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Original Research Article

# Evaluation of Safety, Efficacy and Tolerability of Rabeprazole (Enteric Coated, EC) 20mg with Levosulpride (Sustained Release, SR) 75mg Fixed Dose Combination in Patients with Gastroesophageal Reflux Disease

**Arun R Keshwala[1], Hemal J. Dholakia[2], Arun Hebbar J N[3]**

[1]Assistant Professor, PDU Government Medical College, Rajkot, Gujarat, India
[2]Senior Resident, PDU Medical College, Rajkot, Gujarat, India
[3]MD Pharmacology, Senior Resident, MP Shah Government Medical College, Jamnagar, Gujarat, India

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**Corresponding author: Dr. Arun Hebbar J N**
**Conflict of interest: Nil**

## Abstract

**Background:** Gastroesophageal reflux disease is a highly prevalent gastrointestinal disorder in 10-20% of population. Main treatment possibilities for GERD are lifestyle modifications and pharmacological therapy. New publications have raised questions upon long term safety and over prescription of current therapeutic agents.

**Methodology:** The present study is prospective, single centre, open-label, comparative, observational study initiated to compare the safety, efficacy, and tolerability of rabeprazole (enteric coated, EC) 20mg with levosulpride (sustained release, SR) 75mg fixed dose combination in patients with gastroesophageal reflux disease.

**Results:** Global assessment of efficacy at the end of therapy was rated as "excellent" (17% in group A and 10% in group B),"very good" (63% in group A and 50% in group B) "good" (17% in group A and 23% in group B), and “satisfactory” (3% in group A and 16% in group B). On global assessment of tolerability, the product rated to have "good" (84% in group A and 64% in group B) and “moderate” (16% in group A and 36% in group B) at the end of the study

**Conclusion:** The treatment with levosulpride to rabeprazole in GERD patients with high FSSG score provides better symptomatic relief compared to rabeprazole monotherapy with minimal mild side effects.

**Keywords:** GERD, Levosulpride, Lifestyle Modification, Rabeprazole



## Background

The American College of Gastroenterology (ACG) guideline defines gastroesophageal reflux disease (GERD) as “symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus” in ACG guidelines [1]. Gastroesophageal reflux disease (GERD) is the most common diseases routinely diagnosed by gastroenterologists, surgeons, and physicians in their clinics. It is a highly prevalent gastrointestinal disorder in 10-20% of population characterized by heartburn, acid regurgitation, epigastric

distress, and dysphagia [2]. It significantly impacts quality of life (QOL) directly as well as indirectly due to high healthcare cost [3]. GERD comprises of a number of clinical presentations with or without visible mucosal findings on endoscopic examination [4]. New publications have raised questions upon long term safety and over prescription of current therapeutic agents. Updated ACG Clinical Guideline has provided evidence-based recommendations and practical guidance for the clinical evaluation and management of GERD [1].

Main treatment possibilities for GERD are lifestyle modifications and pharmacological therapy. Proton pump inhibitor (PPI) therapy is the mainstay pharmacologic management for GERD and proven its safety and efficacy for GERD treatment in adult and adolescent populations [1]. However, there is a significant portion of the GERD patients up to 40% have been reported inadequate symptoms relief and healing esophageal mucosal breaks with a standard once-daily PPI regimen [5,6]. Non response to PPI in GERD patients reported more frequent reflux symptoms, sleep disorders, impaired quality of life (QOL), work loss and consumption of health care resources [7-10].

Rabeprazole is a proton pump inhibitor (PPI), inhibits gastric acid production and raises gastric pH. It has been reported more effective in suppressing nocturnal gastric acid secretion in the management of GERD patients [11]. Rabeprazole differs from other PPI as it gives highest pKa, having shortest activation half-life, optimal acid suppression since the first administration resulting in a higher median 24-hour intragastric pH and non-enzymatic metabolism [11-13].

Levosulpiride is a well-known antiemetic and antipsychotic agent [14]. It has been reported prokinetic activity with selective D2-receptor antagonism and serotonergic (5-HT4) activity. Due to these actions, levosulpride has a therapeutic role as a modulator of the motor activity in management of functional dyspepsia [15,16]. Different studies has demonstrated role of levosulpride with high efficacy in dyspeptic symptoms control and favorable safety profile [17-19].

Most of the patients with GERD symptoms in our hospital set up, treated empirically with proton pump inhibitors and H2 antihistaminic in the out patients departmental visits and do not diagnosed by undergoing different diagnostic modalities advances. However, patients with severe clinical findings, non-responders to PPI and patients with alarming symptoms are investigated with an upper GI endoscopy. The choice of management strategy becomes personalized to the patient's need and clinical finding in PPI non-responders includes other pharmacological and invasive interventions [20].

Few studies have been reported role of PPI with prokinetic combination in patients with acid reflux diseases, but there is a lacuna of studies reported comparative benefits of PPI alone versus combination with prokinetic in GERD patients [14,21]. The present study is initiated to compare the safety, efficacy and tolerability of rabeprazole (enteric coated, EC) 20mg with levosulpride (sustained release, SR) 75mg fixed dose combination in patients with gastroesophageal reflux disease.

## Methods

This was a prospective, single centre, open-label, comparative, observational study conducted between March 2022 and June 2022 at tertiary care hospital in western Gujarat. The primary objective of the study was to evaluate the safety, efficacy and tolerability of fixed dose combination of rabeprazole (enteric coated, EC) 20mg with levosulpride (sustained release, SR) 75mg in compare to rabeprazole (enteric coated, EC) 20mg alone for treatment of GERD. The study was approved by an institutional ethics

committee and was conducted in compliance with ICH-GCP, New Drugs and Clinical Trial Rules-2019, ICMR guidelines as well as policy statements of declaration of Helsinki revised edition (2013). All patients were explained and given a detailed description of the study and their written informed consent was obtained prior to study.

The patients who visited the gastroenterology out patients department with suspicious GERD symptoms and requiring fixed dose combination of Rabeprazole (enteric-coated, EC) 20 mg + levosulpride (sustained release, SR) 75mg treatment according to the consultant's judgment were eligible for enrolment for the study. Patients with the highest specificity of GERD symptoms were diagnosed as a presumptive GERD cases and therapy was initiated empirically to avoid comprehensive and costly evaluation in every patient. In the absence of typical symptoms, further diagnostic testing upper GI endoscopy and esophageal pH monitoring were done to confirm the diagnosis as well as to assess for complications or alternate causes for the symptoms.

Specific inclusion criteria for GERD patients in the present study included the following: patients with more than 18 years of age, GERD-related symptoms (heartburn, acid regurgitation, epigastric distress, and dysphagia), and those willing to give consent. Patients who had history of receiving radiotherapy or surgery in the head and neck, lactating and pregnant women, known hypersensitivity to any of the study drugs and refuse to give consent were excluded from the study.

The patients were enrolled in the study on Day 1 (baseline) and were administered fixed dose combination of Rabeprazole (enteric-coated, EC) 20 mg + Levosulpride (sustained release, SR) 75mg one tablet daily in Group A or Rabeprazole (enteric-coated, EC) 20 mg one tablet daily in group B for 30 days on consultant’s judgment and fulfillment of the inclusion and exclusion criteria. Further study visits were scheduled at 30 days of treatment. All patients diagnosed with GERD were asked to self-report a questionnaire of frequency scale for the symptoms of GERD (FSSG) with the treatment of GERD during outpatient visit. The efficacy of the study medication was assessed by the change of FSSG from baseline to day 30. FSSG is the standard questionnaire used for the diagnosis of GERD and assessment of the response to the treatment [22]. The FSSG contains the 12 symptoms most commonly experienced by GERD patients. Each symptom is divided into 5 phases according to its frequency of expression (never=0, occasionally=1, sometimes=2, often=3, and always=4) and divided into 2 subscales: acid reflux-related symptoms, including 7 of 12 items (Nos. 1, 4, 6, 7, 9, 10, and 12), and dysmotility, including 5 of 12 items (Nos. 2, 3, 5, 8, and 11). The FSSG score became a good correlation with the extent of endoscopic improvement and was useful for objectively evaluating the therapeutic response of GERD [22]. At the end of the study (30 days), global assessment for efficacy was done on a 5-point scale (1=Excellent, 2=Very Good, 3=Good, 4=Satisfactory, 5=Poor) and global assessment for tolerability was done on a 3-point scale (1=Good, 2=Moderate, 3=Poor) by both investigator and patient.

The safety and tolerability of the study drug was assessed by physical examination, collection, and monitoring of AEs, serious adverse events, and their relationship to study drug was performed at each visit. The concomitant medications were also reviewed throughout the study

**Statistical analysis**

The clinical characteristics were presented as means± standard deviation or as number (%) of patients. Statistical analysis was performed with the SPSS statistics program (version. 25; SPSS Inc., Chicago, IL). Data describing categories or nominal data were expressed as numbers with

percentages. Measurement data was expressed as means with standard deviation. Paired t-test was performed to analyse the statistical significance of the difference between the baseline and follow-up visits for total scores for FSSG. A p value <0.05 was considered statistically significant.

## Results

A total of 76 patients were screened to enrolled 60 in the study. All the enrolled patients successfully completed the study. The demographic details and sex distribution of the enrolled patients are presented in Table 1 and 2.

**Table 1: Sex distribution of the patients (n=60)**

| | Total subjects | Group A | Group B |
|---|---|---|---|
| Number of subjects (%) | 60(100) | 30(50%) | 30(50%) |
| **Gender** | | | |
| Female | 38(63%) | 17(57%) | 21(70%) |
| Male | 22(37%) | 13(43%) | 9(30%) |

**Table 2: Demographic details of the patients (n=60)**

| | Mean | SD | Min. | Max. |
|---|---|---|---|---|
| Age (years) | 46.70 | 9.70 | 26 | 67 |
| Height (cm) | 164.34 | 5.67 | 149 | 178 |
| Weight (kg) | 67.50 | 9.72 | 52 | 83 |
| BMI | 25.24 | 3.74 | 19.59 | 31.68 |
| BMI: Body mass index; SD: Standard deviation; Min. Minimum; Max: Maximum | | | | |

The mean age was found to be 46.70 years old and 63% of the patient populations in the study were females while 37% of the patients were male. Global assessment of efficacy at the end of therapy was rated as "excellent" (17% in group A and 10% in group B),"very good" (63% in group A and 50% in group B) "good" (17% in group A and 23% in group B), and “satisfactory” (3% in group A and 16% in group B) (figure 1). On global assessment of tolerability the product rated to have "good" (84% in group A and 64% in group B) and “moderate” (16% in group A and 36% in group B) at the end of the study (figure 2).

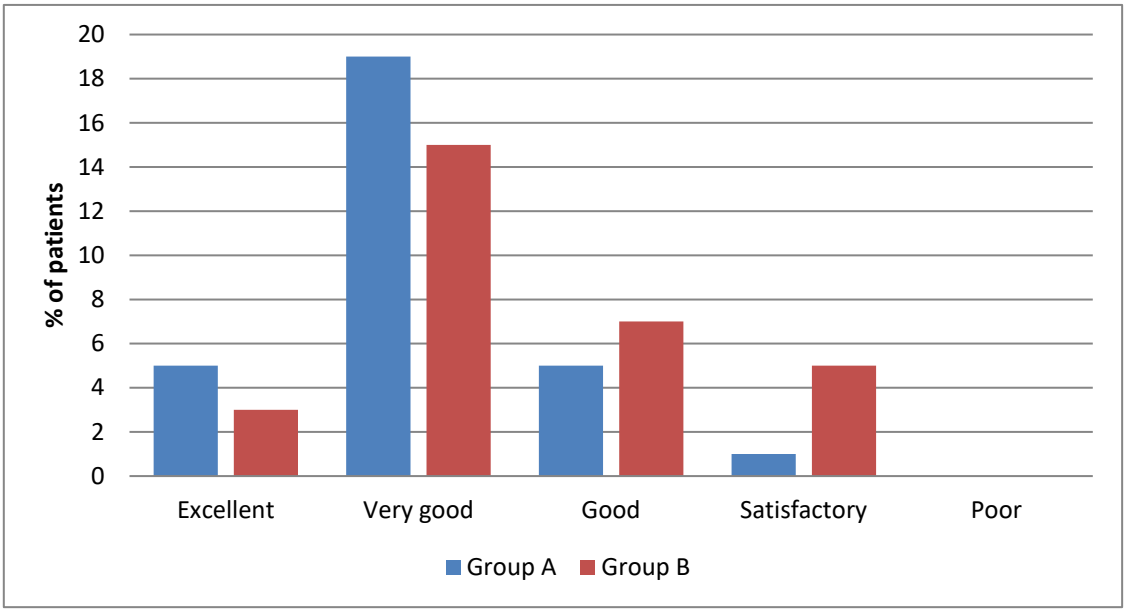


**Figure 1: Global assessment for efficacy day 30**

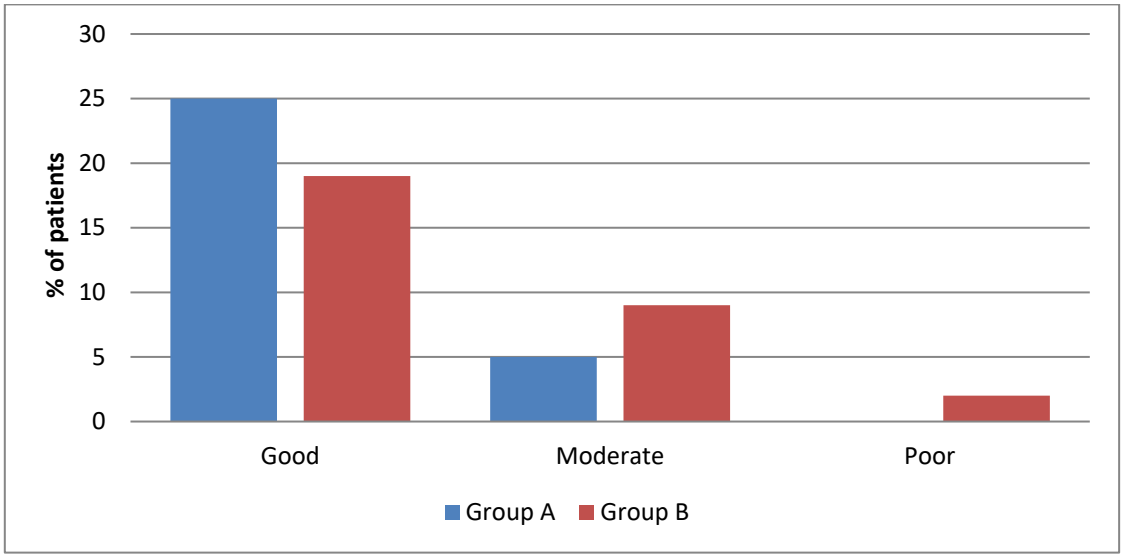


**Figure 2: Global assessment for tolerability at Day 30**

**Table 3: Results of the mean improving of FSSG score in Group A and Group B**

| Variables | Before (Mean ± SD) | After (Mean ± SD) | Different (Mean ± SD) | P value |
|---|---|---|---|---|
| FSSG score group A | 25.6±9.8 | 17.8±5.7 | 7.9±5.7 | <0.001 |
| FSSG score group B | 22.7±6.2 | 17.9±8.9 | 4.8±3.6 | <0.001 |
| Mean Improvement score | | | 3.1±3.2 | <0.02 |

Analysis of data using statistical test showed that the FSSG score in group A after treatment (17.8±5.7) was significantly lower than before treatment (25.6±9.8, p<0.001). The same result was found in group B, with FSSG score after treatment reduced significantly (from 22.7±6.2 to 17.9±8.9, p<0.001).

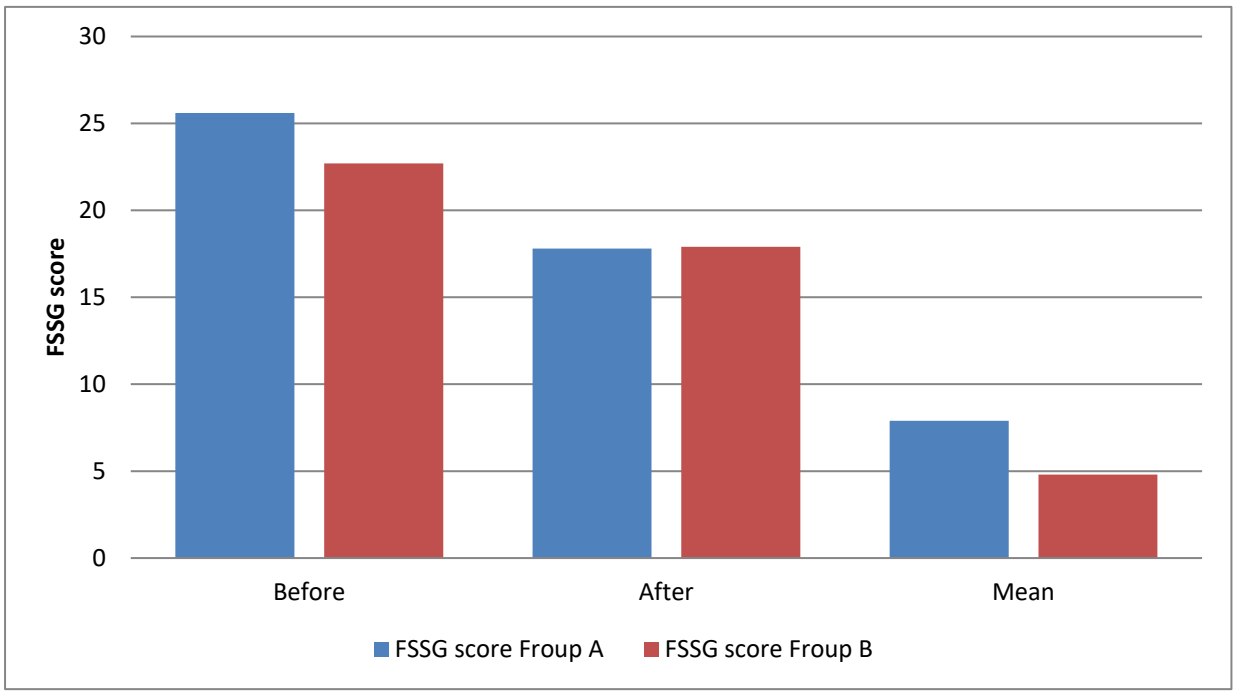


**Figure 3: Mean improving of FSSG score**

The gradient score in each group, called improvement score, was compared using unpaired t test. The mean improvement score in the group A was 7.9±5.7, while in group B was of 4.8±3.6, and this difference was statistically significant (p=0.02) as shown in Table 3 and Figure 3.

The additional side effects found in only 3 patients which were indigestion, diarrhea and constipation which were mild in nature and well controlled during treatment.

## Discussion

The present study found to be having GERD incidence more in females (63%). The study by Yaseri *et al.* found that gender (female and male) difference was not a significant factor in heartburn and regurgitation symptoms [23]. Few studies found female patients with GERD are dominant compared to male [24]. A study done by Mantynen *et al*. examined 3378 patients with GERD, and got the ratio of male: female was 1: 1.3 [25]. Another study from Japan by Miyamoto *et al*. studied 163 patients with GERD found 60.7% were women. According to that, female gender is a factor associated with failure of PPI mono therapy.(14) Thus, from the point of gender, this study showed that probability of failure of PPI mono therapy is higher. Gender predominance of female in this study was also more in line with Asian populations [26,27].

The mean Body mass Index (BMI) was 25.24 kg/m2. Of all study participants, 61.5% had above-normal BMI (BMI > 24.9).The study conducted by Suazana Ndraha found mean BMI 25.2 and 70% was normal, overweight (BMI 25-30 kg/m2) was found in only 12.5 patients, 15% met the criteria of underweight (BMI <18.5 kg/m2), and there is only 1 patient (2.5%) who met the criteria of obese (BMI >30 kg/m2) which is comperable with this study. Another study in 176 patients by Vaishnav *et al*. in 2017 results showed that the mean age of the study participants was 46 years and the mean BMI was 25.2 kg/m2. Of all study participants, 37.5% had above-normal BMI (BMI > 24.9) [28]. According to the WHO fact sheet on obesity, 39% of adults aged 18 years and above were overweight in 2014 (38% of men and 40% of women) [29]. These findings were not in accordance with the literature that states obesity is a major risk factor in GERD [30].

A study by Anna Taraszewska in 2021 reviewed lifestyle risk factors that may contribute to GERD symptoms include excessive body weight, particularly obesity, moderate/high alcohol consumption, smoking, postprandial and vigorous physical activity, as well as lack of regular physical activity [31]. Another study by Malekzadeh *et al* reported some significant risk factors for the occurrence of GERD, such as obesity, high fat diet, too much eating, spicy food, tight clothing, emotional stress, regular fast food, tea and coffee, pregnancy, drugs, and habit of lying down immediately after eating [32]. It may consider that life style habits and obesity plays significant role in occurrence of GERD. Due to low sample size and confounding factors related to life style modifications was not considered, this study stated lack of conformity of these risk factors.

The global assessment of efficacy was rated “very good” or excellent in majority of GERD patients (80%) in PPI with levosulpride group compare to PPI alone group (50%) by patients and investigator which is well acceptable. The assessment of tolerability was rated “good” in 84% of PPI with levosulpride compared to 64% of PPI alone group.

In our study, we found the mean FSSG score quite high before the treatment, which was 25.6 ± 9.8. The FSSG score ≥8 is considered to indicate probable GERD [33]. The high FSSG score may leads to failure of PPI monotherapy according to the study by Miyamoto *et al*. Miyamoto *et al*. found that a group that failed with PPI

monotherapy had a mean FSSG score of 17.4, and then that group was given a combination therapy of PPI with prokinetic [14]. Miyamoto proposed that high FSSG scores before treatment may predict the need for the addition of a prokinetic agent to PPI therapy [14]. In this case, it is proposed that instead of doubling the dose of PPI, addition of prokinetic to PPI may consider as a better drug of choice for high FSSG scored GERD patient. A study results of 12 RCTs done by Ren *et al*. including 2403 patients summarize that addition of prokinetic to PPI was not associated with significant relief of symptoms or alterations in endoscopic response relative to single therapy but combined therapy was associated with a greater symptom score change [34]. A study results of another prokinetic drug mosapride showed the improvement of the symptom score was significantly greater than that in the PPI alone group without significant heterogeneity [35].

We found that there was an improvement in FSSG score after treatment in group A (which was given rabeprazole and levosulpride) as well as in group B (rabeprazole monotherapy). Both improvements, were statistically significant (group A 25.6±9.8 before treatment, 17.8+5.7 after treatment, $p<0.001$; group B 22.7±6.2 before treatment, 17.9±8.9 after treatment, $p<0.001$). The improvement of mean FSSG score was higher in group A (7.9±5.7) compare to group B (4.8±3.6) ($p=0.02$). It is found from this study addition of levosulpride to PPI will have better chances of cure than PPI alone therapy, especially in high FSSG score patients. The results of our study supports the theory proposed by Miyamoto *et al*. that addition of prokinetics to PPIs improves the effect of PPIs. The prokinetic action of levosulpride will increase gastric emptying time and abolish an impaired acid suppressive effect of PPI due to low pH instability and long retention time of PPI in stomach [14].

About the safety of PPI with prokinetic, we found only 3 patients to be having side effects during drug therapy. The results were quite different from the systemic review done by Ren *et al* from 12 RCTs showed the proportion of patients with adverse effects undergoing combined therapy was significantly higher than for PPI therapy alone [34].

## Conclusion

The treatment with levosulpride to rabeprazole in GERD patients with high FSSG score provides better symptomatic relief compared to rabeprazole monotherapy with minimal mild side effects. Few more studies are needed to evaluate efficacy and safety of this combination with larger sample size and improved study design for longer duration of GERD drug therapy.

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