A Comparative Study to Assess the Tolerability of Proton Pump Inhibitors and Prokinetic agents as a Combination therapy Versus Monotherapy in patients with Gastroesophageal Reflux Disease

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is a chronic condition that develops when the reflux of gastric contents into the esophagus in significant quantities causes troublesome symptoms with or without mucosal erosions and relevant complications. Proton Pump Inhibitors (PPIs) remains the mainstay in the treatment of GERD but addition of Prokinetic drugs like Itopride helps in relieving the symptoms of GERD which in turn leads to improvement in quality of life of patient.

Aim & Objective: To assess tolerability among the patients with GERD with or without Prokinetic supplementation along with Proton Pump Inhibitors.

Materials & Methods: Hundred patients diagnosed with GERD were randomly assigned into two groups, Group A and Group B. Group A received tablet Pantoprazole 40 mg twice daily alone and group B received tablet Pantoprazole 40 mg twice daily and tablet Itopride 50 mg thrice daily 30 minutes before food for 4 weeks. Incidence of Adverse Drug Reaction (ADR) and tolerability was assessed using a standardized questionnaire given to the patient at the time of enrolment.

Results: The total incidence of ADR was less in group B compared to group A (22% vs 30%, p= 0.172). Group B patients experienced less incidence of ADR in terms of Nausea (2/50 vs 3/50), diarrhoea (1/50 vs 3/50), abdominal pain (5/50 vs 7/50), and headache (3/50 vs 4/50) relative to Group A patients. Tolerability was better in Group B compared to Group A at the end of 4 weeks but was not statistically significant.

Conclusion: Addition of a Prokinetic agent like Itopride along with PPIs increase patient compliance by decreasing drug related side effects and by improving tolerability in patients with GERD.

Keywords: Pantoprazole, GERD, Itopride, PPIs, Prokinetics, ADR, tolerability.

DOI: http://dx.doi.org/10.31975/NJBMS.2019.9402
INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common and chronic gastrointestinal disorder with a significant negative impact on health-related quality of life\(^1\). Reflux from stomach causes symptoms like heartburn and regurgitation, which are the cardinal symptoms of GERD, and other symptoms, such as chest pain, asthma, hoarseness, and sleep disturbance, are also considered as atypical or extra esophageal symptoms of GERD\(^3\). Troublesome symptoms of GERD have adverse impact on health-related quality of life (HRQL)\(^4\), and patients with more frequent or more severe symptoms have lower HRQL, work productivity, and sleep quality\(^4,5\). Chronic reflux is also an important risk factor of esophageal adenocarcinoma\(^6\).

GERD includes all individuals exposed to the risk of physical complications from gastroesophageal reflux or who experience clinically significant impairment of quality of life due to reflux related symptoms after reassurance of the benign nature of their symptoms\(^7\).

Currently PPIs are the drug of choice for the treatment of GERD, inhibiting the production of acid by the stomach parietal cells. However, presence of dyspeptic symptoms along with adverse drug reactions makes the PPIs therapy intolerable to the patients.

Since the pathophysiology of GERD also involves the lower esophageal sphincter dysfunction addition of a Prokinetic agent like Itopride, which acts by increasing the lower esophagial sphincter tone, may reduce the incidence of dyspeptic symptoms along with the adverse drug reactions. Therefore, the present study was designed to compare the tolerability of Pantoprazole alone and the combination of Pantoprazole and Itopride in patients with GERD.

MATERIALS & METHODS

After obtaining the informed consent, 100 patients with more than one upper dyspeptic symptom such as regurgitation, epigastric pain, nausea, vomiting, dysphagia, chest pain lasting for more than 4 weeks and grade I-III esophagitis by endoscopic examination were enrolled in the study. The present study was undertaken after approval from Institutional Ethics Committee. They were randomly assigned into two different treatment groups of 50 each. Group A received tablet Pantoprazole 40 mg twice daily alone 30 minutes before food for 4 weeks and Group B received tablet Pantoprazole 40 mg twice daily and tablet Itopride 50 mg thrice daily 30 minutes before food for 4 weeks.

Patients were followed up at the end of 4 weeks after starting the therapy. Incidence of ADR were assessed using a standardized
questionnaire given to the patient at the time of enrollment and was filled in during treatment period, indicating the type and degree of interference with daily activity of the patient and also by clinically significant abnormal laboratory investigations. Tolerability was analysed in all patients based on the side effects grading. At the end of 4 weeks treatment compliance was estimated by using a scale. Incidence of ADR and tolerability in both the groups were collected, analysed and results are tabulated using appropriate statistical tests.

STATISTICAL ANALYSIS

Parametric variables were analysed using Student's t-test and Z test. Non-parametric variables were analysed using Fischer Exact test and Chi-Square test.

RESULTS

Study was conducted in Department of Surgical Gastroenterology, Bangalore Medical College and Research Institute, Bangalore. Hundred patients were enrolled in the study and incidence of ADR and tolerability was assessed at the end of treatment.

At the end of 4 weeks 26 patients experienced side effects, 15 (30%) in Group A and 11 (22%) in Group-B. Occurrence of side effects were less in Group-B compared to Group-A but was not statistically significant (p=0.495) (Table 1).

Table 1: Comparison of side effects (present/absent) in two groups of patients studied (Group A Vs Group B)

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>15(30.0%)</td>
<td>11(22.0%)</td>
<td>26(50.0%)</td>
<td>0.495</td>
</tr>
<tr>
<td>Absent</td>
<td>35(70.0%)</td>
<td>39(78.0%)</td>
<td>74(50.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Nausea (3/50 vs. 2/50), diarrhoea (3/50 vs 1/50), abdominal pain (7/50 vs 5/50), and headache (4/50 vs 3/50) were noted in both the treatment group but it was not statistically significant. (p=0.314) (Figure 1). Side effects stopped within one week after stopping the drug.

Tolerability was analysed in both the groups and it was better in Group B compared to GroupA (Figure 2) but was not statistically significant. (p=0.710) (Table 2).

Figure 1: Side effects at the end of 4 weeks

Figure 2: Comparison of tolerability in the two groups.
Table 2: Comparison of tolerability grading in two groups of patients studied (Group A Vs Group B)

<table>
<thead>
<tr>
<th>Tolerability grading</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. No side effects (A)</td>
<td>35 (70.0%)</td>
<td>39 (78.0%)</td>
<td></td>
</tr>
<tr>
<td>b. Slight discomfort, not interfering with daily activity (B)</td>
<td>11 (22.0%)</td>
<td>8 (16.0%)</td>
<td>0.710</td>
</tr>
<tr>
<td>c. Moderately side effects, sometimes interfering with daily activity (C)</td>
<td>4 (8.0%)</td>
<td>3 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>d. Severe side effects, work not possible (D)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>e. Side effects severe enough to discontinue treatment (E)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of Tolerability grading as excellent, good and poor at the end of 4 weeks showed that group B (94%) had excellent tolerance compared to group A (92%) and poor tolerance was not seen in both the groups (Table 3). Global Evaluation of Overall Tolerability was better in Group B compared to Group A but was not statistically significant (p=0.761) (Table 4).

Table 3 : Comparison of tolerability in two groups of patients studied (Group A Vs Group B).

<table>
<thead>
<tr>
<th>Tolerability grading</th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent (A/B)</td>
<td>46 (92.0%)</td>
<td>47 (94.0%)</td>
<td></td>
</tr>
<tr>
<td>Good (C)</td>
<td>4 (8.0%)</td>
<td>3 (6.0%)</td>
<td>0.761</td>
</tr>
<tr>
<td>Poor (D, E)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION:

Achieving optimal efficacy with least side effects is desired in the treatment of GERD. Side effects associated with drug therapy is a major hindrance for medication compliance. Existence of high rates of ADR would demotivate patients who are willing to continue and complete the therapy.

Although proton pump inhibitor is the most potent acid suppressant and provides good efficacy in esophagitis healing and symptom relief, about one third of patients with GERD still have persistent symptoms with poor response to standard dose of PPI.

In this regard addition of a Prokinetic agent like Itopride along with PPI like pantoprazole, results in complete resolution of dyspeptic symptoms and improvement in the quality of life.

Following the restriction imposed on Cisapride usage and the subsequent report of the arrhythmic potential of Mosapride, safety of a Prokinetic drug has been a cause of concern. Itopride is well tolerated and has no affinity for 5HT4 receptors which makes this drug a better and safer Prokinetic agent.

Common adverse drug reactions seen in our study in both the groups were Diarrhoea (4%), abdominal pain (12%) and headache (7%) and are of mild severity. Incidence of abdominal pain, headache and diarrhoea were the most common side effect in the Group A, whereas abdominal pain was seen more frequently in
the Group B. This is similar to a study conducted by Bochenek et al that has reported the incidence of adverse effects 11% headache, 7% diarrhoea with pantoprazole. Another study by Vigneri et al had reported the adverse effects like diarrhoea, abdominal cramps, flatulence with the pantoprazole and Mosapride and they were of mild type and most of them disappeared spontaneously. Both the treatment groups had tolerated the treatment very well without any discontinuation of therapy. Comparison of Tolerability grading as excellent, good and poor at 4 weeks showed that Group B had excellent tolerability 94% compared to Group A 92%. Also, Global evaluation of overall tolerability was better in Group B compared to Group A.

In a study conducted by Robinson et al which reported the Patient global assessment of medication with pantoprazole was rated to be either good or excellent was 88.1% in treating symptoms related to erosive GERD.

Randomized, double-blind, controlled trials in patients with GERD have shown that oral pantoprazole 40 mg/day has a comparable tolerability profile to oral omeprazole 20 mg/day and lansoprazole 30 mg/day after 8 weeks of therapy. Our study has shown that addition of Prokinetic agent along with PPIs has better tolerability compared to PPIs monotherapy.

So, in the conclusion Prokinetic agent like Itopride along with PPIs helps in relieving the dyspeptic symptoms, improves patient compliance and also minimizes the adverse drug reactions associated with PPIs Monotherapy.

CONCLUSION

Addition of a Prokinetic agent like Itopride along with PPIs increase patient compliance by decreasing drug related side effects and by improving tolerability in patients with GERD.

LIMITATION

The present study was done only on hundred patients, and there is a necessary to do the same in larger population.

CONFLICT OF INTEREST: NONE

REFERENCES:


