

## Original Articles

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# Need of Combining Proton Pump Inhibitors with Prokinetics: A Prospective Observational Survey Conducted in India

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### Abstract:

**Background:** Gastro esophageal reflux disease (GERD), a highly prevalent disorder has adverse impact on quality of life. An estimated 40% of GERD patients have incomplete response to standard PPI therapy. For these PPI refractory patients, doubling the PPI dose or switching to another PPI are pursued by the treating physicians that might not be optimal. Therefore, an appropriate second line treatment should focus on addition of gastro-prokinetic drugs that stimulates gastric motility.

**Materials & Methods:** This was a prospective observational study conducted in 118 patients suffering from symptoms suggestive of GERD, at four centers in Indian National Capital region to assess the overlap between GERD and delayed gastric emptying and to predict the need for combination therapy of PPI with pro-kinetic drug using Frequency Scale for the Symptoms of GERD (FSSG) score.

**Results:** The mean total FSSG score was  $16.37 \pm 7.50$ . From 118 patients, 98 (83.05%) met the criteria for GERD with FSSG total score more than eight. The mean reflux score was  $7.43 \pm 4.08$ , while the mean dysmotility score was  $8.94 \pm 4.83$ . GERD patients in this study have a high mean FSSG score, whereas dysmotility symptoms proved to be more dominant than acid reflux.

**Conclusion:** Based on the findings of this study, combination therapy of PPI with prokinetics is recommended in subsets of patients with high FSSG score.

**Key Words:** Delayed gastric emptying, Dysmotility score, FSSG score, Gastroparesis, GERD, Reflux score.

DOI: <http://dx.doi.org/10.3329/jom.v19i2.37223>

### Introduction:

Gastroesophageal reflux disease (GERD) is a chronic condition which develops when the reflux of stomach contents cause troublesome symptoms and/or complications.<sup>1</sup> The prevalence of GERD in India ranges from 8-20% according to recently conducted studies based on different case definitions and study methodology.<sup>2</sup> The subtypes of GERD include erosive esophagitis (EE), non-erosive reflux disease (NERD) and Barrett's esophagus. Approximately 70% of patients with GERD have NERD, EE accounts for approximately 25 % of GERD patients whereas Barrett's esophagus for ~5 %.<sup>3</sup>

The gastrointestinal motility disorder called gastroparesis is characterized by delayed gastric emptying in the absence of a mechanical obstruction. Although symptoms of gastroparesis may vary from patient to patient, which generally include nausea, vomiting, early satiation, bloating, and upper abdominal discomfort, along with objective evidence of gastric retention.<sup>4</sup> Well established reports suggest that greater number of patients with GERD has delayed gastric emptying. A study of the incidence of gastroparesis in 100 patients with gastroesophageal reflux showed 41% had delayed gastric emptying. However, certain patient populations, such as diabetic patients, may be at an increased risk for both conditions.<sup>4-6</sup>

Proton pump inhibitors (PPIs) are the most effective agents for increasing the intragastric pH and have become the mainstay pharmacotherapy for acid disorders. PPIs suppress gastric acid by inactivating gastric proton pumps responsible for acid secretion.<sup>7-8</sup> Several studies have shown that up to 40% of GERD patients reported either partial or complete lack of response of their symptoms to a standard

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**Received:** 09 February, 2017;

**Accepted:** 17 July, 2018

PPI dose once daily.<sup>9</sup> Refractory GERD is diagnosed in patients who are unresponsive to PPI treatment that has been administered for 4 to 8 weeks, once daily. Patients with refractory GERD typically need more aggressive acid suppressive therapy or the use of other therapeutic modalities like transient lower esophageal sphincter relaxation reducers and, in the case of gastroparesis, co-administration of prokinetic agents to regulate gastric emptying. It remains difficult to identify the particular subset of GERD patients who have gastroparesis, particularly if patients do not report classic symptoms of gastroparesis, including bloating, nausea, vomiting, and early satiety, or these symptoms are misinterpreted as GERD-related. Therefore, it is important that gastroparesis be considered in all patients with GERD, allowing physicians to develop an optimal therapeutic strategy that addresses both disease states directly.<sup>4</sup> The most frequently used prokinetic drugs like levosulpiride and domperidone augment gastric emptying, avert retention and reflux of acid or food, increase lower esophageal sphincter pressure and enhance esophageal peristalsis. Domperidone and levosulpiride have both antiemetic and prokinetic properties since they antagonize dopamine receptors in the central nervous system as well as in the gastrointestinal tract where dopamine apply compelling inhibitory effects on motility.<sup>10-11</sup>

The diagnosis of GERD has evolved over the years influenced by technologic and therapeutic progresses. Currently, a scoring system called the frequency scale for the symptoms of GERD (FSSG) has been developed in Japan to evaluate GERD symptoms. This questionnaire specific to GERD contains 12 questions which include seven questions for reflux score and five questions to score the dysmotility. FSSG score has been validated against the endoscopic findings in Japan with the cut-off score at 8 (FSSG score 8 or above), showed sensitivity of 62%, specificity 59% and accuracy of 60%.<sup>12-14</sup> Miyamoto et al found that high score FSSG is one of the factors related to failure of PPI monotherapy, in addition to female, alcohol consumption and obesity. Thus, GERD with a high FSSG score requiring PPI combination therapy with pro-kinetic drug for a more satisfactory outcome.<sup>15</sup>

This study was undertaken to evaluate the symptom profile of GERD patients and the symptom overlap between GERD and delayed gastric emptying so as to determine FSSG score in order to predict the need for combination therapy of PPI with pro-kinetic drug or PPI monotherapy only.

### **Materials & Methods:**

This was a prospective, multicenter, observation study conducted in seven gastroenterology clinics across Delhi, Gurgaon and Noida in Indian National Capital region. The study was conducted in accordance with the Indian Council of Medical Research guidelines for Biomedical Research on Human subjects and the Declaration of Helsinki. Ethical clearance was not obtained as it was a questionnaire based observation study.<sup>16-17</sup> Outpatients who visited these seven gastroenterology clinics during the period of April 2016 to July 2016 and willing to participate were enrolled in this study. On study entry, patients provided a medical history and underwent a physical examination.

### **Inclusion Criteria:**

Ambulatory patients (male and females) aged between 18 to 65 years, and at least a 3-month history of symptoms suggestive of GERD and/or delayed gastric emptying were eligible for inclusion in this study.

### **Exclusion Criteria:**

The patients with history of cancer of the gastrointestinal tract or major illnesses (end-stage heart, liver, or lung disease, alcoholism, any other cancer or malignancy, or AIDS), pregnancy, hepato-biliary disease, patients who were receiving dialysis or who had undergone prior gastric surgery, those known or suspected to be using illicit drugs and lactating mothers were excluded from the present study. Unresponsive patients would be excluded if they refused to answer the study questionnaire.

### **FSSG Score Evaluation:**

Seven questions in FSSG questionnaire in Table 1 (question number 1, 4, 6, 7, 9, 10 and 12) were related to acid reflux, and 5 questions (question number 2, 3, 5, 8 and 11) were related to dysmotility disorder. There were 5 answer choices were provided for each question in FSSG scale, never (for score = 0), occasionally (for score = 1), sometimes (for score = 2), often (for score = 3), and always (for score = 4).

Thus, the score for reflux/acid-related symptoms ranged between 0-28; the score for dysmotility symptoms was ranged between 0-20. High FSSG score is one of the factors related to failure of PPI mono therapy, thus, GERD with a high FSSG score requires PPI combination therapy with prokinetic drug for a more satisfactory outcome.

**Table-I**  
*FSSG questionnaire*

Sl.No.	Questionnaire	Indicative disorder
1	Do you get heartburn?	Reflux/acid-related symptoms
2	Does your stomach get bloated?	Dyspeptic/ dysmotility symptoms
3	Does your stomach ever feel heavy after meals?	Dyspeptic/dysmotility symptoms
4	Do you sometimes subconsciously rub your chest with your hand?	Reflux/acid-related symptoms
5	Do you ever feel sick after meals?	Dyspeptic/ dysmotility symptoms
6	Do you get heartburn after meals?	Reflux/ acid-related symptoms
7	Do you have an unusual (e.g. burning) sensation in your throat?	Reflux/acid-related symptoms
8	Do you feel full while eating meals?	Dyspeptic/ dysmotility symptoms
9	Do some things get stuck when you swallow?	Reflux/acid-related symptoms
10	Do you get bitter liquid (acid) coming up into your throat?	Reflux/acid-related symptoms
11	Do you burp a lot?	Dyspeptic/dysmotility symptoms
12	Do you get heartburn if you bend over?	Reflux/ acid-related symptoms

**Statistical Analysis**

All the data was recorded in the entry form, and further organized using descriptive statistics, presented as mean ± SD for numerical data, and proportion (%) for the categorical data. The statistical analysis was carried out by using graph pad prism 7 using paired T test. Values of p <0.05 were considered statistically significant.

**Results:**

In all, 118 patients completed the FSSG score questionnaire of which 57.6% were males and 42.4 % females (68 males, 50 females). The mean age of the patients was 36.8 year. (Between 18 to 65 years). Refer Table 2 for patient demographics at study entry.

**Table-II**  
*Patient Demographics at study entry*

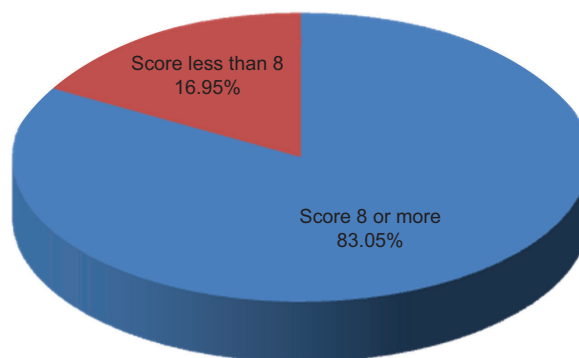
SlNo	Parameter	N (Mean ±S.D.)
1	Gender (Male to Female)	69:53 (56.5:43.5)
2	Age	18-65
3	Chief complaint	
	1. Heartburn	99 (83.8 %)
	2. Regurgitation	85 (72.0 %)
	3. Heartburn+ Regurgitation	81 (68.6 %)
4	FSSG Score (Total)	16.37 ± 7.50 (Mean ±S.D.)
	1. Reflux Score	7.43 ± 4.08 (Mean ±S.D.)
	2. Dysmotility/ Dyspeptic score	8.94 ± 4.83 (Mean ±S.D.)

FSSG score that was conducted on 118 patients, revealed the mean total score of 16.37 ± 7.50 with the lowest score of 5 (reported in two patients), and the highest total score of 37 (reported in one patient).

When used the cut off 8 (FSSG score 8 or above), then from 118 of patients with GERD suggestive symptoms, 98 (83.05%) patients met criteria for GERD with cut off 8. Patients having total FSSG score of more than or equals to 8 are more likely of having GERD where combination therapy of PPI and prokinetics is required. The rest is only 20 (16.95%) who do not qualify for GERD FSSG score.

From 118 patients studied, the symptoms of dysmotility (8.94 ± 4.83) were predominant than symptoms of acid reflux (7.43 ± 4.08).

**Percentage of patients with GERD based on FSSG score**



**Figure 1:** Percentage of patients with FSSG score cut off more than/ less than 8

Mean score of reflux (7.43 ± 4.08) represents 26.53% of the total reflux score (total score 28), while the mean dysmotility score was 8.94 ± 4.83 which is 44.70% of the total score of dysmotility (total score 20). Thus from 118 patients studied, the dysmotility symptoms were predominant than symptoms of reflux.

**Discussion:**

The relationship between gastroparesis and GERD is multifactorial. The delay in gastric emptying associated with gastroparesis can lead to prolonged gastric retention of food that may have a propensity to reflux.<sup>4</sup> It is believed that in this group of patients delayed gastric emptying is associated with a progressive dilatation of the proximal stomach which, in turn, shortens the length of the lower esophageal sphincter until it becomes incompetent – similar to the way distention of a balloon shortens its neck. With a shortened sphincter, and with greater amounts of solid and liquid materials in the stomach after meals because of its defective emptying, reflux occurs. Not surprisingly, these patients complain more often than those with normal gastric emptying of dyspepsia, postprandial distention, generalized bloating and abdominal pain, in addition to the usual symptoms of gastroesophageal reflux.<sup>5</sup>

In patients with GERD refractory to standard therapy, a higher index of gastroparesis suspicion is therefore recommended. In a patient with GERD symptoms of heartburn, other gastrointestinal symptoms such as early satiety, nausea, and vomiting indicates that the patient may also have gastroparesis. The presence of delayed gastric emptying could be a reason for a suboptimal treatment response in these patients.<sup>4</sup> Furthermore, a meta-analysis by Ren LH et al (2014) has reported that, combination therapy with PPI and prokinetics improve patient quality of life, by decreasing number of reflux episodes.<sup>11</sup>

In this study, mean FSSG score was quite high ( $16.37 \pm 7.50$ ). Findings of this study are in accordance with the previous findings reported by Miyamoto et al. According to the Miyamoto et al, a high FSSG score becomes a factor associated with failure of PPI monotherapy.<sup>15</sup> In his study, 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 prokinetics. Miyamoto proposed that pretreatment FSSG scores can be used to predict the need for the addition of a prokinetic agent to PPI therapy prior to treatment.<sup>15</sup> Japanese physicians usually add prokinetic agent to the standard dose of a PPIs instead of doubling the dose of the PPI for cases refractory to PPI monotherapy. PPIs are unstable at a low pH dysmotility will slow down gastric emptying, resulting in retention of PPIs. Based on these findings, combination of PPIs with prokinetic will improve the effect of PPIs.<sup>14,15</sup> Furthermore, S. Ndraha et al, validated similar findings in their clinical experience and stated that combination of PPIs with prokinetics improves the effect of PPIs.<sup>18</sup>

**Conclusions:**

GERD patients in this study have a high mean FSSG score, suggesting that dysmotility symptoms are more dominant than acid reflux. Based on these findings, combination therapy of PPI with prokinetics is recommended in subsets of patients with high FSSG score. Since the FSSG score is high which is suggestive of dysmotility predominance, likelihood of patients responding to combination of PPI with prokinetics is much higher compared to PPI alone. Furthermore, there is a need of future studies to evaluate the FSSG score improvement in patients receiving combination therapy of PPIs with prokinetic compared to PPIs monotherapy alone.

**Acknowledgements:**

Author acknowledges the immense help received from the scholars whose articles are cited and included in references of this manuscript. Writing support was provided by Mr. Altamash Momin (M. Pharm. Pharmacology).

**Conflict of interest:** None.

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