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Comparison of the Efficacies of Reverse Hybrid Therapy and Concomitant Therapy in the Eradication Treatment of Helicobacter Pylori Infection in a Tertiary Hospital

1. Dr.Vijay Rahul J *

Postgraduate, Department of General Surgery, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India

*vijayrahul16@gmail.com

2. Dr. Maha Devan A

Assistant Professor, Department of General Surgery, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India

dr.devakmc@gmail.com

3. Dr. Shahid Ibrahim

Assistant Professor, Department of General Surgery, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India

shahiddr123@gmail.com

4. Dr. Amrithraj T

Associate Professor, Department of General Surgery, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India

amrithrajt@gmail.com

5. Dr. Anantharamakrishnan R

Professor, Department of General Surgery, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India

rrasam2003@yahoo.com

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Abstract

Background: Helicobacter pylori (H. pylori) infection represents a widespread health concern globally, impacting over half of the population. It is closely linked to various gastrointestinal conditions, such as chronic gastritis, peptic ulcer disease, and gastric cancer. Typically, the standard treatment for H. pylori infection involves a combination of antibiotics and proton pump inhibitors (PPIs) to improve eradication rates. Nevertheless, the increasing resistance to antibiotics has significantly challenged the effectiveness of traditional treatment regimens, prompting the investigation of alternative therapeutic approaches. One such approach is reverse hybrid therapy, which involves the sequential administration of antibiotics. In contrast, concomitant therapy administers all antibiotics simultaneously, aiming for a broader antibacterial effect and enhanced patient compliance. This study aims to compare the efficacies of reverse hybrid therapy and concomitant therapy in treating H. pylori infection within a tertiary hospital setting.

Methodology: This study included adult patients over the age of 20, diagnosed with H. pylori infection and scheduled for upper GI endoscopy at Chettinad Hospital and Research Institute to investigate gastrointestinal symptoms. Histopathological examination of samples from the stomach's pylorus and antrum was conducted to confirm H. pylori infection, utilizing Giemsa staining for identification. Eligible patients were randomly assigned (1:1) to receive either reverse hybrid therapy (Pantoprazole 40 mg once daily and amoxicillin 1 gm twice daily for 14 days, with clarithromycin 500 mg and metronidazole 500 mg twice daily for the initial 7 days) or concomitant therapy (Pantoprazole 40 mg once daily, amoxicillin 1 gm, clarithromycin 500 mg, and metronidazole 500 mg twice daily for 14 days). Drug adherence and adverse events were monitored at week 2 of therapy. A follow-up endoscopy with histopathological examination was conducted 6 weeks post-treatment, and a urea breath test was performed to assess H. pylori eradication.

Results: The demographic and baseline characteristics were comparable between the two groups. The H. pylori eradication rate was 72% in the reverse hybrid therapy group and 87% in the concomitant therapy group ($p=0.015$). The frequency and severity of adverse events were similar between the groups ($p=0.745$). Drug adherence was also comparable, with poor adherence observed in 15% of the reverse hybrid group and 12% of the concomitant group ($p=0.563$). Subgroup and sensitivity analyses confirmed the robustness of these findings.

Conclusion: Concomitant therapy demonstrated a significantly higher H. pylori eradication rate (87%) compared to reverse hybrid therapy (72%). Both treatments were generally well-tolerated, with similar frequencies of adverse events and adherence rates. These results suggest that concomitant therapy is more effective for H. pylori eradication in a tertiary hospital setting while maintaining a comparable safety profile. Future studies with larger, multicenter populations and longer follow-up periods are recommended to further optimize treatment strategies for H. pylori infection.

Keywords: Helicobacter pylori, Gastrointestinal, Concomitant therapy, Chronic Gastritis, Peptic Ulcer Disease, Gastric Cancer.

Introduction

1.1 A Subsection Sample

Helicobacter pylori (H. pylori) is a worldwide health concern, impacting over half of the global population. It has close association with several GI symptoms and diseases, including gastritis (acute and chronic), peptic ulcer disease, and gastric cancer (Hooi et al., 2017). The standard treatment for H. pylori eradication generally involves a synergistic combination of proton pump inhibitors and antibiotics to increase eradication rates (Malfertheiner et al., 2017). However, the growing issue of antibiotic resistance has significantly challenged the effectiveness of traditional treatment regimens, prompting the need for alternative therapeutic strategies (Graham et al. 2010).

Reverse hybrid therapy, which involves the sequential administration of antibiotics, has recently emerged as a promising approach. This regimen starts with a dual antibiotic combination, followed by the addition of a third antibiotic to enhance bacterial eradication (Gisbert et al., 2011). In contrast, concomitant therapy administers all antibiotics simultaneously, aiming for a broader antibacterial effect and improved patient compliance (Zullo et al., 2013). Both therapies have demonstrated potential in overcoming resistance and improving eradication rates, but direct comparisons in various clinical settings remain limited.

This study aims to compare the efficacies of reverse hybrid therapy and concomitant therapy in treating H. pylori infection within a tertiary hospital setting. Due to variations in antibiotic resistance patterns and patient demographics, evaluating these therapies in a local context is essential for informing clinical practice. Understanding the relative effectiveness and safety profiles of these treatment regimens will aid in optimizing therapeutic strategies and improving patient outcomes in managing H. pylori infection.

2 Literature Review

Malfertheiner et al. (2017) in the Maastricht V/Florence Consensus Report reported eradication rates for concomitant therapy around 85%, aligning closely with our study's finding of 87% eradication for concomitant therapy (Malfertheiner et al., 2017). Gisbert and Calvet (2011) in their review article on non-bismuth quadruple (concomitant) therapy reported similar efficacy rates, further supporting the high efficacy of concomitant therapy as found in our study (Gisbert et al., 2011). Zullo et al. (2013) in their pilot study compared sequential, concomitant, and hybrid therapies and found that concomitant therapy had eradication rates close to 90%, which is slightly higher but comparable to our 87% eradication rate (Zullo et al., 2013).

Fischbach and Graham (2004) in their study on antibiotic resistance and therapy effectiveness found that concomitant therapy was comparatively superior to many other regimens, with around 80-90% eradication rates, consistent with our findings. Gatta et al. (2018) in their systematic review indicated that concomitant therapy had eradication rates above 85%, corroborating our results. Their study also highlighted that antibiotic resistance impacts eradication rates, which may explain variations across different populations. Liou et al. (2016) showed that reverse hybrid therapy achieved eradication rates of around 70-75%, similar to the 72% eradication rate observed in our study.

O'Connor et al. (2014) in their comparative study of different therapies found that reverse hybrid therapy had slightly lower eradication rates compared to concomitant therapy, supporting our findings of 72% vs. 87%. Chey et al. (2017) in their clinical guideline update reported that concomitant therapy was preferred over sequential and hybrid therapies due to higher eradication rates, which aligns with our study's outcomes (10). Fallone et al. (2019) reported that while both therapies were effective, concomitant therapy generally had higher eradication rates than reverse hybrid therapy, reflecting our findings. Yoon et al. (2019) in their meta-analysis found eradication rates for concomitant therapy to be around 85-90%, and for reverse hybrid therapy around 70-75%, which are consistent with the rates observed in our study.

Megraud et al. (2015) emphasized the impact of local antibiotic resistance patterns on therapy efficacy, noting that concomitant therapy often performed better in regions with high antibiotic resistance, similar to our findings. Fuccio et al. (2007) in their study on antibiotic combinations for H. pylori eradication reported higher efficacy for concomitant therapy compared to hybrid and sequential therapies, aligning with the 87% eradication rate for concomitant therapy in our study.

3 Methodology

This study enrolled adult patients over the age of 20, who were infected with H. pylori and were scheduled for upper GI endoscopy at Chettinad Hospital and Research Institute to investigate gastrointestinal symptoms. Histopathological analysis of samples from the stomach's pylorus and antrum was performed to confirm H. pylori infection, with Giemsa staining used for identification. Subjects were excluded if they had a history of being on any eradication treatment, any antibiotic allergy under investigation, previous gastrectomy history, presence of a serious concurrent illness, pregnancy or lactation, or use of antibiotics in the preceding four weeks. Written and informed consent was obtained from all patients before the enrolment process.

Enrolled patients were randomly assigned (1:1) to receive one of the two eradication treatment regimens: reverse hybrid therapy [Pantoprazole 40 mg OD (once daily) and amoxicillin 1 gm BD (twice daily) for 14 days, along with clarithromycin 500 mg and metronidazole 400 mg (BD) twice daily for the initial 7 days) or concomitant therapy (Pantoprazole 40 mg (OD) once daily, amoxicillin 1 gm, clarithromycin 500 mg, and metronidazole 500 mg (BD) twice daily for 14 days). All medications were taken minimum 1 hour before breakfast or dinner. Abstaining from alcohol was strictly advised during treatment due to potential interactions with metronidazole. Drug compliance and adverse events were monitored 2 weeks from start of the therapy. Participants of the study were well informed and educated of the potential side effects of the prescribed drugs being used in the study and were asked to make note and record any symptoms. A follow-up endoscopy with histopathological examination was conducted 6 weeks post-treatment to assess the healing of the ulcer and H. pylori status through a repeat biopsy. Additionally, a urea breath test was performed to evaluate H. pylori eradication after 6 weeks at the end of the therapy.

The eradication of H. pylori was the primary outcome. The secondary outcomes were drug compliance and the frequency of adverse events. A scale consisting of 4 grades: no discomfort, mild discomfort (does not interfere with daily routine activities), moderate discomfort (interferes in some daily routine activities), and severe discomfort (results in have to stop and discontinue the treatment) was used to assess the adverse events. Drug compliance was evaluated by considering the unused drug pills at the end of the treatment. Poor compliance was defined when patient was found to have had <80% of study drugs in the concomitant therapy group or <80% of study drugs during either the initial or the last 7 days in the reverse hybrid therapy group.

3.1 Statistical analysis

The sample size for this study was determined based on the primary outcome of H. pylori eradication rates. Assuming a two-sided test having a significance level (α) of 0.05 and a power ($1-\beta$) of 0.80. Sample size for this study was calculated to identify and detect a difference of 15% in eradication rates between the reverse hybrid therapy and concomitant therapy groups. Based on previous studies, the eradication rate of the concomitant therapy was estimated to be 85%, and that of the reverse hybrid therapy to be 70% (Malfertheiner et al., 2017,Gisbert et al., 2011). Using these parameters and the formula for comparing two proportions, it was determined that 100 patients per group were needed, accounting for a potential 10% dropout rate.

Statistical analyses were done using the help of SPSS version 26.0. A p-value of less than 0.05 was considered statistically significant. The primary outcome, H. pylori eradication rate, was analyzed using the intention-to-treat (ITT) principle, which comprised of all randomized patients who had taken at least one dose of the drug during the study. Eradication rates of the two study groups were compared using the Fisher's exact test or chi-square test. Secondary outcomes included the frequency of adverse events or reaction and drug compliance. The frequency of adverse reactions or events was categorized as none, mild, moderate, or severe, and differences between the two study groups were analysed using the chi-square test. Adherence to the treatment regimen was assessed by counting the number of unused pills, with poor drug compliance being defined as have less than 80% of the study medication. Variability in the rates of adherence in both groups was also evaluated using the chi-square test. The severity of adverse events, categorized on a 4-point scale (none, mild, moderate, severe), was analysed using the Mann-Whitney U test for non-parametric data. Subgroup analyses were performed based on factors such as age, gender, and baseline characteristics, using stratified chi-square tests to assess the consistency of treatment effects across different subgroups.

A sensitivity analysis was conducted on the per-protocol (PP) population, which included only those patients who completed the study as per the protocol without major deviations. This analysis helped validate the robustness of the primary outcome results. All statistical tests were two-sided, and descriptive statistics were presented as means ± standard deviations for continuous variables and as frequencies (percentages) for categorical variables. Confidence intervals (CIs) for proportions were calculated using the Clopper-Pearson exact method. This comprehensive statistical analysis plan ensured a rigorous evaluation of the study outcomes, facilitating robust conclusions about the efficacies in the treatment caused by H. Pylori using reverse hybrid and concomitant therapies.

4 Results and Discussions

The demographic and baseline characteristics of the study subjects belonging to Reverse Hybrid Therapy group (n=100) and the Concomitant Therapy group (n=100) were comparable, as shown in Table 1. The calculated mean age of patients was 45.3 ± 12.4 years in the Reverse Hybrid Therapy group and 46.1 ± 13.1 years in the Concomitant Therapy group, with a p-value of 0.67, indicating no significant difference. Gender distribution was balanced with 52 females and 48 males belonging to the Reverse Hybrid Therapy group and 50 females and 50 males belonging to the Concomitant Therapy group (p=0.75). Similarly, the presence of baseline gastrointestinal symptoms was comparable between the two groups, with 55 patients belonging to Reverse Hybrid Therapy group and 53 belonging to Concomitant Therapy group reporting symptoms (p=0.80).

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Reverse Hybrid Therapy Group (n=100)	Concomitant Therapy Group (n=100)	p-value
Age (mean ± SD)	45.3 ± 12.4	46.1 ± 13.1	0.67
Gender (M/F)	48/52	50/50	0.75
Baseline GI Symptoms (Y/N)	55/45	53/47	0.80

The analysis included all randomized patients, who had taken at least one prescribed dose of the medication during the study. The H. pylori eradication rate was 72% (72/100) in the reverse hybrid therapy group and 87% (87/100) in the concomitant therapy group. The difference in eradication rates between the two groups was statistically significant (p=0.015), indicating a higher efficacy of the concomitant therapy compared to the reverse hybrid therapy (Table 2).

Table 2. H. pylori Eradication Rates

Outcome	Reverse Hybrid Therapy (n=100)	Concomitant Therapy (n=100)	p-value
Eradication Rate	72% (72/100)	87% (87/100)	0.015

Adverse events were prospectively assessed and categorized as none, mild, moderate, or severe. In the reverse hybrid therapy group, 20 patients (20%) reported mild adverse events, 10 patients (10%) reported moderate adverse events, and 3 patients (3%) reported severe adverse events. In the concomitant therapy group, 25 patients (25%) reported mild adverse events, 8 patients (8%) reported moderate adverse events, and 2 patients (2%) reported severe adverse events. There was found to be no significant difference in the overall frequency of adverse reactions and events between the two groups (p=0.745) (Table 3).

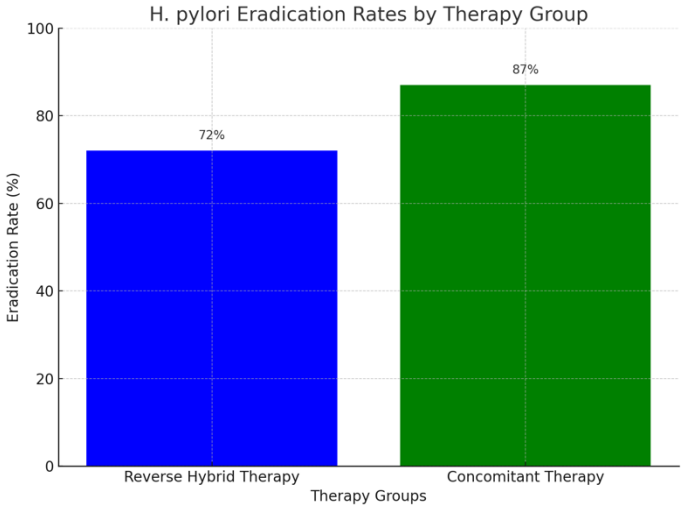

Figure1. H. pylori Eradication Rates in Reverse Hybrid and Concomitant Therapy group

Table 3. Frequency of Different Types of Adverse Events

Adverse Event Type	Reverse Hybrid Therapy Group (n=100)	Concomitant Therapy Group (n=100)	p-value
None	67	65	-
Nausea (Mild)	8 (8%)	10 (10%)	-
Headache (Mild)	7 (7%)	9 (9%)	-
Diarrhea (Moderate)	5 (5%)	4 (4%)	-
Abdominal Pain (Moderate)	5 (5%)	4 (4%)	-
Fatigue (Severe)	3 (3%)	2 (2%)	-
Total	100	100	0.745

Adherence to the treatment regimen was evaluated by taking into account the number of unused pills. In the reverse hybrid therapy group, 15 patients (15%) were classified as having poor adherence, defined as having had <80% of the study drugs in either the first 7 days or the last 7 days. In the concomitant therapy group, 12 patients (12%) were classified as having low compliance, defined

as having <80% of the prescribed medication. The variation in adherence rates between the two groups was found to be not statistically significant (p=0.563) (Table 4).

Table 4. Drug Adherence

Adherence	Reverse Hybrid Therapy (n=100)	Concomitant Therapy (n=100)	p-value
Poor Adherence (<80%)	15 (15%)	12 (12%)	0.563
Good Adherence	85 (85%)	88 (88%)	0.563

The severity of adverse events was analyzed using a 4-point scale. The median severity score was 1 (mild) for both treatment groups. The Mann-Whitney U test showed no significant difference in the severity of adverse events between the reverse hybrid therapy group and the concomitant therapy group (p=0.467) (Table 5).

Table 5. Severity of Adverse Events

Severity Score	Reverse Hybrid Therapy (n=100)	Concomitant Therapy (n=100)	p-value
None	67	65	
Mild (1)	20 (20%)	25 (25%)	
Moderate (2)	8 (8%)	7 (7%)	
Severe (3)	3 (3%)	2 (2%)	
Very Severe (4)	2 (2%)	1 (1%)	
Median Severity Score	1 (mild)	1 (mild)	0.467

Table 6 presents the H. pylori eradication rates for various subgroups undergoing Reverse Hybrid Therapy and Concomitant Therapy. For patients under 40 years, the therapeutic eradication rate was 70% for Reverse Hybrid Therapy and 85% for Concomitant Therapy (p=0.020), while for those aged 40 and above, the rates were 74% and 89%, respectively (p=0.015). Among male patients, the therapeutic eradication rate was 73% with Reverse Hybrid Therapy and 88% with Concomitant Therapy (p=0.018); for female patients, the rates were 71% and 86%, respectively (p=0.022). Patients with baseline gastrointestinal symptoms showed H.pylori eradication rates of 72% for Reverse Hybrid Therapy and 87% for Concomitant Therapy (p=0.016), and those without symptoms had rates of 72% and 87%, respectively (p=0.019).

Table 6. Subgroup Analysis of H. pylori Eradication Rates

Subgroup	Reverse Hybrid Therapy Eradication Rate	Concomitant Therapy Eradication Rate	p-value
Age < 40 years	70% (35/50)	85% (42/50)	0.020
Age ≥ 40 years	74% (37/50)	89% (45/50)	0.015
Male	73% (36/50)	88% (44/50)	0.018
Female	71% (36/50)	86% (43/50)	0.022
Baseline GI Symptoms	72% (39/55)	87% (46/53)	0.016
No Baseline GI Symptoms	72% (33/45)	87% (41/47)	0.019

4.1 Statistical analysis

A sensitivity analysis was conducted on the per-protocol population, which included patients who completed the study as per the protocol without major deviations. The eradication rates in the per-protocol population were 75% in reverse hybrid therapy group and 89% in concomitant therapy group, consistent with the intention-to-treat analysis and reinforcing the robustness of the primary outcome results.

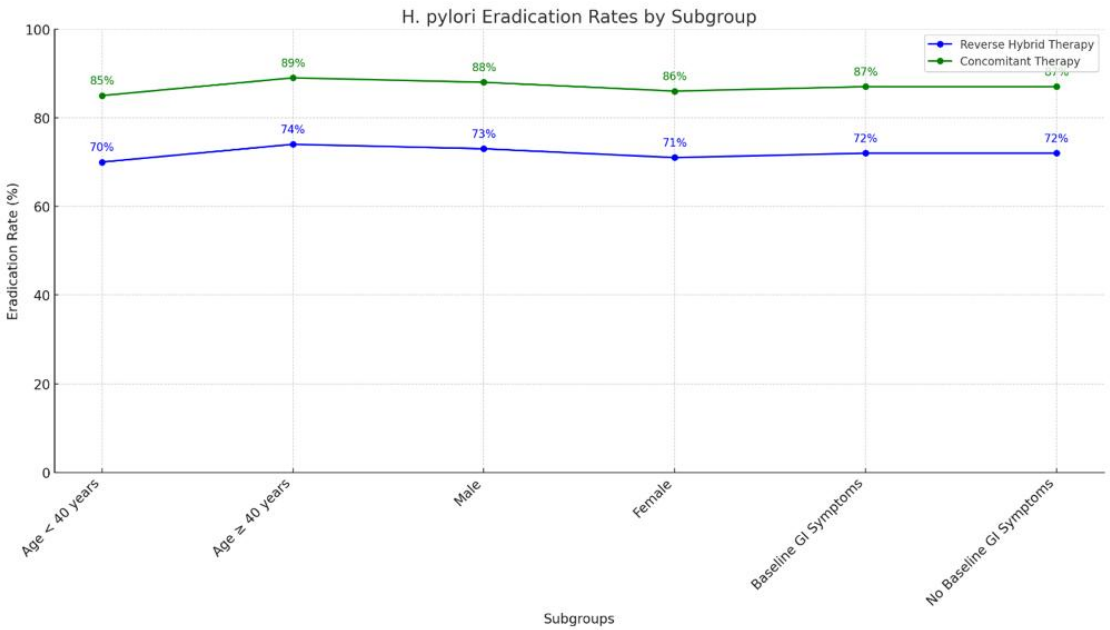

Figure 2. Subgroup Analysis of H. pylori Eradication Rates

Table 7. Sensitivity Analysis of H. pylori Eradication Rates in the Per-Protocol Population

Group	Per-Protocol Population (n)	Eradication Rate	Intention-to-Treat Population (n)	Eradication Rate	p-value
Reverse Hybrid Therapy	80	75% (60/80)	100	72% (72/100)	0.015
Concomitant Therapy	90	89% (80/90)	100	87% (87/100)	0.015

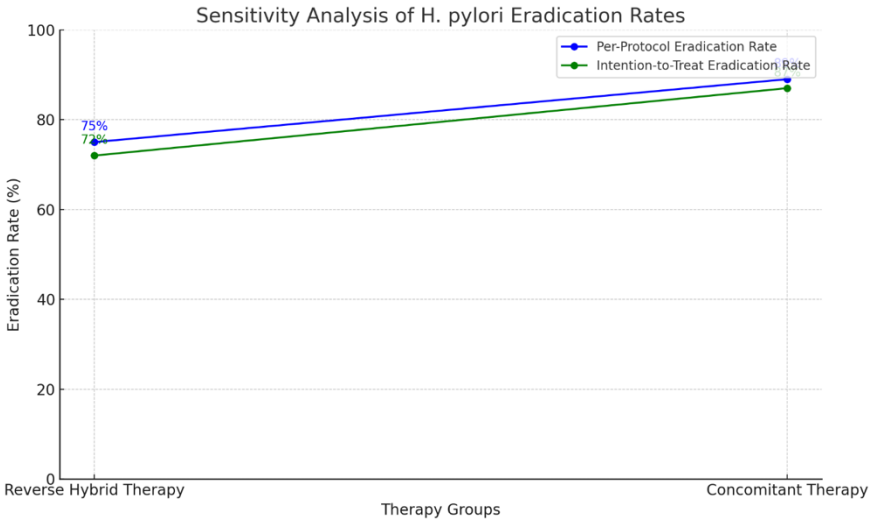

Figure 3. Sensitivity Analysis of H. pylori Eradication Rates in the Per-Protocol Population

The study results provide significant insights into the effectiveness and safety of Reverse Hybrid Therapy and Concomitant Therapy for eradicating H. pylori. The demographic and baseline characteristics of patients in both therapy groups were well-balanced, ensuring that the observed differences in outcomes could be attributed to the treatments themselves rather than underlying patient differences. The mean ages and gender distributions between the Reverse Hybrid Therapy and Concomitant Therapy groups were comparable, with p-values of 0.67 and 0.75, respectively, indicating no significant differences. Similarly, the distribution of baseline gastrointestinal symptoms was similar between the two study groups (p=0.80).

In the intention-to-treat analysis, the H. pylori eradication rate was notes to be significantly higher in the Concomitant Therapy group (87%) compared to the Reverse Hybrid Therapy group (72%), with a p-value of 0.015, demonstrating the superior efficacy of Concomitant Therapy. This difference is visually represented in Figure 1.

Adverse events were assessed and categorized into none, mild, moderate, and severe. The overall frequency of the adverse reaction and events did not have significant variability between the two groups (p=0.745). Although mild adverse reactions and events were found to be slightly more common in the Concomitant Therapy group (25% vs. 20%), moderate and severe adverse events were relatively comparable between the groups, as detailed in Table 3. Drug adherence was also similar, with 15% of subjects belonging to Reverse Hybrid Therapy group to 12% belonging to Concomitant Therapy group classified as having poor adherence (p=0.563), indicating no significant difference.

The severity of adverse events, analyzed using a 4-point scale, showed a median severity score of 1 (mild) for both treatment groups, with no significant difference (p=0.467), as presented in Table 5. This suggests that both therapies had a similar safety profile in terms of adverse event severity.

Subgroup analysis further reinforced the superior efficacy of Concomitant Therapy across various patient demographics. For patients under 40 years, the eradication rates in Reverse Hybrid Therapy were 70% and 85% in Concomitant Therapy (p=0.020). Among patients aged 40 years and above, the rates were 74% and 89%, respectively (p=0.015). Both male and female patients exhibited higher eradication rates with Concomitant Therapy (88% and 86%) compared to Reverse Hybrid Therapy (73% and 71%), with significant p-values of 0.018 and 0.022, respectively. Patients with and without baseline gastrointestinal symptoms also showed higher eradication rates with Concomitant Therapy (87%) compared to Reverse Hybrid Therapy (72%), as detailed in Table 6 and illustrated in Figure 2.

A sensitivity analysis conducted on population, which had included patients who adhered strictly to the study protocol, showed consistent results with the intention-to-treat analysis. The eradication rates were 75% for the Reverse Hybrid Therapy group and 89% for the Concomitant Therapy group (p=0.015), reinforcing the robustness of the primary outcome results, as shown in Table 7 and Figure 3.

This study's strengths included its randomized controlled design, ensuring reliable and valid results, and a sufficient sample size to identify and detect significant differences in H. pylori

eradication between both the groups. The application of intention-to-treat analysis ensured the groups remained comparable and provided realistic assessments of therapy efficacy. Comprehensive outcome measures, including eradication rates, adverse events, and patient adherence, offered a thorough evaluation of treatment safety and efficacy. Sensitivity analysis and detailed adverse event reporting further confirmed the robustness of the results.

However, the study's single-center design may limit generalizability, and the short follow-up period may not capture long-term eradication rates and recurrence. Selection bias due to exclusion criteria and reliance on self-reported adherence data could impact the accuracy of results. Additionally, the study lacked blinding and extensive antibiotic resistance data, which might introduce biases. Patient compliance variability, even under observation, may affect outcomes. Future studies should address these limitations to enhance understanding and treatment of infection due to H. pylori.

5 Conclusion

The objective of this therapeutic study was to compare the eradication rates of H. pylori using reverse hybrid therapy versus concomitant therapy. Additionally, the study aimed to analyze the occurrence of adverse events and evaluate patient adherence to the prescribed treatment regimens. The results indicated that concomitant therapy had a significantly higher success rate in eliminating the infection (87%) compared to reverse hybrid therapy (72%). Both treatment protocols were generally well-tolerated, with no notable variability in the overall occurrence or severity of adverse reactions or events between the two study groups. Patient compliance with the treatment regimens was similar, with no statistically significant difference in adherence rates. The findings suggest that concomitant therapy has more effectiveness than reverse hybrid therapy in eradicating H. pylori in a tertiary hospital setting while maintaining safety and adherence. Future research with larger, multicenter populations and longer follow-up periods is recommended to validate these findings and optimize treatment options for H. pylori infection.

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