First-Line Therapy in Patients with *Helicobacter pylori* Infection: A Prospective Comparative Study from Southern Central Nepal

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Abstract

Background *Helicobacter pylori* eradication rates of the commonly used regimens vary among countries and even among different regions of the same country. We aimed to compare the eradication rate and safety of sequential therapy with levofloxacin-based triple therapy.

Methods A comparative single-center study was conducted between October 2022 and November 2023 after obtaining ethical approval. Patients in group A received 14 days of levofloxacin-based triple therapy and those in group B received 14 days of sequential therapy. The eradication of *H. pylori* was assessed 4 weeks after the completion of the assigned regimens. The data regarding adverse events were also recorded.

Results Among 150 patients (group A: 70, group B: 80) with mean age of 41.7 ± 15.0 years, 67 (44.6%) were male. The eradication was achieved in 65 (92.9%) in group A and 63 (78.8%) in group B, respectively ($p = 0.01$). All the patients in group A and 76 (95%) patients in group B had good compliance with medication. Adverse events were noticed in 7 (10%) in group A compared to 31 (38.7%) in group B ($p < 0.001$). The most common adverse events in group A and group B were drug-related diarrhea (3 [4.3%] vs. 11 [13.7%]), gastrointestinal intolerance (2 [2.8%] vs. 6 [7.5%]), and bad/metallic taste (1 [1.4%] vs. 22 [27.5%]). No serious adverse events were noted in both groups.

Conclusion Sequential therapy is significantly less effective and has more nonserious adverse events compared to levofloxacin-based triple therapy in eradication of *H. pylori*.

Keywords

- ▶ *Helicobacter pylori*
- ▶ sequential therapy
- ▶ levofloxacin-based triple therapy
- ▶ eradication
- ▶ adverse events
- ▶ first line therapy

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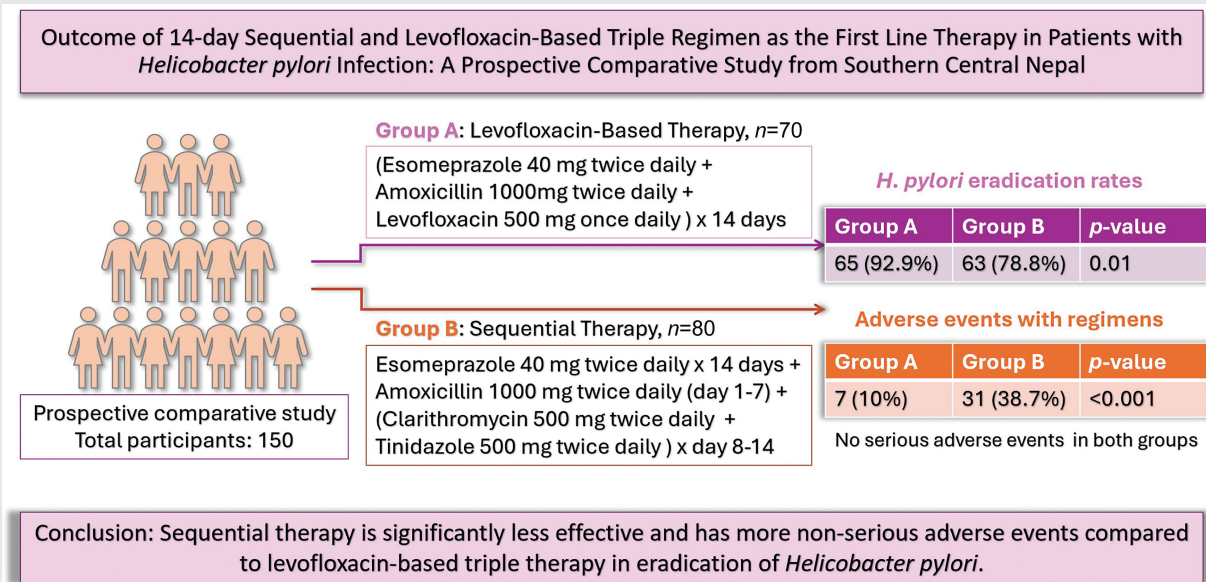
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Graphical Abstract



Introduction

Helicobacter pylori is a Gram-negative bacterium known to infect over half of the world's population.¹ The prevalence of *H. pylori* infection is found to be highest in developing countries with a very high prevalence of 57.7% (49.9–65.5) in South Asia.^{2,3} Though the true prevalence of *H. pylori* is not known in Nepal, the prevalence in dyspeptic patients is found to be 38.4%.⁴ *H. pylori* is implicated in the development of gastritis, gastroduodenal ulcers, and gastric malignancy.⁵ In fact, *H. pylori* is known to be the most robust risk factor for gastric cancer and is classified as class I carcinogen.⁶ Guidelines recommend treatment for all those who have been diagnosed with *H. pylori* infection.^{7,8} It is estimated that the risk of gastric malignancy decreases by as high as 50 to 75% after eradication of *H. pylori*.^{6,9} Different treatment regimens of varying duration with varying success rates are used for *H. pylori* eradication. There is a rising concern about ever-increasing antimicrobial resistance to these regimens.¹⁰ This is evident from the fact that the eradication rate of the usual first-line clarithromycin- and amoxicillin-based standard triple therapy is < 80%.^{11,12} The situation is more grave in developing nations with no proper guidelines on antibiotics use. All these regimens consist of multiple antibiotics which are also used for indications other than *H. pylori* eradication. Moreover, it is not uncommon to find anti-*H. pylori* treatment being administered without prior testing solely based on symptoms. These factors along with other bacterial factors have led to a very high resistance rate to the commonly used antibacterials and possibly to those regimens containing these antibiotics. It is accepted widely that the treatment regimens used should be based on local microbial resistance pattern which is lacking in this part of the world.⁸ It is recommended that bismuth-based quadruple therapy be used in area of high clarithromycin resistance which is found

to be 22% in Nepal.^{13,14} However, bismuth is not available in Nepal. Through this study, we aim to compare the eradication rates of a 14-day sequential therapy and levofloxacin-based therapy and hence to know whether sequential therapy can serve as the first line of therapy in this setting.

Methodology

This is a prospective comparative study conducted between October 2022 and November 2023 in the department of gastroenterology at a referral tertiary care center. The study was approved by the institute's review committee. The study included all the consecutive patients aged 16 years or above who were willing to provide written informed consent. The patients with pregnancy, cirrhosis of liver, chronic kidney disease, exposure to any antibiotics in the past 4 weeks, previous exposure to anti-*H. pylori* regimens, known allergy to amoxicillin, clarithromycin, tinidazole, or levofloxacin, and those not willing to provide consent were excluded. Since levofloxacin is also used as an antitubercular agent, symptoms suggestive of tuberculosis (TB) were also an exclusion criterion.

Diagnosis of *H. pylori* infection in patients deemed eligible was made with stool for *H. pylori* antigen in patients not requiring endoscopic evaluation. For patients undergoing endoscopy, the diagnosis was made with rapid urease test (RUT) or on histopathological examination of gastric biopsy. A gastric biopsy was obtained as per the updated Sydney protocol.¹⁵

Before considering recruitment, a detailed history was obtained regarding prior exposure to anti-*H. pylori* treatment, any antibiotics exposure, and known allergy to the antimicrobials used in this study. The data were recorded in a predefined pro forma.

Treatment Allocation

The patients were divided into two groups as per the treatment regimens used as follows.

Group A: Levofloxacin-Based Triple Therapy for 14 Days

The patients in this group received a combination of esomeprazole 40 mg twice daily for 14 days + amoxicillin 1000 mg twice daily for 14 days + levofloxacin 500 mg once daily for 14 days all started together.

Group B: Sequential Therapy for 14 Days

Patient in this group received esomeprazole 40 mg twice daily + amoxicillin 1000 mg twice daily for first 7 days (day 1 to day 7) followed by esomeprazole 40 mg twice daily + clarithromycin 500 mg twice daily + tinidazole 500 mg twice daily for next 7 days (day 8 to day 14). Patients were properly taught about the consumption of medications as per instructions by placing the medications for the first week and the second week in two different plastic bags.

Patients in both the groups received esomeprazole 40 mg once daily for another 2 weeks after completion of 14 days of assigned eradication therapy.

To ensure even distribution and to mitigate possible bias, patients were allocated to each group in the blocks of 10 where the first block of patients received group A treatment and the second block received group B treatment and so on. To assess the adverse events arising out of any regimens, patients were suggested to visit in person or to make a call on a provided number should any event occur. Any patient who consumed the treatment regimen for less than 7 days was not considered for analysis. The eradication of *H. pylori* was assessed after 4 weeks of completion of antibiotics and at least 2 weeks after stopping esomeprazole. Patients visiting outpatient

department 3 months after treatment completion or those taking other antibiotics after completion of anti-*H. pylori* treatment were excluded. To document eradication, stool for *H. pylori* antigen was assessed except for those patients in whom a second endoscopy was warranted. In these patients RUT or biopsy (if obtained) were used to document eradication.

The primary aim of this study was to evaluate the eradication rates of *H. Pylori* infection with a 14-day levofloxacin-based triple therapy and 14-day sequential therapy. The secondary objectives were to assess the tolerability of these regimens.

Statistical Analysis

The details of the patients and procedure were entered manually into a predefined pro forma and finally into the Excel sheet. The data analysis was performed using STATA 14.2 (StataCorp LLC, United States). The categorical variables were expressed as number (%), continuous variables with normal distribution as mean \pm standard deviation, and skewed continuous variables as median (interquartile range). A chi-square test was used to assess the significance of *p*-value for categorical variables. Whereas for nonparametric variables, the Mann–Whitney *U* test or Kruskal–Wallis test was used wherever applicable. A two-way *p*-value of < 0.05 was considered as significant for comparison.

Results

Baseline Features

Among 180 patients considered for this study, 150 patients (70 patients in the levofloxacin group [group A] and 80 patients in sequential therapy [group B]) were considered for final analysis (► Fig. 1). Of these 150 patients, 67 (44.6%) were male and the mean age of the cohort was 41.7 ± 15.0 years. The

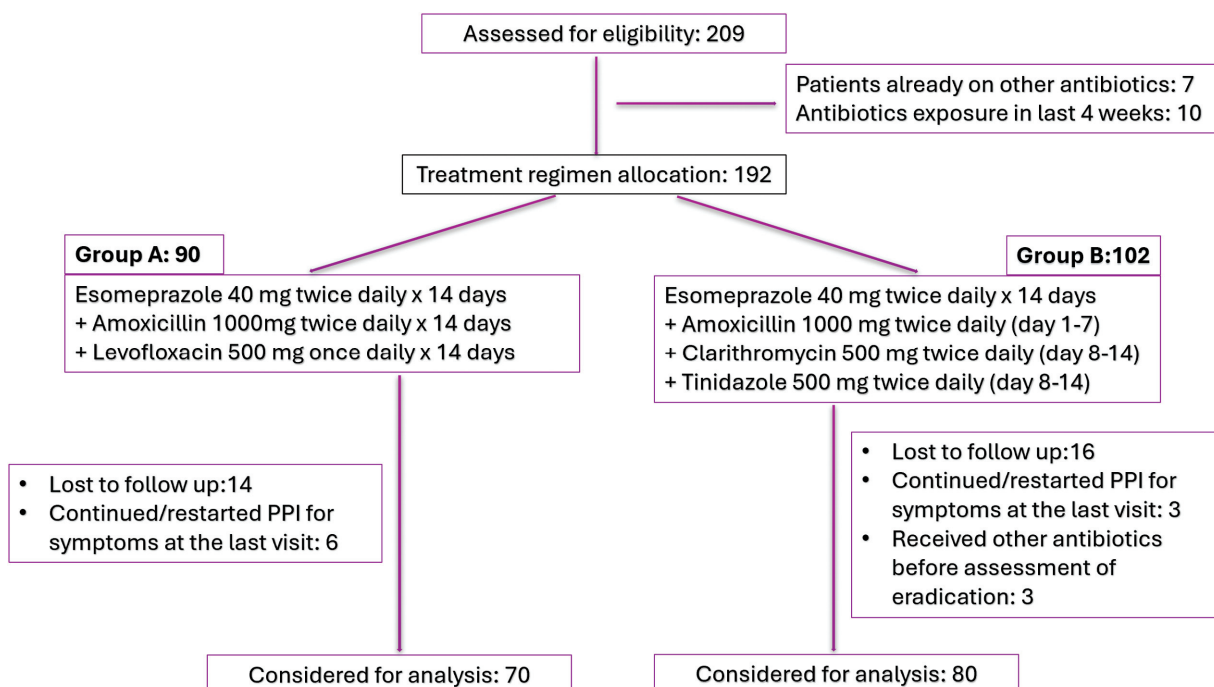


Fig. 1 Study flow diagram.

proportion of male patients in group A and B were 27 (38.5%) and 40 (50.0%), respectively, with mean age being 43.7 ± 15.6 years in group A and 40.0 ± 14.4 years in group B. Presence of comorbidities were comparable between the groups as shown in ► **Table 1**. The most common presenting complaints that led to *H. pylori* testing were epigastric pain in 89 (59.3%) followed by postprandial distress in 31 (20.6%), gastroesophageal reflux in 27 (18%), voluntary testing in 14 (9.3%), nonspecific pain abdomen in 10 (6.6%), and hematemesis/melena in 7 (4.6%) patients. The indications for *H. pylori* testing in individual groups are shown in ► **Table 1**.

Tests to Detect *H. pylori* Infection and to Document Eradication

For diagnosis of *H. pylori* infection, the tests performed were stool for *H. pylori* antigen in 57 (38%) followed by histopathological examination of gastric biopsy in 50 (33.3%) and RUT in 43 (28.7%) patients. The high percentage of histopathological examination in this study is due to an ongoing parallel study which aimed to assess the prevalence of atrophic gastritis in symptomatic patients undergoing gastric biopsy in our department.¹⁶ For confirmation of eradication, stool for *H. pylori* antigen was used in 134 (89.3%) patients followed by RUT in 11 (7.4%) and histopathological examination in 5 (3.3%) patients. The indications for repeat endoscopy in these 16 patients were presence of symptoms despite treatment in 11 patients and presence of deep gastric ulcer in the remaining 5 patients. There was significant ulcer healing in two patients and persis-

tent ulcer in the remaining three patients (► **Supplementary Table S1**, available in the online version).

Primary Outcome: Eradication Rate of Treatment Regimens Used

Among 70 patients treated with levofloxacin-based therapy in group A, eradication of *H. pylori* was achieved in 65 (92.9%) patients. On the other hand, of the 80 patients treated with sequential therapy in group B, eradication was achieved in 63 (78.8%) patients. The eradication rate with levofloxacin-based therapy was significantly higher than the sequential therapy ($p = 0.01$) (► **Fig. 2**, ► **Table 2**).

Secondary Outcome: Adverse Events and Tolerability

Patients in both the treatment groups showed good compliance with the treatment. All the patients in levofloxacin group and 76 (95%) in the sequential group had good compliance to the treatment. Adverse events of any kind were noticed in only 7 (10%) of the patients in the levofloxacin group compared to 31 (38.7%) of the patients in the sequential therapy group ($p < 0.001$). The most common adverse events noticed in the levofloxacin group were drug-related diarrhea in 3 (4.3%), gastrointestinal intolerance in 2 (2.8%), and bad taste in 1 (1.4%) patient. In the sequential therapy group, the most common adverse events noted were bad/metallic taste in 22 (27.5%), drug-related diarrhea in 11 (13.7%), gastrointestinal intolerance in 6 (7.5%), and drug-related hypersensitivity in 2 (2.5%) patients.

Table 1 Baseline characteristics

	Entire cohort (n = 150)	Levofloxacin-based triple therapy (n = 70)	Sequential therapy (n = 80)	p-Value
Male, n (%)	67 (44.6)	27 (38.5)	40 (50.0)	0.16
Age, mean \pm SD (y)	41.7 \pm 15.0	43.7 \pm 15.6	40.0 \pm 14.4	0.14
Alcohol use, n (%)	22 (14.6)	15 (21.4)	7 (8.7)	0.029
Smoking, n (%)	7 (4.6)	4 (5.7)	3 (3.7)	0.55
Comorbidities, n (%)	46 (30.8)	26 (37.1)	20 (25.0)	0.10
Diabetes	8 (5.3)	6 (8.5)	2 (2.5)	
Hypertension	17 (11.3)	9 (12.8)	8 (0.0)	
Chronic obstructive pulmonary disease	1 (< 1)	0	1 (1.2)	
Coronary artery disease	6 (4.0)	2 (2.8)	4 (5.0)	
Hypothyroidism	9 (6.0)	6 (8.5)	3 (3.7)	
Dyslipidemia	2 (1.3)	0	2 (2.5)	
Chronic liver disease	3 (2.0)	3 (4.3)	0	
Indications for <i>H. pylori</i> testing, n (%)				
Postprandial distress	31 (20.6)	14 (20.0)	17 (21.2)	
Epigastric pain	89 (59.3)	38 (54.2)	51 (63.7)	
Gastroesophageal reflux	27 (18)	13 (18.5)	14 (17.5)	
Nonspecific pain abdomen	10 (6.6)	5 (7.1)	5 (6.2)	
Hematemesis/melena	7 (4.6)	3 (4.2)	4 (5.0)	
Voluntary testing	14 (9.3)	10 (14.2)	4 (5.0)	

Abbreviations: *H. pylori*, *Helicobacter pylori*; SD, standard deviation.

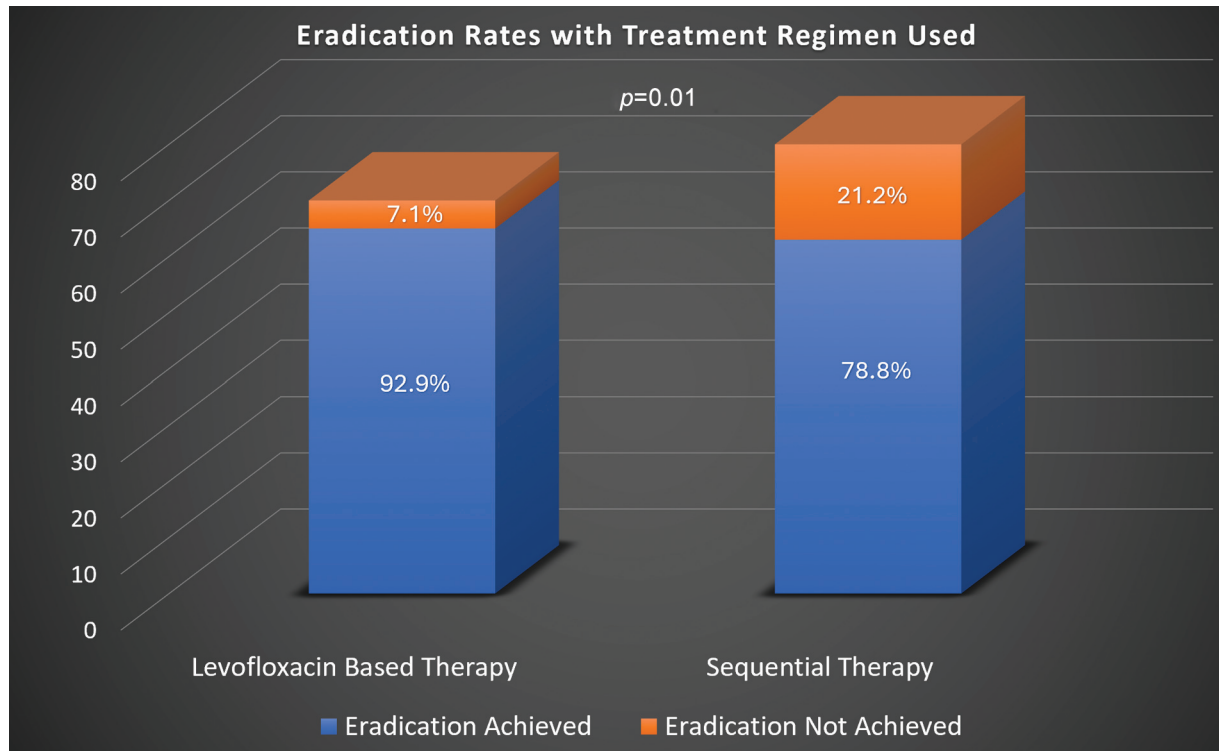


Fig. 2 *Helicobacter pylori* eradication rates with regimens used.

Table 2 *Helicobacter pylori* eradication rates with the regimens used

Eradication achieved	Levofloxacin-based triple therapy (n = 70)	Sequential therapy (n = 80)	p-Value
Yes	65 (92.9%)	63 (78.8%)	0.01
No	5 (7.1%)	17 (21.2%)	

Of the two patients with features suggestive of mild hypersensitivity, one patient stopped amoxicillin on day 3 and continued the rest of the therapy. The other stopped taking therapy on day 8. *H. pylori* eradication was achieved in both these patients. Two of the patients in the sequential therapy group consumed medications concomitantly. No serious adverse event was reported in any of the patients (► **Table 3**).

Discussion

The current prospective comparative study demonstrates that sequential therapy is effective but significantly less compared to the levofloxacin-based triple therapy. Of the two regimens used in this study, only levofloxacin-based regimen achieved the recommended eradication rate which

Table 3 Compliance and adverse events with treatment regimens used

	Levofloxacin-based triple therapy (n = 70)	Sequential therapy (n = 80)	p-Value
Compliance to treatment	70 (100%)	76 (95%)	0.24
No adverse effects	64 (91.4%)	49 (61.2%)	< 0.001
Adverse effects			
Drug-related diarrhea	3 (4.3%)	11 (13.7%)	
Gastrointestinal intolerance	2 (2.8%)	6 (7.5%)	
Bad/metallic taste	1 (1.4%)	22 (27.5%)	
Hypersensitivity	0	2 (2.5%)	
Stopping therapy due to adverse events	0	1 (1.3%)	

is 90%. Both the regimens were well tolerated with mild, nonserious adverse events which were significantly more with sequential therapy.

Different regimens are used across the globe for *H. pylori* eradication. The ever-rising resistance to amoxicillin and clarithromycin has rendered the standard triple therapy with suboptimal eradication rates.^{17,18} For this reason, the standard triple therapy is being doubted as the first choice. We aimed to assess and compare the efficacy of a 14-day sequential therapy to a 14-day levofloxacin-based triple therapy. In the current study, the eradication rate of sequential therapy was 78.8% which is significantly less compared to that of levofloxacin-based triple therapy (92.9%, $p = 0.01$). Moreover, the eradication rate achieved with sequential therapy was less than the recommended optimal eradication rate for any regimen which is 90%.^{13,19} A recent meta-analysis showed that the sequential therapy has an overall eradication rate of 83% which is similar to the finding in the current study.²⁰ In the observational study by Bhattarai et al in similar geographic set up, the eradication rate of 83.3% was reported with sequential therapy.²¹ However, another prospective study in similar setting by Shrestha et al reported relatively better eradication rate (89%) with sequential therapy.²² In a recent randomized controlled trial from India, the eradication rate with sequential therapy was found to be 92.9%, which is much higher than the current study.²³ These differences in the eradication rates of sequential therapy can be explained on the basis of different population groups with possibly varying resistance rates to the antibiotics. Resistance rates to nitroimidazole and clarithromycin, two important components of sequential therapy, in Nepali population is reported to be 88.1 and 21.4%, respectively.¹⁴

Levofloxacin-based anti-*H. pylori* regimens are usually used as second-line treatment. However, with declining eradication rates with usual standard treatment, exploration of levofloxacin-based therapy as first line has also been attempted. The levofloxacin-based triple therapy in the current study showed an excellent eradication rate (92.9%) which meets the suggested optimal eradication rate. A high eradication rate with levofloxacin-based therapy in the current study is consistent with studies by Dib et al²⁴ (94.8%) in Venezuelan population and Rakici et al²⁵ (92%) in Turkish population. In a prospective study by Bhattarai et al²¹ conducted in similar setting as that of the current study, the eradication rate with levofloxacin-based therapy was found to be 77.8%. This could be possibly because the former study used levofloxacin-based therapy for 10 days only compared to 14 days in the current study. It is seen that a 14-day levofloxacin-based therapy has better eradication rate compared to a 10-day regimen.^{26,27} A decline in eradication rates in recent years with levofloxacin-based regimens is reported largely due to growing resistance.²⁸ However, despite a high reported levofloxacin resistance (42.9%) in our region, the eradication rate in the current study is significantly better.¹⁴ This difference can be attributed to varying resistance rates in different parts of a country.

Both the regimens were well tolerated by the patients. Good compliance was seen in all the patients in levofloxacin-based triple therapy and in 95% patients in sequential

therapy. Numerically, less compliance with sequential therapy can be explained because of a greater number of pills needed to be consumed in this regimen. A metallic taste because of tinidazole in sequential therapy can also contribute to reduced compliance.²⁹ Adverse events were reported in < 9% patients in the levofloxacin group which was significantly less compared to that in the sequential therapy group (38.8%). This difference in adverse events is largely because of the higher rate of bad/metallic taste in the sequential group which could be attributed to tinidazole (27.5%). Moreover, a greater number of pills in sequential therapy can contribute to more adverse events such as diarrhea due to dysbiosis in this regimen.³⁰ Previous studies have also demonstrated excellent compliance and fewer adverse events with levofloxacin-based triple therapy.²⁷ Similarly, a randomized controlled trial reported adverse events with 14-day sequential therapy comparable to the current study.³¹ No serious adverse event was noted in either groups.

There are a few limitations of the current study. First, this is a single-center study. Since the resistance rates to the commonly used antibiotics vary among the regions, the generalizability of the outcomes of this study should be done with caution. Second, the patients who did not turn up for follow-up and those in whom eradication was not assessed were excluded from analysis. This could potentially alter the outcome even if little. Third, the test used for eradication assessment was not uniform. In 16 (10.7%) patients, RUT or histology was used as the test to assess eradication. But this should not alter the outcome much as RUT, histology, and stool antigen have comparable sensitivity for *H. pylori* detection.^{32,33} Fourth, we did not use treatment regimens based on susceptibility testing since the same was not available for this region. This could inadvertently lead to mycobacterium resistance to levofloxacin.

Sequential therapy is effective in only three-fourths of the patients compared to levofloxacin-based triple therapy which is effective in more than 90% of the patients for eradication of *H. pylori*. Moreover, the eradication rate with sequential therapy did not meet the optimal eradication rate of 90% expected for any regimen. Both the regimens were tolerated well by the patients. No serious adverse events were noted with any of the regimens. The overall adverse events were significantly higher with sequential therapy but did not lead to discontinuation of therapy. Though levofloxacin-based triple therapy has significantly higher eradication rate and fewer adverse events compared to sequential therapy, the upfront use of levofloxacin-based triple therapy as first-line treatment should be discouraged. This is because for TB endemic regions, levofloxacin should be preserved as antitubercular therapy. Hence, other first-line regimens need to be explored in further studies.

Ethical Approval

Ethical approval was obtained by the institute's review committee with approval number CMC-IRC/079/080062.

Consent to Participate

All the patients provided written informed consent.

Authors' Contributions

M.K.R.: Conceptualization of the study, data collection and supervision, data analysis, writing the manuscript, revision and editing of the manuscript. P.N.: Data collection, review of literature, data analysis, writing the manuscript. B.M.: Data collection, review of literature, data analysis, writing the manuscript. S.K.S.: Data collection, review of literature, data analysis, writing the manuscript. R.K.Y.: Data collection, review of literature, data analysis, writing the manuscript. A.S.: Data collection, review of literature, data analysis, writing the manuscript. S.R.P.: Review of literature, data analysis, manuscript writing and revision of the manuscript. S.S.: Data collection, data analysis, review of literature, writing the manuscript. S.K.: Data collection, data analysis, review of literature, writing the manuscript. S.G.: Data collection, data analysis, review of literature, writing the manuscript.

Data Availability Statement

The data can be obtained from the corresponding author on a reasonable request.

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Conflict of Interest

None declared.

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