Randomised Controlled Trial

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Lansoprazole plus levosulpiride versus esomeprazole in participants with gastroesophageal reflux disease and erosive esophagitis: a double blinded randomized control trial

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Aim: The aim was to compare the efficacy and safety of lansoprazole plus levosulpiride over esomeprazole.
Methodology: This randomized control trial recruited 1000 participants having symptomatic gastroesophageal reflux disease (GERD) and erosive esophagitis and they were blindly randomized into two groups in a 1:1 ratio with appropriate concealment. Group 1 was given lansoprazole plus levosulpiride combination twice daily whereas group 2 was prescribed only esomeprazole twice daily. The primary efficacy endpoint was the healing of erosive esophagitis and GERD at week 49. Secondary assessments included improvement in quality of life. Participants' quality of life was assessed before starting the treatment and post-treatment using a short-form health survey questionnaire (SF-36).
Results: The lansoprazole plus levosulpiride group had significantly lower rates of positive postintervention GERD and erosive esophagitis status, and higher rates of sustained resolution of heartburn compared to the esomeprazole alone group. However, the lansoprazole plus levosulpiride group also had a higher risk of nausea.
Conclusion: Lansoprazole plus levosulpiride is a more effective and safe treatment for GERD than esomeprazole alone. Participants in the lansoprazole plus levosulpiride group showed a significantly higher rate of sustained resolution of GERD, lower rates of postintervention GERD and erosive esophagitis status, and a higher incidence of nausea compared to the esomeprazole alone group. Although quality of life worsened in both groups, adverse effects did not significantly differ. These findings strongly support the use of lansoprazole plus levosulpiride as a preferred treatment option for GERD and erosive esophagitis, which could have significant clinical implications for managing this common condition.

Keywords: esomeprazole, gastroesophageal reflux, lansoprazole, levosulpiride, quality of life

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HIGHLIGHTS

- Lansoprazole plus levosulpiride is a more effective treatment for gastroesophageal reflux disease (GERD) than esomeprazole alone.
- The lansoprazole plus levosulpiride group showed significantly higher rates of sustained resolution of GERD, lower rates of postintervention GERD status and erosive esophagitis status compared to the esomeprazole alone group.
- The quality of life significantly worsened in both groups after 7 months of follow-up.
- The incidence of adverse effects did not differ significantly between the two groups, despite a higher likelihood of nausea in the lansoprazole plus levosulpiride group.

Introduction

Dyspepsia is described as a complex of many symptoms referred to the gastroduodenal region of the gastrointestinal tract. It includes epigastric burning or pain, postprandial fullness, or early

satiety[1]. Initially, dyspepsia was classified as ulcer-like, reflex-like, or dysmotility-like functional dyspepsia. However, now two syndromes are used, which are epigastric pain syndrome and postprandial distress syndrome[2]. One of the causes of functional dyspepsia is gastroesophageal reflux disease (GERD)[3]. GERD is a condition in which the contents of the stomach flow back into the esophagus, leading to esophageal and extraesophageal symptoms. It appears that GERD symptoms are more prevalent nowadays than 25 years ago, and the condition is widespread globally, with the highest prevalence observed in North America (19.8%) and the lowest in East Asia (5.2%). The primary treatment for GERD is acid suppression, with proton pump inhibitors (PPIs) being the most commonly used therapy for fast relief of symptoms in the majority of participants. Currently, there are five PPIs available for treating GERD, namely omeprazole, pantoprazole, lansoprazole, rabeprazole, dexlanzoprazole, and esomeprazole[4]. One of the PPIs used for the treatment of GERD is esomeprazole. It has been demonstrated to be even more effective than omeprazole in the treatment of GERD, according to a meta-analysis performed by Teng *et al*.[5]. Lansoprazole is another PPI used for treating GERD[6]. Fennerty *et al*.[7] compared the effectiveness of esomeprazole (40 mg) with lansoprazole (30 mg) in the treatment of erosive esophagitis and reported that esomeprazole had significantly higher healing rates than lansoprazole[7]. Levosulpiride is a well-known antipsychotic drug that is also used to treat dyspeptic symptoms[8]. It mainly blocks the dopamine D2 receptor[9]. It has also been shown to improve symptoms in participants who suffer from functional dyspepsia[10,11]. We attempted to use levosulpiride in combination with lansoprazole and compare it with esomeprazole alone. Our study aimed to compare the effectiveness and safety of two drug therapies in treating symptomatic GERD and erosive esophagitis. We compared lansoprazole plus levosulpiride (Group 1) and esomeprazole alone (Group 2) to determine which treatment was safer and more effective. The future treatment of GERD and erosive esophagitis participants will be made more successful by determining the better drug therapy.

Methodology

Sampling strategy and sample size calculation

This randomized control trial was conducted at a tertiary care hospital from March 2022 to October 2022. A sample size of 1000 participants was recruited. One of the four PPI (omeprazole, lansoprazole, pantoprazole, or esomeprazole, which were packaged in sealed envelopes) was administered after written informed consent for participation in this study was acquired. One of the four PPIs was placed into a sealed envelope at random. Each PPI was given once in the morning: 20 mg omeprazole, 40 mg pantoprazole, 30 mg lansoprazole, and 20 mg esomeprazole. H2-RAs and prokinetic medications were not allowed to be taken by the subjects while they were being studied. Men and women (mean age, 18–50 years) were present. All patients were required to keep a symptom diary in which they noted the intensity of symptoms (heartburn and acid reflux) both before and during the first seven days of PPI medication. A six-point scale was used to measure the intensity of the symptoms, with 0 denoting none, 1 mild, 2 mild-moderate, 3 moderate, 4 moderate-severe, and 5 denoting severe and/or intolerable. Mild symptoms were classified as heartburn or acid reflux that did not interfere with the patients' regular daily activities. According to this definition, moderate symptoms are those that interfere with daily activities but don't prevent the patients from performing their tasks effectively. High-grade symptoms that prevented the patients' everyday productive activity were considered severe symptoms. The patients were given instructions to keep track of the intensity of their symptoms during the course of the previous day the next morning. Heartburn and acid reflux symptoms' daily variations in intensity were each given their own analysis. The primary purpose of this study was to determine whether quick symptom reduction in the first week of drug delivery differed between the four types of PPI.

Inclusion and exclusion criteria

In our study, we selected participants of both genders between the ages of 18 and 50 with no comorbidities except for GERD and erosive esophagitis as eligible participants based on several factors. One reason for including this age range was that individuals within this range generally have better health and fewer chronic health conditions, making them more likely to tolerate medical interventions or participate in studies. Additionally, selecting younger participants minimized the potential influence of confounding factors associated with comorbidities that are more prevalent in older participants. We also considered ethical considerations, as older participants may be more vulnerable to harm from certain medical interventions. Moreover, studying a younger population was more cost-effective and facilitated recruitment, as younger participants were more likely to participate in clinical trials or interventions. Therefore, the inclusion of participants between the ages of 18 and 50 as eligible participants was a deliberate and carefully considered decision based on multiple factors. Participants that presented to the outpatient clinic were included in our study. Participants who experienced any bleeding disorder, had a history of gastric or esophageal surgery, or had primary esophageal motility disorders (achalasia, scleroderma, and/or primary esophageal spasm) were excluded from the study. Patients having a history of PPIs, H2 blockers, NSAIDs, dexamethasone use within the previous 14 days, any disorders that potentially impact the gaster mucosa, and any digestive procedures were excluded.

Data analysis

Data analysis was performed using the intention-to-treat analysis approach. Descriptive statistics were used to calculate age in both groups. An independent samples *t*-test was done at baseline as well as after 7 months of follow-up for GERD status, erosive esophagitis status to assess whether there was any significant difference between both groups at baseline and after 7 months of study duration. A paired samples *t*-test was done to assess whether there was any significant improvement in quality of life preintervention and postintervention. Odds ratios and descriptives for healing of erosive esophagitis and GERD were calculated for both groups to see which group was superior in efficacy and safety. The Mantel–Haenszel test was used to estimate the common odds ratio and test whether the overall degree of association was significant. Sustained resolution of GERD 3 months after the study's end was calculated, Pearson's χ^2test was used to assess the association of sustained resolution of GERD 3 months after the study's end to both interventions, and odds ratios were calculated for sustained resolution of GERD 3 months after the

study's end and adverse events diarrhea, constipation, nausea, headache, gynecomastia or an irregular menstrual period, and an anaphylactic reaction. Data was analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp.).

The sample size was calculated using the following formula for achieving a CI of 95% and a power of 0.9 from ClinCalc[12], as shown in Table 1.

A CONSORT flowchart has been displayed in Figure 1.

Study design

We employed a randomized-controlled trial design, whereby participants were assigned to one of two groups based on a 1:1 randomization ratio. The randomization process was conducted using a computer-generated randomization sequence, which ensured that each patient had an equal chance of being assigned to the experimental group. The allocation sequence was concealed from both the participants and the investigators to ensure that the assignment of participants to the groups was unbiased. This randomized-controlled trial design allowed us to compare the effectiveness of the interventions between both groups while minimizing the risk of bias, thereby increasing the validity of our results.

Study outcomes

The primary outcomes of this randomized-controlled trial control trial were to compare the effectiveness and safety of lansoprazole plus levosulpiride versus esomeprazole alone in endoscopic as well as symptomatic healing of GERD with respect to endoscopically confirmed GERD status, endoscopically confirmed erosive esophagitis status, and quality of life. The aim of the study was to determine which treatment option is safer and effective in managing GERD as well as erosive esophagitis. The secondary outcomes of the study were the incidence of adverse effects, such as diarrhea, headache, constipation, anaphylactic reaction, and nausea, sustained resolution of GERD.

Definitions of terms used

Baseline GERD status: presence (positive status) or absence (negative status) of endoscopically confirmed symptomatic GERD at the start of the study.

Table 1

Formula used for sample size calculation.

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.87 * 0.13 * (1 + \frac{1}{1})} + 1.28 * \sqrt{0.9 * 0.1 + (\frac{0.8301 * 0.17}{1})} \right\}^2 / 0.0699^2$$

$$N_1 = 500$$

$$N_2 = K * N_1 = 500$$

p1, p2 = proportion (incidence) of groups #1 and #2
Δ = |p2-p1| = absolute difference between two proportions
n1 = sample size for group #1
n2 = sample size for group #2
α = probability of type I error
β = probability o f type II error
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

Baseline erosive esophagitis status: presence (positive status) or absence (negative status) of endoscopically confirmed symptomatic erosive esophagitis at the start of the study.

Quality of life preintervention: participant's subjective quality of life measured using the short-form health survey questionnaire (SF-36) at the start of the study. SF-36 questionnaire scores a participant's quality of life on a scale from 0 to 100, with 0 being the worst quality of life and 100 being the best. Due to the abundance and complexity of the data, the participant responses on the questionnaire were divided into 10 uniform and distinct categories. Participants with SF-36 scores of 0–10 were placed in category 1, 11–20 in category 2, 21–30 in category 3, 31–40 in category 4, 41–50 in category 5, 51–60 in category 6, 61–70 in category 7, 71–80 in category 8, 81–90 in category 9 and 91–100 in category 10.

Outcome GERD status: presence (positive status) or absence (negative status) of endoscopically confirmed symptomatic GERD at the end of 7 months of follow-up.

Outcome erosive esophagitis status: presence (positive status) or absence (negative status) of endoscopically confirmed symptomatic GERD at the end of 7 months of follow-up.

Quality of life postintervention: Participant's subjective quality of life was measured using the SF-36 questionnaire at the start of the study. Due to the abundance and complexity of the data, the participant responses on the questionnaire were divided into 10 categories as done during the preintervention quality of life assessment.

Study protocol and ethics

Our study is fully compliant with the CONSORT 2010 guidelines[13]. A complete CONSORT check list has been provided as a supplementary file (Supplemental Digital Content 1, http://links.lww.com/MS9/A237). Our research adheres to the principles outlined in the Helsinki Declaration. Participants were randomized into two groups. Group 1 was given lansoprazole 30 mg plus levosulpiride 25 mg twice daily, whereas group 2 was only prescribed esomeprazole 40 mg twice daily. Investigators evaluated erosive esophagitis and GERD using an endoscopic approach. To ensure accurate and consistent measurement of healing rates, we employed an experienced gastrointestinal endoscopist who specialized in esophageal disorders. This specialist performed endoscopic evaluations on all participants at both baseline and follow-up visits. By measuring healing rates for erosive esophagitis and GERD at both time points, we were able to assess the effectiveness of both interventions in healing erosive esophagitis. The use of an experienced specialist ensured that the measurements were taken accurately and consistently, reducing the risk of measurement error and increasing the reliability of our results. Participants' quality of life was assessed preintervention and postintervention using the SF-36 questionnaire. A sample of the questionnaire is also presented in the supplementary file (Supplemental Digital Content 2, http://links.lww.com/MS9/A238) (Supplemental Digital Content 3, http://links.lww.com/MS9/A239).

Results

Baseline study participant characteristics are shown in considerable detail in Table 2.

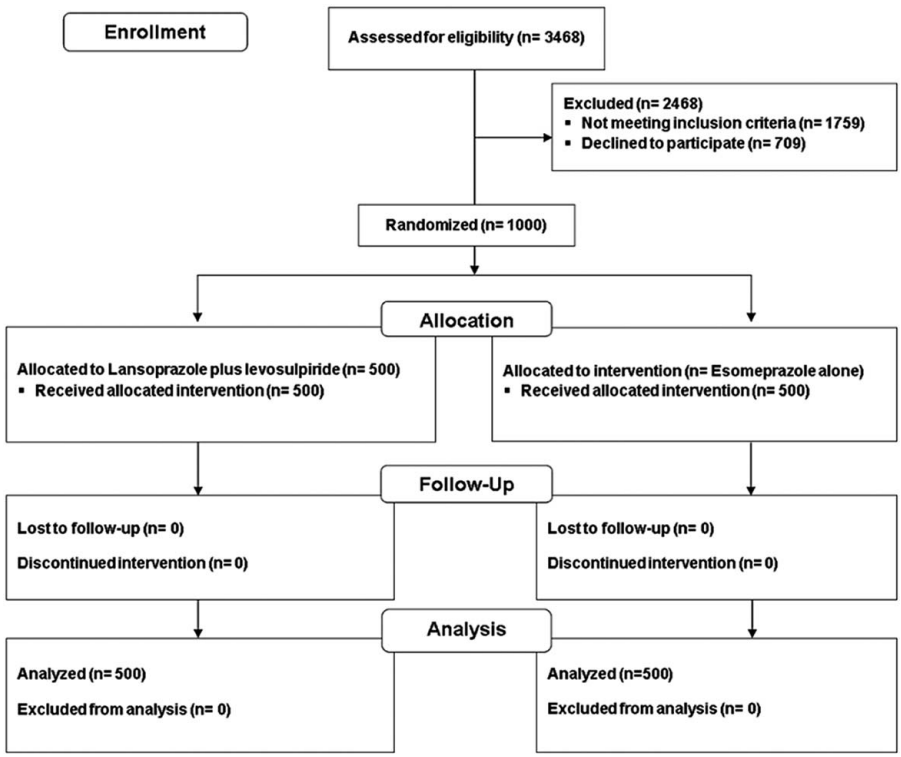

Figure 1. CONSORT flowchart for the study.

Independent samples *t*-test was done at baseline to test the first hypothesis that there was a significant difference in GERD status, erosive esophagitis status, and quality of life between participants in the lansoprazole plus levosulpiride group and the esomeprazole alone group. The outcomes are shown in Table 3. Hence, the first hypothesis was not supported.

After 7 months of follow-up, a separate independent samples *t*-test was performed to test a second hypothesis that there was a significant difference in GERD status, erosive esophagitis status, and quality of life between participants in the lansoprazole plus levosulpiride group and the esomeprazole alone group after 7 months postintervention in both groups. The outcomes are shown in Table 4. Hence, the second hypothesis was supported.

The lansoprazole plus levosulpiride group had a significantly lower percentage of participants with a positive postintervention GERD status compared to the esomeprazole alone group (10.2 vs. 79.4%, respectively). Mantel–Haenszel common odds ratio estimate: a weighted average of the odds ratios for the two treatment groups indicates a common odds ratio estimate of 0.029, with a 95% CI of 0.021–0.042, indicating a significant difference between the two treatment groups in terms of the postintervention GERD status, as shown in Table 5.

To determine the relationship between the positive postintervention erosive esophagitis status compared to the esomeprazole alone group, a χ^2test was used. The lansoprazole plus levosulpiride group had a significantly lower percentage of participants with a positive postintervention erosive esophagitis status compared to the esomeprazole alone group (10.2 vs. 79.4%, respectively) as shown in Table 6. Mantel–Haenszel common odds ratio estimate: a weighted average of the odds ratios for the two treatment groups indicates a common odds ratio estimate of 0.029, with a 95% CI of 0.021–0.042, indicating a significant difference between the two treatment groups in terms of the postintervention erosive esophagitis status, as shown in Table 6.

A χ^2test was conducted to assess the association between the intervention (lansoprazole plus levosulpiride vs. esomeprazole alone) and the outcomes of GERD and healing of erosive esophagitis. The results indicate a significant association between the intervention and both the outcomes that is, negative GERD status and the healing of erosive esophagitis, with a *P*-value of 0.01, as shown in Table 7.

Pearson's χ^2test was used to assess the association between sustained resolution of GERD and 3 months after the end of the study for both interventions, and an odds ratio was also calculated for sustained resolution of GERD 3 months after the end of the study, as shown in Table 8. Three hundred sixty-eight out of 500 participants (73.6%) in the lansoprazole plus levosulpiride group experienced sustained resolution of heartburn, while 252 out of 500 participants (50.4%) in the esomeprazole alone group experienced sustained resolution of heartburn. The difference between the two groups was statistically significant, as indicated by the Pearson's χ^2test with a *P*-value of 0.01. The odds ratio for sustained resolution of GERD was 2.744 (95% CI: 2.105–3.576, *P*-value 0.01), as shown in Table 8.

Observed adverse events were diarrhea, constipation, nausea, headache, gynecomastia or an irregular menstrual period, and an anaphylactic reaction. Table 9 presents the results comparing the incidence of adverse events in both treatment groups. The esomeprazole alone group had a significantly lower incidence of diarrhea and headache compared to the lansoprazole plus levosulpiride group, with an odds ratio and relative risk less than 1.

Table 2

Baseline characteristics of study participants.

Group	Mean age (years)	Number of participants (%)	SD
Lansoprazole plus levosulpiride	33.50	500/10 = (50.0)	7.062
Esomeprazole alone	34.60	500/10 (50.0)	7.925
Total		1000 (100)	
Sex	Number of participants (%)		
Male	500/10 (50.0)		
Female	500/10 (50.0)		
Baseline GERD status	Number of participants (%)		
Positive	500/10 (50.0)		
Negative	500/10 (50.0)		
Baseline erosive esophagitis status	Number of participants (%)		
Positive	500/10 = (50.0)		
Negative	500/10 = (50.0)		
Quality of life preintervention	Number of participants (%)		
SF-score between 0 and 10	105 (10.5)		
SF-score between 11 and 20	105 (10.5)		
SF-score between 21 and 30	105 (10.5)		
SF-score between 31 and 40	105 (10.5)		
SF-score between 41 and 50	105 (10.5)		
SF-score between 51 and 60	105 (10.5)		
SF-score between 61 and 70	105 (10.5)		
SF-score between 71 and 80	106 (10.6)		
SF-score between 81 and 90	106 (10.6)		
SF-score between 91 and 100	53 (5.3)		

Group	Age (years) Mean	SD	*P*
Lansoprazole plus levosulpiride	33.50	7.062	0.06
Esomeprazole alone	34.60	7.925	

Group		Age group 18–25	Age group 26–30	Age group 31–35	Age group 36–40	Age group 41–45	Age group 46–50
	Lansoprazole plus levosulpiride	34.8%	85.8%	50.6%	60.8%	33.3%	29.2%
	Esomeprazole alone	65.2%	14.2%	49.4%	39.2%	66.7%	70.8%

GERD, gastroesophageal reflux disease; SF-score, short-form health survey questionnaire-score.

On the other hand, levosulpiride is a D-2 receptor blocker and known to reduce nausea and vomiting compared to the esomeprazole alone group, which showed a lower number of nausea events.

A paired samples *t*-test was conducted to examine the effect of the intervention on the quality of life in both the lansoprazole plus levosulpiride as well as the esomeprazole alone group, as shown in Table 10.

Table 3

Independent samples *t*-test at baseline.

	Independent samples *t*- test							
	Levene's test for equality of variances	*t*-test for equality of means					95% CI of the difference	
	P	***t***	**df**	***P***	**Mean difference**	**Standard error difference**	**Lower**	**Upper**
Baseline erosive esophagitis status	1.00	−0.758	998	0.448	−0.024	0.032	−0.086	0.038
Baseline GERD status	1.00	−0.758	998	0.448	−0.024	0.032	−0.086	0.038
Quality of life preintervention	0.892	0.436	998	0.663	0.076	0.174	−0.266	0.418

P-values in bold indicate statistically significant values.
df, degree of freedom; *t*, *t*-statistic.

Table 4

Independent samples *t*-test at 7 months of follow-up.

	Independent samples *t*-test								
	Levene's test for equality of variances		*t*-test for equality of means						
								95% CI of the difference	
	F	*P*	*t*	df	*P*	Mean difference	Standard error difference	Lower	Upper
Postintervention GERD status	90.219	**<0.01**	30.602	998	**<0.01**	0.692	0.023	0.648	0.736
Quality of life postintervention	96.197	**<0.01**	30.493	998	**<0.01**	2.660	0.087	2.489	2.831
Postintervention erosive esophagitis status	90.219	**<0.01**	30.602	998	**<0.01**	0.692	0.023	0.648	0.736

P-values in bold indicate statistically significant values.
df, degree of freedom; *t*, *t*-statistic.

Discussion

This parallel-group, randomized-controlled trial compared the effectiveness of lansoprazole plus levosulpiride versus esomeprazole alone in endoscopic and symptomatic healing of GERD with respect to endoscopically confirmed GERD status, endoscopically confirmed erosive esophagitis status, and quality of life. The independent samples *t*-test was used to test the first hypothesis that there was a significant difference in the baseline GERD status, erosive esophagitis status, and quality of life between participants in both treatment groups. The *t*-test results indicated that there was no significant difference in the baseline GERD status, erosive esophagitis status, or quality of life between the two groups. Hence, the first hypothesis was not supported. A separate independent sample *t*-test was conducted to test the second hypothesis that there was a significant difference in GERD status, erosive esophagitis status, and quality of life between participants in the lansoprazole plus levosulpiride group and the esomeprazole alone group after 7 months of follow-up, which indicated that there was indeed a statistically significant difference present. The odds of having a positive GERD status and a positive erosive esophagitis status after the intervention with lansoprazole with levosulpiride were significantly lower compared to the esomeprazole alone group. The association between the interventions and the outcomes that is, negative GERD status and healing of erosive esophagitis revealed a significant association between the interventions and both outcomes (GERD status and erosive esophagitis status). Additionally, sustained resolution of GERD 3 months after the end of the study was calculated and association revealed that the lansoprazole plus levosulpiride combination was more effective than esomeprazole alone for sustained resolution of GERD. Participants in the lansoprazole plus levosulpiride group were 2.744 times more likely to experience sustained resolution of GERD than those in the esomeprazole alone group. A weak positive correlation was seen between the quality of life preintervention and postintervention. The difference in quality-of-life scores between preintervention and postintervention were statistically significant. Participants

Table 5

Descriptive statistics and odds ratio for postintervention gastroesophageal reflux disease status.

	Group			
	Lansoprazole plus levosulpiride		Esomeprazole alone	
Postintervention GERD status	**Positive**	**10.2%**	**79.4%**	
	Negative	**89.8%**	**20.6%**	
		95% CI		
	Value	Lower	Upper	*P*
Odds ratio for a positive postintervention GERD status in lansoprazole plus levosulpiride group compared to esomeprazole alone group	0.029	0.021	0.042	**<0.01**
Relative risk for a positive postintervention GERD status in the lansoprazole plus levosulpiride group	0.140	0.108	0.182	**<0.01**
Relative risk for a positive postintervention GERD status in the esomeprazole alone group	4.749	3.978	5.670	**<0.01**
Mantel–Haenszel common odds ratio estimate				
Estimate				0.029
ln (Estimate)				-3.524
P				**<0.01**
Asymptotic 95% CI	Common odds ratio		Lower bound	0.021
			Upper bound	0.042

P-values in bold indicate statistically significant values.

Table 6

Descriptive statistics and odds ratio for postintervention erosive esophagitis status.

		Group		
		Lansoprazole plus levosulpiride		Esomeprazole alone
Postintervention erosive esophagitis status	Positive	10.2%		79.4%
	Negative	89.8%		20.6%
		95% CI		
	Value	Lower	Upper	*P*
Odds ratio for postintervention erosive esophagitis in lansoprazole plus levosulpiride group compared to esomeprazole alone group	0.029	0.021	0.042	< **0.01**
Relative risk for a positive postintervention erosive esophagitis status in the lansoprazole plus levosulpiride group	0.140	0.108	0.182	< **0.01**
Relative risk for a positive postintervention erosive esophagitis status in the esomeprazole alone group	4.749	3.978	5.670	< **0.01**
Mantel–Haenszel common odds ratio estimate				
Estimate				0.029
ln (Estimate)				-3.524
P				< **0.01**
			Lower bound	0.021
Asymptotic 95% CI	Common odds ratio		Upper bound	0.042

P-values in bold indicate statistically significant values.

reported a statistically significant better quality of life after the intervention. The odds and likelihood of experiencing diarrhea or headache were lower in the esomeprazole alone group compared to the other group. Participants in the lansoprazole plus levosulpiride group were less likely to experience nausea compared to the other group. However, the odds ratio was not statistically significant. No statistically significant difference was found in the incidence of constipation or anaphylactic reaction between the two treatment groups, as the odds ratios and relative risks were not statistically significant. On review of the literature, it is surprising to see very few studies done on the topic. Most of the studies done in the field are at least a decade old and weakly related to the topic. Hence, we compared our results to the most similar studies that we could find in the literature. Li *et al.*[14] conducted a study in the past that compared FDA-recommended dose PPIs in erosive esophagitis and found that esomeprazole 40 mg, pantoprazole 40 mg, esomeprazole 20 mg, and lansoprazole 30 mg were more effective and acceptable than other interventions, with esomeprazole 40 mg demonstrating the most superiority in mucosal erosion healing and heartburn relief[14]. This is in disagreement with our results. On the one hand, we did not compare between multiple PPIs, but on the other hand, our study is superior in that it had a larger sample size and a longer period of follow-up. Pratha *et al.*[15] conducted a randomized

Table 7

Descriptive statistics and χ^2tests for postintervention gastroesophageal reflux disease status and postintervention erosive esophagitis status.

		Group		
		Lansoprazole plus levosulpiride	Esomeprazole alone	
Postintervention GERD status	Positive	10.2%	79.4%	
	Negative	89.8%	20.6%	
Postintervention erosive esophagitis status	Positive	10.2%	79.4%	44.8%
	Negative	89.8%	20.6%	55.2%
Total	100.0%	100.0%	100.0%	
X^2tests	χ^2	df	*P*	
Postintervention GERD status	484.100	1	< **0.01**	
Postintervention erosive esophagitis status	484.100	1	< **0.01**	

P-values in bold indicate statistically significant values.

Table 8

Descriptive statistics, odds ratio, and χ^2tests for sustained resolution of heartburn 3 months after the end of the study.

			Group	
			Lansoprazole plus levosulpiride	Esomeprazole alone
Sustained resolution of heartburn 3 months after the end of study	Yes	*N* (%)	368 (59.4%)	252 (40.6%)
	No	*N* (%)	132 (34.7%)	248 (65.3%)
	χ^2	df	*P*	
Pearson χ^2	57.114	1	< **0.01**	
	Value	95% CI	*P*	
		Lower	Upper	
Odds ratio for sustained resolution of GERD 3 months after the end of study in lansoprazole plus levosulpiride group compared to esomeprazole alone group	2.744	2.105	3.576	< **0.01**

P-values in bold indicate statistically significant values.

Table 9

Descriptive statistics of adverse events along with odds ratios and relative risks.

	Group			
	Lansoprazole plus levosulpiride ($n=500$)		Esomeprazole alone ($n=500$)	
Adverse event: Diarrhea	0.8%		4.4%	
Adverse event: Constipation	1.4%		1.6%	
Adverse event: Nausea	0.4%		1.2%	
Adverse event: Headache	0.4%		5.2%	
Adverse event: Gynecomastia or irregular menstrual period	0.4%		0%	
Adverse event: Anaphylactic reaction	0.4%		0.2%	
		95% CI		
	Value	Lower	Upper	*P*
Odds ratio for diarrhea in esomeprazole alone group compared to lansoprazole plus levosulpiride group	0.175	0.060	0.512	**< 0.01**
Relative risk for diarrhea esomeprazole alone group	1.724	1.446	2.056	**< 0.01**
Odds ratio for constipation in esomeprazole alone group compared to lansoprazole plus levosulpiride group	0.873	0.314	2.427	> 0.05
Relative risk for constipation in esomeprazole alone group	1.068	0.662	1.721	> 0.05
Odds ratio for nausea in esomeprazole alone group compared to lansoprazole plus levosulpiride group	3.024	0.607	15.057	> 0.05
Relative risk for nausea in lansoprazole plus levosulpiride group	0.498	0.150	1.656	> 0.05
Relative risk for nausea in esomeprazole alone group	1.506	1.005	2.258	**< 0.01**
Odds ratio for headache in esomeprazole alone group compared to lansoprazole plus levosulpiride group	0.073	0.017	0.310	**< 0.01**
Relative risk for headache in esomeprazole alone group	1.904	1.687	2.150	**< 0.01**
Relative risk for gynecomastia or menstrual irregularities in lansoprazole plus levosulpiride group	2.004	1.883	2.133	**< 0.01**
Odds ratio for anaphylactic reaction in esomeprazole group compared to lansoprazole plus levosulpiride group	2.004	0.181	22.172	> 0.01
Relative risk for anaphylactic reaction in lansoprazole plus levosulpiride group	1.335	0.598	2.978	> 0.05

P-values in bold indicate statistically significant values.

crossover study in the past to evaluate the onset of action of immediate-release omeprazole 20 mg/sodium bicarbonate 1100 mg and delayed-release lansoprazole 15 mg in 63 healthy fasting adults and found that immediate-release esomeprazole is safe and well tolerated and provides better gastric acid suppression than delayed-release lansoprazole[15]. This is theoretically similar to our study, although significantly different in design. Not only was lansoprazole plus levosulpiride safer, but it was more efficacious than esomeprazole on 7 months of follow-up in our results. Zheng[16] conducted a comparative study in the past to investigate whether different PPIs have different effects on symptom relief in participants with reflux esophagitis. Two hundred and seventy-four participants were randomized to treatment groups and results indicated that esomeprazole was more effective than other PPIs for rapid relief of heartburn and acid reflux symptoms in participants with reflux esophagitis[16]. Our study found the contrary result that lansoprazole plus levosulpiride was superior to esomperazole alone, but our study had a larger sample size and a longer period of follow-up compared to their study. Adachi *et al.*[17] conducted a study to

Table 10

Paired samples *t*-test comparing preintervention and postintervention quality of life.

	Paired samples *t*-test						
	Mean	Number of participants		SD		Standard error mean	
Quality of life preintervention	7.55	1000		1.916		0.061	
Quality of life postintervention	5.27	1000		2.754		0.087	
	Number of participants	Paired sample correlation	*P*				
Quality of life preintervention and quality of life postintervention	1000	0.044	0.016				
	Paired differences						
	Mean	SD	Standard error mean	95% CI of the difference Lower	Upper	*t*	df	*P*
Quality of life preintervention and quality of life postintervention	2.278	3.285	0.104	2.482	2.074	21.927	999	**< 0.01**

P-values in bold indicate statistically significant values.
df, degree of freedom; *t*, *t*-statistic.

determine the speed of symptom relief in participants with reflux esophagitis after administering three different PPIs, and found that rabeprazole was more effective than omeprazole and lansoprazole for rapid relief of heartburn symptoms in participants with reflux esophagitis[17]. This is a limitation to our study that we did not study other PPIs other than lansoprazole and levosulpiride and esomeprazole. Caro *et al*.[18] analyzed 53 clinical trials and found that PPIs were more effective in healing erosive esophagitis and decreasing relapse rates compared to ranitidine and placebo. The study concluded that relapse rates after one year of treatment were similar between lansoprazole and rabeprazole[18]. We discovered that the lansoprazole + levosulpiride group had reduced rates of recurrence at 3 months than the esomeprazole alone group. Pilotto *et al*.[19] conducted a study comparing the effectiveness and tolerability of four PPIs for treating esophagitis in elderly participants over a period of 8 weeks. A total of 320 participants were randomly assigned to receive one of four treatments, and after 8 weeks, endoscopy and clinical evaluation were repeated. Results showed that pantoprazole and rabeprazole were more effective than omeprazole or lansoprazole in healing esophagitis and improving symptoms[19]. This is a limitation to our study. We did not compare lansoprazole and esomeprazole to other PPIs. Jaspersen *et al*.[20] compared the effectiveness of double standard doses of omeprazole, lansoprazole, or pantoprazole for the maintenance treatment of severe oesophagitis with a stricture and reported that omeprazole was superior to lansoprazole or pantoprazole for the maintenance treatment of complicated gastroesophageal reflux disease[20]. We found the opposite results with a larger sample size and a considerably longer duration of follow-up, which makes our study superior to their study. Röhss *et al*.[21] conducted four studies in the past comparing the effects of esomeprazole 40 mg with lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg on intragastric pH in participants with gastroesophageal reflux disorder (GERD) and esomeprazole 40 mg was found to provide better acid control and maintain an intragastric pH greater than 4 for a longer period than the other PPIs in participants with GERD[21]. In our study, lansoprazole plus levosulpiride provided better results. Recently, Yang *et al*.[22] conducted a network meta-analysis to identify first-line therapies for erosive esophagitis and found that all PPIs and vonoprazan significantly improved endoscopic cure rates compared to placebo. Ilaprazole was ranked as the most effective followed by esomeprazole, vonoprazan, pantoprazole, lansoprazole, omeprazole, rabeprazole, and placebo based on the surface under the cumulative ranking curve. There was no significant difference in the rate of adverse events among all PPIs, vonoprazan, and placebo. The study concluded that ilaprazole, esomeprazole, and vonoprazan were more effective in healing mucosal erosion, but no significant differences were observed in terms of safety among all interventions[22]. This is in disagreement to our study. Xiao *et al*.[23] investigated the noninferior efficacy of vonoprazan compared to lansoprazole for treating Asian participants with erosive oesophagitis in a double-blind, multicentre phase III study. The study found that vonoprazan had higher healing rates at 2, 4, and 8 weeks than lansoprazole, particularly in participants with baseline Los Angeles classification grade C/D. The study concluded that vonoprazan is noninferior to lansoprazole for erosive oesophagitis healing rate at 8 weeks in this population, and both treatments have similar safety outcomes[23]. We did not study vonoprazan compared to PPIs which makes this a limitation to our study. Lee *et al*.[24] conducted a randomized, double-blind study to confirm the non-inferiority of tegoprazan, a novel potassium-competitive acid blocker, compared to esomeprazole in treating 302 Korean participants with erosive esophagitis. The study found that tegoprazan was noninferior to esomeprazole in terms of healing erosive esophagitis confirmed by endoscopy up to 8 weeks, with a similar incidence of adverse events and tolerability. Therefore, once-daily administration of tegoprazan was shown to have noninferior efficacy and tolerability compared to esomeprazole[24]. We did not study tegoprazan compared to PPIs which makes this a limitation to our study. Mori and Suzuki[25] reported that PPIs are commonly used to treat gastric acid-related diseases, peptic ulcer disease, and low-dose aspirin or nonsteroidal anti-inflammatory drug-induced peptic ulcers. However, vonoprazan, a first-in-class potassium-competitive acid blocker, has unique benefits over other traditional PPIs due to its strong acid suppression capabilities. As a result, vonoprazan is an effective treatment for GERD and Helicobacter pylori infection[25]. We did not study vonoprazan compared to PPIs, which makes this a limitation to our study.

Limitations

Our study has a generalizable sample, an appropriate follow-up period, and efforts were made to reduce potential biases, there are still some limitations to consider. One major limitation is the narrow focus on PPIs. This limits the potential for the study to inform treatment decisions for participants who may not be suitable candidates for PPI therapy. Additionally, the effect size of 0.9 may be considered a large effect size, but it may not be clinically significant or relevant for all participants, as there may be individual variability in treatment response. Finally, the study may have limited applicability to certain populations, as it is unclear how the results may differ for participants with comorbid conditions or those taking other medications. It is possible that these factors may impact treatment response and should be considered in future studies. Overall, while the study has many strengths, these limitations should be considered when interpreting the results and determining the appropriate use of PPI therapy for GERD and erosive esophagitis.

Conclusion

Lansoprazole plus levosulpiride is a more effective treatment option for GERD than esomeprazole alone. The results of the study showed that the lansoprazole plus levosulpiride group had a significantly higher rate of sustained resolution of GERD, as well as significantly lower rates of postintervention GERD status and erosive esophagitis status compared to the esomeprazole alone group. Quality of life significantly improved in both the lansoprazole plus levosulpiride and esomeprazole alone group after 7 months of follow-up. Despite a higher likelihood of nausea in the lansoprazole plus levosulpiride group, the incidence of adverse effects such as diarrhea, headache, constipation, and anaphylactic reaction did not differ significantly between the two groups. In conclusion, the current study discovered that esomeprazole 40 mg daily may be more beneficial than omeprazole 20 mg daily, pantoprazole 40 mg daily, or lansoprazole 30 mg daily in patients with endoscopically verified reflux esophagitis for the

immediate treatment of heartburn symptoms. Patients treated with omeprazole, pantoprazole, lansoprazole, or esomeprazole experienced no difference in symptom relief after several days of treatment, nor did they experience any difference in reflux esophagitis healing rates after 8 weeks of treatment. This study provides strong evidence to support the use of lansoprazole plus levosulpiride as a safer and more effective treatment option for GERD and erosive esophagitis compared to esomeprazole alone, which may have important clinical implications for the management of this common condition.

Ethical approval

Ethical approval was granted by institutional review board of Jinnah Sindh Medical University dated 1 August 2022 under reference number ERC/JSMU/DME/8-01/022.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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All authors contributed significantly to conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review and editing. H.M.: played a supervisory role in addition to the other roles common to all authors; M.S.: played additional role of visualization and statistical analysis in addition to the other roles common to all authors. All authors read the final version of the manuscript and approved it for submission and publication.

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The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Guarantor

Muhammad Rizwan Umer.

Data availability statement

De-identified data will be made available by the corresponding author to those who submit a formal request for access to the data to the corresponding author. All requests will be subject to an independent review by our Institutional Review Board (IRB) to ensure that they meet the criteria for scientific merit, ethical soundness, and appropriate use. If the IRB deems the request to be sincere and in accordance with our data sharing policies, we will make the data available in a secure and controlled environment.

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