

## Comparative Study of Efficacy of Addition of Prokinetics to Proton Pump Inhibitors in Patients with Gastroesophageal Reflux Disease

Kakaraparthy Rupa Sree\*, V. Umarani, D. Swathi, K. Shravan Kumar

Samskruti College of Pharmacy, Kondapur, Ghatkesar, Medchal, Hyderabad-501301, Telangana, India

\*Corresponding E-Mail: [principal.y7@gmail.com](mailto:principal.y7@gmail.com)

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### ABSTRACT

Gastroesophageal reflux disease (GERD) remains a prevalent gastrointestinal disorder characterized by acid reflux and associated symptoms that significantly impact quality of life. This prospective observational study evaluated the efficacy, safety, and tolerability of combination therapy comprising proton pump inhibitors (PPIs) with three different prokinetic agents in 86 GERD patients aged 20–80 years (mean age: 35.5 years) at Krishna Institute of Medical Sciences (KIMS), Secunderabad, with male predominance (57%). Baseline symptom assessment using the Frequency Scale for the Symptoms of GERD (FSSG) identified belching as the most prevalent symptom (62 patients, 68.9%), followed by chest pain, regurgitation, and heartburn. Patients were stratified into three treatment groups: domperidone (51.2%), itopride (25.6%), or cinitapride (23.3%), all administered in combination with standard PPI therapy. Clinical evaluations were conducted at baseline, 4 weeks, 8 weeks, and 12 weeks. The results demonstrated substantial symptom improvement across all three prokinetics when combined with PPIs, with marked variation in therapeutic efficacy. Cinitapride exhibited the superior efficacy profile, achieving 65% improvement in heartburn, 90% in regurgitation, 70% in belching, and 50% in chest pain. Itopride demonstrated moderate efficacy with 49.09% improvement in heartburn, 59.09% in regurgitation, and 45.45% in both belching and chest pain. Domperidone showed modest improvement rates of 59.09% in heartburn, 56.81% in regurgitation and belching, and 34.09% in chest pain. Overall, 65.1% of patients reported clinically significant improvement after 12 weeks of combination therapy, while 34.9% showed no meaningful change. The safety profiles of all three prokinetics were favorable, with minimal adverse effects reported. These findings establish the clinical value of combination therapy (PPI + prokinetic) in managing GERD, particularly in patients with persistent or refractory symptoms unresponsive to PPI monotherapy. The superior efficacy of cinitapride suggests the importance of individualized prokinetic agent selection based on symptom profile and patient-specific factors. Future large-scale randomized controlled trials are recommended to validate these outcomes, establish optimal prokinetic dosing regimens, and refine evidence-based guidelines for prokinetic utilization in GERD management within the Indian population.

**Keywords:** Gastroesophageal reflux disease (GERD), proton pump inhibitors, prokinetic agents, domperidone, itopride

### INTRODUCTION

#### Etiology:

In gastroesophageal reflux disease (GERD), disruption of the esophagogastric junction barrier due to intrinsic, structural, or combined factors allows acidic gastric contents to enter the esophagus [8]. Under normal conditions, the lower esophageal sphincter (LES) and diaphragm protect against reflux. GERD may occur when the LES weakens, relaxes inappropriately, or is overwhelmed by elevated intra-abdominal pressure.

Risk factors include:

- Obesity or overweight
- Pregnancy
- Smoking or second-hand smoke exposure
- Certain medications, such as benzodiazepines, calcium channel blockers, asthma drugs, tricyclic antidepressants, and NSAIDs

Additionally, a hiatal hernia may predispose individuals to GERD or exacerbate symptoms [9]. While occasional reflux is often triggered by large meals, recumbency after eating, or specific foods chronic and recurrent reflux suggests GERD, which carries more serious risk factors and complications [10].

#### Pathophysiology

The pathophysiology of GERD is multifactorial, involving mucosal integrity, symptom perception, esophageal clearance, refluxate characteristics, gastric motility, and the anti-reflux barrier [18]. The two central mechanisms are LES dysfunction and impaired esophageal clearance [19].

#### 1. Offensive Factors

The esophagus is normally exposed to a neutral environment, whereas gastric contents are acidic. Prolonged exposure of the esophageal mucosa to gastric acid is the primary driver of GERD pathogenesis, with both acidity and duration of exposure playing key roles [20]. Bile reflux, observed in up to 60% of GERD patients, may also contribute to mucosal injury and treatment-resistant esophagitis, though evidence remains inconclusive [21].

#### 2. Structural Abnormalities and Functional Defects

- Normally, the LES and diaphragm act as a coordinated barrier to reflux [22].
- GERD patients often experience increased transient LES relaxations [23].
- Delayed gastric emptying and impaired esophageal motility may further contribute [23,24].

- Hiatal hernia is associated with increased reflux, though reflux may also occur without hernia, and vice versa [25].
- Additional factors include reduced salivary clearance, impaired bicarbonate secretion, and decreased acid resistance of esophageal epithelial cells [23].

### Symptoms

The hallmark symptom of GERD is heartburn [13]. Other symptoms include:

- Acid regurgitation
- Non-burning retrosternal chest pain radiating to the back
- Dysphagia (difficulty swallowing)
- Extra-esophageal manifestations: sore throat, cough, hypersalivation, thirst, shortness of breath [14]

### Diagnosis

GERD is typically diagnosed clinically, based on characteristic symptoms and response to acid suppression. Heartburn—especially when worsened by meals or lying down—is highly suggestive [16].

Diagnostic approaches include:

- Upper GI endoscopy (EGD): Most commonly used to evaluate GERD and detect complications.
- Ambulatory 24-hour esophageal pH or pH-impedance monitoring: Recommended for patients unresponsive to proton pump inhibitors (PPIs).
- Clinical tools: Symptom questionnaires and therapeutic trials of acid suppression are useful but not definitive.

A normal endoscopy does not rule out GERD, but pH-impedance monitoring can strengthen diagnostic certainty. Emerging parameters such as mean nocturnal baseline impedance (MNBI) and the post-reflux swallowing peristaltic wave (PSPW) index provide additional diagnostic insights [16,17]. Histopathological findings (e.g., dilated intercellular spaces), motility studies (e.g., hypotensive LES, hiatal hernia), and impedance-based markers further refine diagnosis when standard methods are inconclusive.

### Epidemiology

Population-based studies in Asia report GERD prevalence ranging from 2.5–7.1% [11]. Global estimates vary widely:

- North America: 18.1–27.8%
- Europe: 8.8–25.9%
- East Asia: 2.5–7.8%
- Middle East: 8.7–33.1%
- Australia: 11.6%
- South America: 23.0%

Incidence in the general population is ~5 per 1000 person-years in the UK and US, and 0.84 per 1000 person-years among children aged 1–17 in the UK. Evidence shows GERD prevalence has risen significantly since 1995, particularly in North America and East Asia ( $p < 0.0001$ ) [12].

### Management

The cornerstone of GERD treatment is acid suppression, as symptoms and complications result from mucosal injury due to refluxate [26]. GERD is primarily considered a motor disorder, and long-term management aims to:

- Relieve symptoms
- Heal esophagitis and prevent recurrence
- Prevent complications

- Maintain remission with safe, cost-effective therapy

### Therapeutic Stages:

- Stages I–IV: Medical therapy, including PPIs, H2 receptor antagonists, antacids, and lifestyle modifications.
- Stage V: Surgical intervention for refractory or severe cases.

The overall goal is to minimize esophageal acid exposure, thereby reducing symptoms, promoting mucosal healing, and preventing progression [26].

## METHODOLOGY

### Study Location

The study was conducted at the Outpatient Gastroenterology Unit, Krishna Institute of Medical Sciences (KIMS), Secunderabad.

### Study Design

- Type of study: Prospective observational study
- Ethical approval: Obtained from the Institutional Human Ethics Committee (Approval No: KIMS/ECBMHR/2024/56-02)
- Confidentiality: The identities of patients and clinicians were kept confidential.
- Permissions: Approval was obtained from the Head of Department prior to initiation.

### Study Period

The study was carried out over a six-month period.

### Sample Size

A total of 86 patients were included.

### Ethical Considerations

- Approval was granted by the Institutional Human Ethics Committee.
- Written informed consent was obtained from all participants before enrollment.
- Participation was voluntary, and confidentiality of patient information was strictly maintained.
- The project was reviewed and approved as part of the thesis requirements.

### Inclusion Criteria

- Adults aged >18 years
- Both male and female patients
- Diagnosed cases of GERD

### Exclusion Criteria

- Patients unwilling to provide consent
- Pregnant and lactating women
- Patients with gastrointestinal obstructions

### FSSG Score Evaluation

The Frequency Scale for the Symptoms of GERD (FSSG) was used to evaluate patient symptoms.

- The questionnaire includes 12 items: 7 related to acid reflux symptoms (Q1, 4, 6, 7, 9, 10, 12) and 5 related to dysmotility symptoms (Q2, 3, 5, 8, 11).
- Each question had 5 response options:
  - Never (0)
  - Occasionally (1)
  - Sometimes (2)
  - Often (3)
  - Always (4)

- Patients with an FSSG score >10 were included and treated with prokinetics in combination with PPI therapy.

**RESULTS AND DISCUSSION**

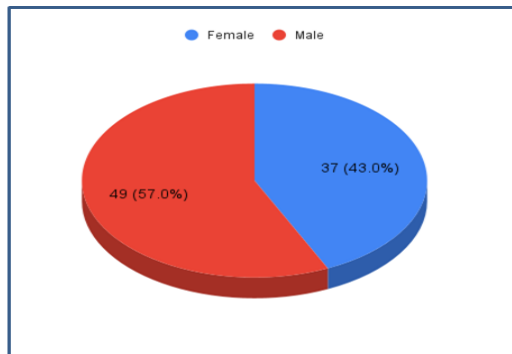


Fig.1: Pie Chart representing no. of patients, percentage according to sex

Fig.1: Gender-wise distribution of GERD patients

Gender	No. of Patients	Percentage (%)
Male	49	57.0
Female	37	43.0

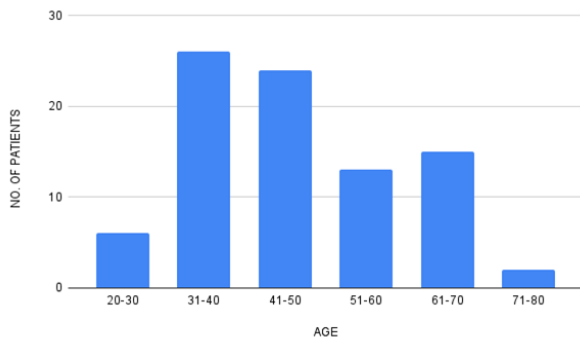


Fig.2: Subject's Distribution Based on Age Group

Fig.2: Age Wise Distribution

AGE	NO. OF PATIENTS (n=87)	PERCENTAGE (%)
20-30	6	7.0%
31-40	26	30.2%
41-50	24	27.9%
51-60	13	15.1%
61-70	15	17.4%
71-80	2	2.3%

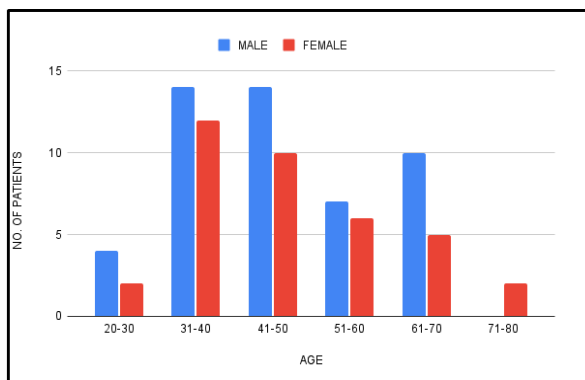


Fig.3: Subject Distribution Based on Age Groups and Sex

Fig.3: Subject Distribution Based on Age Groups and Sex

AGE	MALE	FEMALE	TOTAL
20-30	4	2	6
31-40	14	12	26
41-50	14	10	24
51-60	7	6	13
61-70	10	5	15
71-80	0	2	2

Table.4: Subject Distribution Based on FSSG Score

FSSG SCORE	NO. OF PATIENTS
0-5	7
6-10	11
11-15	21
16-20	31
21-25	13
26-30	3

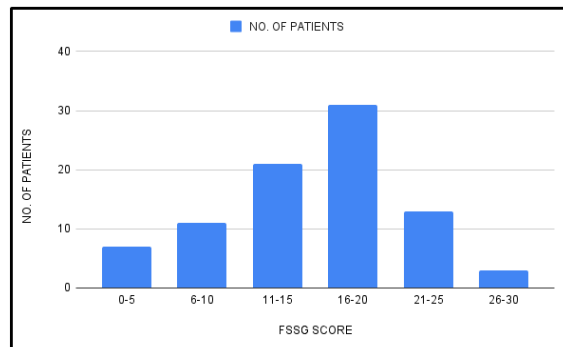


Fig.4: Subject Distribution Based on FSSG Score

Table.5: Patients Distribution Based on Type of Prokinetic

Prokinetic	No. of patients	Percentage (%)
DOMPERIDONE	44	51.2
ITOPRIDE	22	25.6
CINITAPRIDE	20	23.3

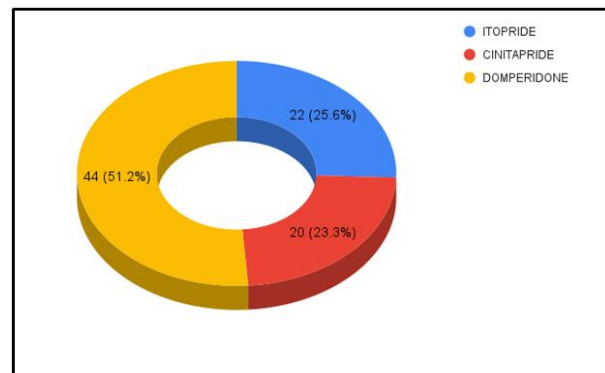


Fig.5: Patients Distribution Based on Type of Prokinetic

**Discussion:**

Several researchers have reported that the addition of prokinetics to proton pump inhibitor (PPI) therapy in the management of gastroesophageal reflux disease (GERD) significantly reduces the likelihood of hospitalization by improving symptom control and patient outcomes. The present study was designed to address gaps in the literature by evaluating the usage patterns, effectiveness, and acceptability of prokinetics in an Indian patient population with GERD. A total of 86 patients, aged 20–80 years (mean age: 35.5 years), were enrolled. Of these, 49 were male and 37 were female. Symptom relief was observed in the majority of patients receiving prokinetic therapy in addition to standard PPI treatment.

The therapeutic efficacy of prokinetics was assessed by comparing symptom improvement from baseline to each follow-up visit. Among the agents studied, Cinitapride demonstrated the greatest overall benefit, with improvement rates of 65% for heartburn, 90% for regurgitation, 70% for belching, and 50% for chest pain. In comparison, Itopride showed improvements of 49.09% in heartburn, 59.09% in regurgitation, and 45.45% in both belching and chest pain, while Domperidone demonstrated 59.09% improvement in heartburn, 56.81% in regurgitation, 56.81% in belching, and 34.09% in chest pain. These findings suggest that while all three agents are beneficial, Cinitapride offers superior symptom relief across most GERD-related complaints when combined with PPI therapy.

## CONCLUSION

The study findings confirm that prokinetic agents, when used in combination with PPIs, significantly enhance symptom relief in GERD patients, reducing the burden of common complaints such as heartburn, regurgitation, belching, and chest pain. Among the evaluated agents, Cinitapride demonstrated superior efficacy across most symptom domains compared to Domperidone and Itopride. These results reinforce the clinical value of combination therapy (PPI+ prokinetic), particularly in patients with persistent or refractory symptoms, while also highlighting the importance of individualized therapy selection. Future large-scale randomized trials are recommended to further validate these outcomes and to refine guidelines for prokinetic use in GERD management within the Indian population.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest

## ETHICS APPROVAL

Not applicable

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This study received no specific funding from public, commercial, or not for profit funding agencies.

## AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

## DATA AVAILABILITY

Data will be available on request

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