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Evaluation of Therapeutic Effect of Buspirone in Improving Dysphagia in Patients with GERD and Ineffective Esophageal Motility: A Randomized Clinical Trial

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Abstract: Background: Ineffective esophageal motility (IEM) is the most common esophageal motility disorder associated with low-to-moderate amplitude contractions in the distal esophagus in manometric evaluations. Despite recent new conceptions regarding the pathophysiology of esophageal motility and IEM, there are still no effective therapeutic interventions for the treatment of this disorder. This study aimed to investigate the effect of buspirone in the treatment of concomitant IEM and GERD. Methods and Materials: The present study was a randomized clinical trial conducted at the Imam Khomeini Hospital, Tehran. Patients with a history of gastroesophageal reflux disease and dysphagia underwent upper endoscopy to rule out any mechanical obstruction and were diagnosed with an ineffective esophageal motility disorder based on high-resolution manometry. They were given a package containing the desired medication(s); half of the packets contained 10 mg (for 30 days) of buspirone and 40 mg (for 30 days) of pantoprazole, and the other half contained only 40 mg (for 30 days) of pantoprazole. Dysphagia was scored based on the Mayo score, as well as a table of dysphagia severity. Manometric variables were recorded before and after the treatment. Results: Thirty patients (15 pantoprazole and 15 pantoprazole plus buspirone) were included. Females comprised 63.3% of the population, with a mean age of 46.33 ± 11.15. The MAYO score and resting LES pressure significantly changed after treatment. The MAYO and Swallowing Disorder Questionnaire scores significantly decreased after treatment in both groups of patients. Our results revealed that the post-intervention values of manometric variables differed significantly between the two groups after controlling for the baseline values of the variables. This analysis did not demonstrate the superiority of buspirone. Conclusion: Buspirone seems to have no superiority over PPI. Treatment with concomitant IEM and GERD using proton pump inhibitors improves the patient's clinical condition and quality of life. However, adding buspirone to the treatment regimen did not appear to make a significant difference in patient treatment.

Keywords: ineffective esophageal motility; dysphagia; mayo score; buspirone; manometry

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1. Background

Ineffective esophageal motility disorder is the most common esophageal motility disorder and is associated with low to moderate amplitude contractions (less than 30 mm Hg) in the distal esophagus in conventional manometric studies. It is characterized by a distal contractile integral (DCI) of less than 450 mm Hg/s/cm in high-resolution magnetometry in more than 50% of swallowing test cases, which can be defined as either failed (less than

100 mm Hg/s/cm) or weak swallows (100–450) according to the Chicago classification IV [1,2].

This disorder is mainly seen along with symptoms such as dysphagia or heartburn and is associated with diseases such as gastroesophageal reflux disease (GERD). IEM has been reported to be the primary motility disorder, in 50% of patients with GERD [3]. Other diseases contribute to this disorder, like diabetic neuropathy, amyloidosis, ethanol consumption, chronic calcium-induced neuropathy, adenocarcinoma, eosinophilic esophagitis, chronic cough, and rheumatic diseases [4,5]. Based on the results obtained for esophageal impedance, ineffective esophageal motility can result in the ineffective transfer of food through the esophagus [6,7]. This disorder occurs in 20–30% of individuals who undergo manometric evaluations [8,9].

Esophageal motor peristalsis is controlled by the inhibitory and excitatory neuronal activity of the CNS, vagal dorsal motor, and intramuscular interstitial cells of Cajal (ICC), which are pacemakers of esophageal cells. Numerous sensory and motor neuron receptors modulate vagal activity. IEM is thought to be associated with an abnormal vagal tone derived from abnormal sensory and/or motor vagal pathways from the stomach via the solitary nucleus to the esophagus.

Buspirone is an anxiolytic drug, a relative agonist of 5-HT1A (hydroxytryptamine) receptors and an antagonist of dopamine D2 receptors, and evidence of a weak agonist effect on 5-HT2 receptors. In the intestinal nervous system, activation of 5-HT1A receptors can release acetylcholine from nerve endings and stimulate esophageal motor function via muscarinic receptors on smooth muscle cells [10]. Buspirone has been shown to increase the esophageal peristaltic amplitude in healthy individuals.

There is still no effective drug for the treatment of ineffective esophageal motility disorders. One of the therapies introduced to improve patients with this disorder is buspiron [11,12]. However, despite some preliminary studies, there is no consensus on the efficacy of this drug, and its efficacy in Iranian patients has not yet been studied. Considering the prevalence of this disorder among patients with GERD and dysphagia, this study aimed to determine the effect of buspirone on concomitant GERD and ineffective esophageal motility.

2. Methods and Materials

2.1. Study Design

The present study was a randomized clinical trial. This study was approved by the Medical Research Ethical Committee of Tehran University of Medical Sciences (IRB) (IR.TUMS.IKHC.REC.1399.181) and the Iranian Randomized Clinical Trial Committee (IRCT20210418051005N1). Thirty patients with GERD who also had dysphagia were included. High-resolution manometry was performed using a catheter with 36 sensors spaced 1 cm apart while the patients were supine (high-resolution impedance manometry (HRIM); Medical Measurement System, Enschede, The Netherlands). Patients were advised to fast for eight hours prior to the procedure. Ineffective esophageal motility was classified using the fourth edition of the Chicago Classification [13].

2.2. Randomization and Blinding

Patients were categorized based on random numbers. Based on a random score, the participants were given a package containing the desired medications/s. Half of the packets contained 10 mg of buspirone and 40 mg of pantoprazole, and the other half contained only 40 mg of pantoprazole. The treatment duration was four weeks in both groups. The packets were distributed to the patients by a registered nurse who was unaware of the details of the study. All patients were monitored by a registered nurse for buspirone–drug interactions with other drugs used by the patient. All patients were provided with the necessary training on when and how to take medication. Patient follow-up occurred weekly with the nurse to ensure that they were consuming the medication. At the end of every week, starting from the first day of consuming the medication, the registered nurse contacted the patients,

asking about their adherence to the treatment plan and any side effects. If patients were suffering from any side effects, a physician contacted them and gave them the necessary instructions. They were contacted again at the end of week 4 and told to stop using the drug(s), and were also reminded of their second medication session (follow-up manometry) (Figure 1). The final analysis of the data was performed by a person who was not aware of the objectives of the study.

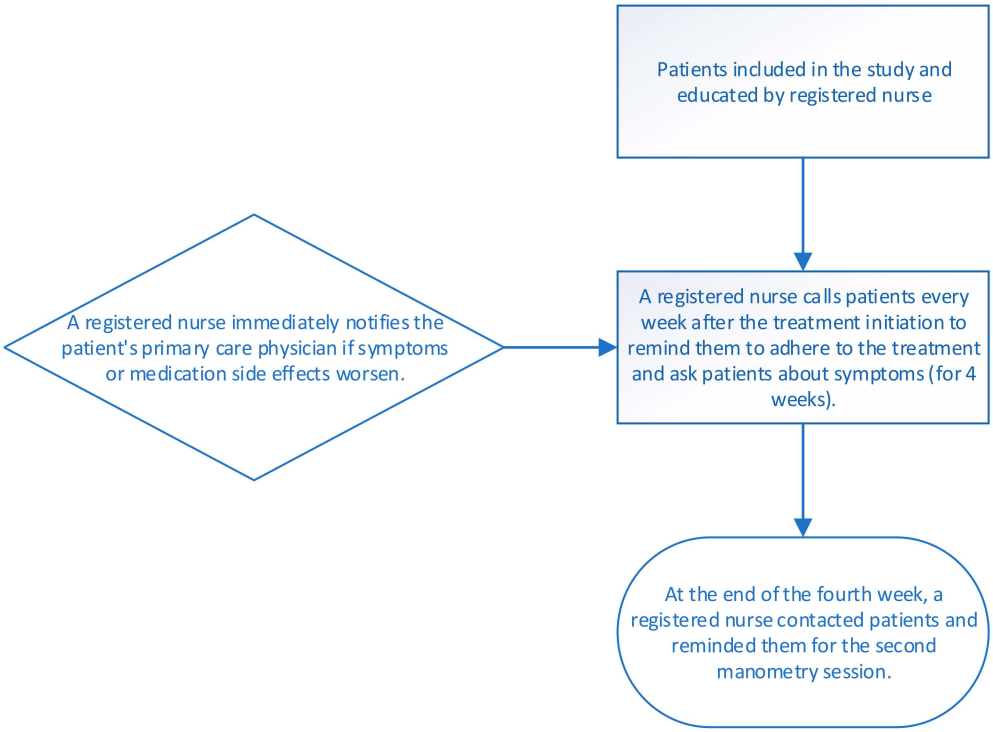

Figure 1. Flowchart of Patients' Adherence to the Treatment.

2.3. Study Tools and Data Collection

All participants provided informed consent after the study was authorized by a registered nurse (Figure 2). Patients aged > 18 years and older than 75 years with a history of esophageal reflux for >3 months who had been referred for manometry due to the presence of dysphagia were included. All patients underwent an upper endoscopy to exclude any cases of medical obstruction. The study was performed in both groups after the discontinuation of at least one week of PPI. Patients with a history of any type of active malignancy, mechanical obstruction, eosinophilic esophagitis, diabetes, opium addiction, collagen vascular disease, Barrett's esophagus, diabetes with neuropathy, amyloidosis, acute ethanol ingestion, chronic alcoholism with neuropathy, or endoscopic submucosal dissection were excluded. The exclusion criteria were based on patient history and endoscopic findings.

The MAYO score questionnaire and dysphagia severity table (swallowing disorder questionnaire) were completed before and after treatment. For the MAYO score [14], patients answered questions about their dysphagia, focusing on their symptoms in the past 30 days. The questions revolve around the severity and frequency of dysphagia as well as whether they modify their diet for better swallowing. They were also asked about their difficulty swallowing pills or liquids. Avoidance of or difficulty in swallowing different foods (oatmeal, banana, apple, ground beef, bread, and meat) is also being investigated. All 30 patients underwent high-resolution manometry by a trained nurse, which was performed by the same gastroenterologist, and their dysphagia was scored based on Mayo and a table of dysphagia severity. Manometric pressure variables were recorded before and after treatment.

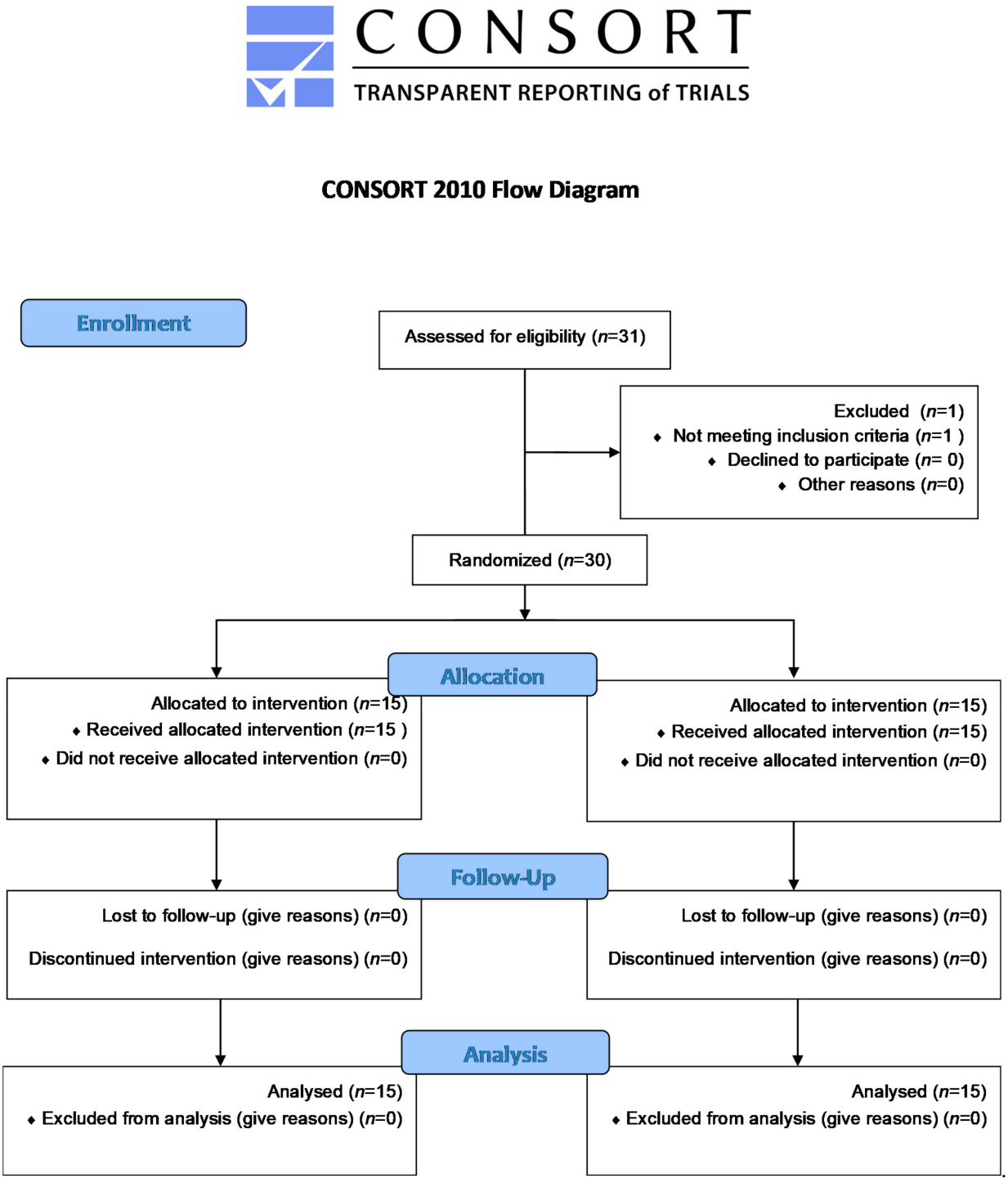

Figure 2. CONSORT follow chart of patients included in the study.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS 26 software. An alpha level of less than 5% was considered statistically significant. Qualitative variables (nominal and categorical) were reported as frequencies and percentages, and quantitative (continuous) variables were reported as means (medians) and standard deviations. A paired *t*-test (or Wilcoxon test) was used to evaluate the differences between the variables before and after the intervention. An analysis of variance (ANCOVA) was also used to evaluate the differences

between the measured variables before and after the treatment intervention based on the medication group.

3. Results

Thirty-one patients were enrolled. One patient did not complete the study due to the COVID pandemic. Of the remaining 30 participants, 15 patients received pantoprazole and 15 patients received pantoprazole plus Buspirone (63.3% of patients were female and the mean age was 45.33 ± 11.15 (Table 1).

Table 1. Patient's demographic data.

Age		**45.33 ± 11.16 ***
Swallowing Disorder Questionnaire before treatment		1.70 ± 0.95
MAYO score before treatment		12.17 ± 6.01
Resting LES pressure before treatment		10.53 ± 5.08
DCI before treatment		283.97 ± 196.77
Integrated relaxation pressure before treatment		4.14 ± 2.93
Swallowing Disorder Questionnaire after treatment		0.93 ± 0.87
MAYO score after treatment		8.60 ± 5.39
Resting LES pressure after treatment		14.87 ± 8.66
DCI after treatment		509.60 ± 448.36
Integrated relaxation pressure after treatment		4.62 ± 4.09
Group	Pantoprazol	15(50%) **
	Pantoprazol + Buspirone	15(50%)
Age grouping	<40	11(36.7%)
	>40	19(63.3%)
Gender	Male	11(36.7%)
	Female	19(63.3%)
Solid Swallowing disorder before treatment	No	7(23.3%)
	Yes	23(76.7%)
Liquid Swallowing disorder before treatment	No	16(53.3%)
	Yes	14(46.7%)
Solid Swallowing disorder after treatment	No	11(36.7%)
	Yes	19(63.3%)
Liquid Swallowing disorder after treatment	No	22(73.3%)
	Yes	8(26.7%)

* Mean ± SD, ** Count (%).

The results of the Mann–Whitney U test showed that all of the manometric, MAYO scores (13.33 ± 5.16 in the Pantoprazole group and 11.00 ± 6.72 in Pantoprazole + Buspirone group before treatment, $p = 0.29$ vs. 8.80 ± 4.72 in the Pantoprazole group and 8.40 ± 6.13 in Pantoprazole + Buspirone group after treatment, $p = 0.84$), and swallowing disorder questionnaire variables were no different across the two groups of patients (1.93 ± 0.88 in the Pantoprazole group and 1.46 ± 0.99 in Pantoprazole + Buspirone group before treatment, $p = 0.18$ vs. 1.13 ± 0.83 in the Pantoprazole group and 0.88 ± 0.73 in Pantoprazole + Buspirone group after treatment, $p = 0.21$) (Table 2).

Table 2. Comparison of different variables according to patient groups.

Age (Mean ± SD)		***p***
Pantoprazole	46.46 ± 13.16	
Pantoprazole + Buspirone	44.20 ± 9.04	0.58
Swallowing Disorder Questionnaire before treatment		
Pantoprazole	1.93 ± 0.88	
Pantoprazole + Buspirone	1.46 ± 0.99	0.18
Swallowing Disorder Questionnaire after treatment		
Pantoprazole	1.13 ± 0.83	
Pantoprazole + Buspirone	0.88 ± 0.73	0.21
MAYO score before treatment		
Pantoprazole	13.33 ± 5.16	
Pantoprazole + Buspirone	11.00 ± 6.72	0.29
MAYO score after treatment		
Pantoprazole	8.80 ± 4.72	
Pantoprazole + Buspirone	8.40 ± 6.13	0.84
Resting LES pressure before treatment		
Pantoprazole	9.40 ± 5.08	
Pantoprazole + Buspirone	11.66 ± 4.99	0.22
Resting LES pressure after treatment		
Pantoprazole	15.00 ± 9.97	
Pantoprazole + Buspirone	14.73 ± 7.47	0.93
DCI before treatment		
Pantoprazole	311.33 ± 223.74	
Pantoprazole + Buspirone	256.60 ± 168.92	0.45
DCI after treatment		
Pantoprazole	581.26 ± 473.86	
Pantoprazole + Buspirone	437.93 ± 425.27	0.39
Integrated relaxation pressure before treatment		
Pantoprazole	3.66 ± 2.79	
Pantoprazole + Buspirone	4.61 ± 3.08	0.38
Integrated relaxation pressure after treatment		
Pantoprazole	4.82 ± 3.90	
Pantoprazole + Buspirone	5.00 ± 4.40	0.9

The results of the Wilcoxon test showed that the Swallowing Disorder Questionnaire, MAYO score, DCI, and resting LES pressure significantly changed after treatment (Table 3) (Figures 1–5). The MAYO score and Swallowing Disorder Questionnaire significantly decreased after treatment in both groups of patients. The difference (md) of the MAYO score in the Pantoprazole group was +4.533 (p = 0.009) and 2.600 in the Pantoprazole + Buspirone group (p = 0.015). The Swallowing Disorder Questionnaire md was also 0.800 in the Pantoprazole group (p = 0.028) and 0.733 in the Pantoprazole + Buspirone group (p = 0.005) (Figures 3–7).

Resting LES pressure (md = −5.6 pantoprazole group, p = 0.017, and −3.066 in Pantoprazole + Buspirone group, p = 0.014) and DCI (md = −269.933 pantoprazole group, p = 0.007, and −181.333 in Pantoprazole + Buspirone group, p = 0.023) experienced a significant increase after treatment in both groups. Meanwhile, integrated relaxation pressure increased across both groups, but it was not statistically significant (md = −1.162 pantoprazole group, p = 0.196, and −0.390 in the Pantoprazole+ Buspirone group, p = 0.706).

An ANCOVA was performed to examine the mean differences in post-intervention manometric variables (Resting LES, DCI, IRP) among the two groups after adjusting for the baseline. The results indicated that the post-intervention values of manometric variables

did significantly differ between the two groups after controlling for the baseline values of the variables.

Table 3. Comparison of variables before and after treatment between two groups of patients.

	Variables	Mean Differences(md)	Statistic Test	*p*
Pantoprazole	Swallowing Disorder Questionnaire	0.800	z = −2.200	0.028
	MAYO score	4.533	z = −2.621	0.009
	Resting LES pressure	−5.600	z = −2.378	0.017
	DCI	−269.933	z = −2.698	0.007
	Integrated relaxation pressure	−1.162	z = −1.294	0.196
Pantoprazole + Buspirone	Swallowing Disorder Questionnaire	0.733	z = −2.810	0.005
	MAYO score	2.600	z = −2.422	0.015
	Resting LES pressure	−3.066	z = −2.451	0.014
	DCI	−181.333	z = −2.272	0.023
	Integrated relaxation pressure	−0.390	z = −0.377	0.706

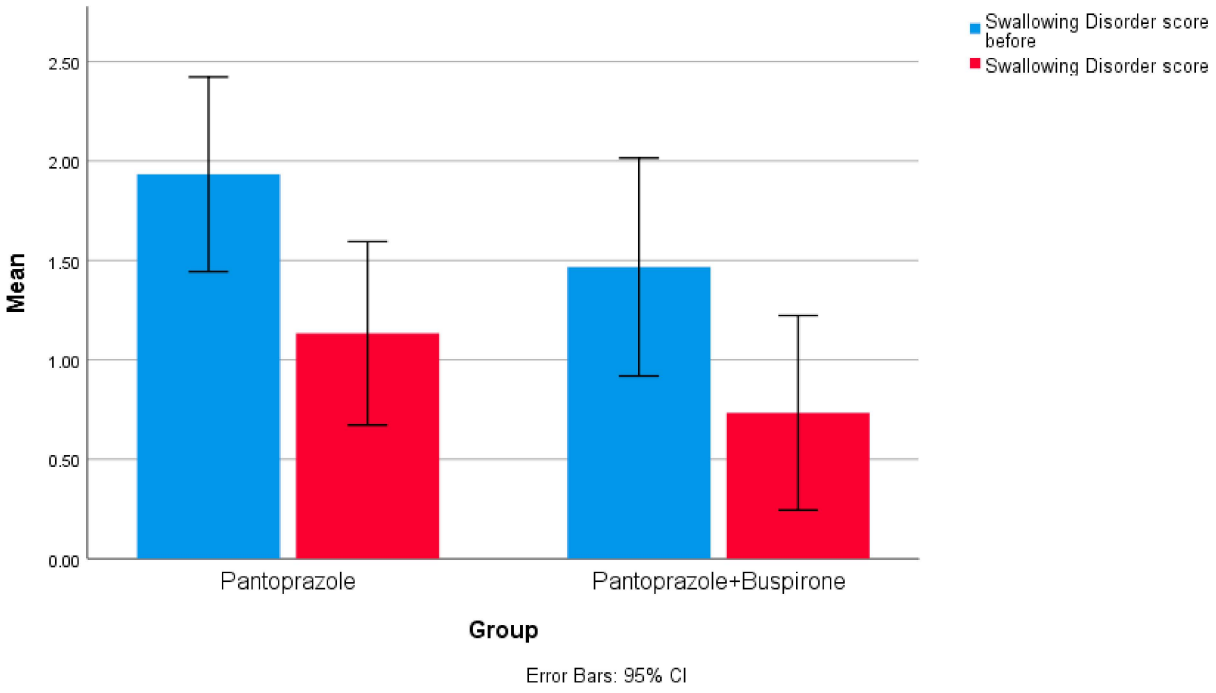

Figure 3. Clustered Bar Mean of Swallowing Disorder score before and after by group of treatment.

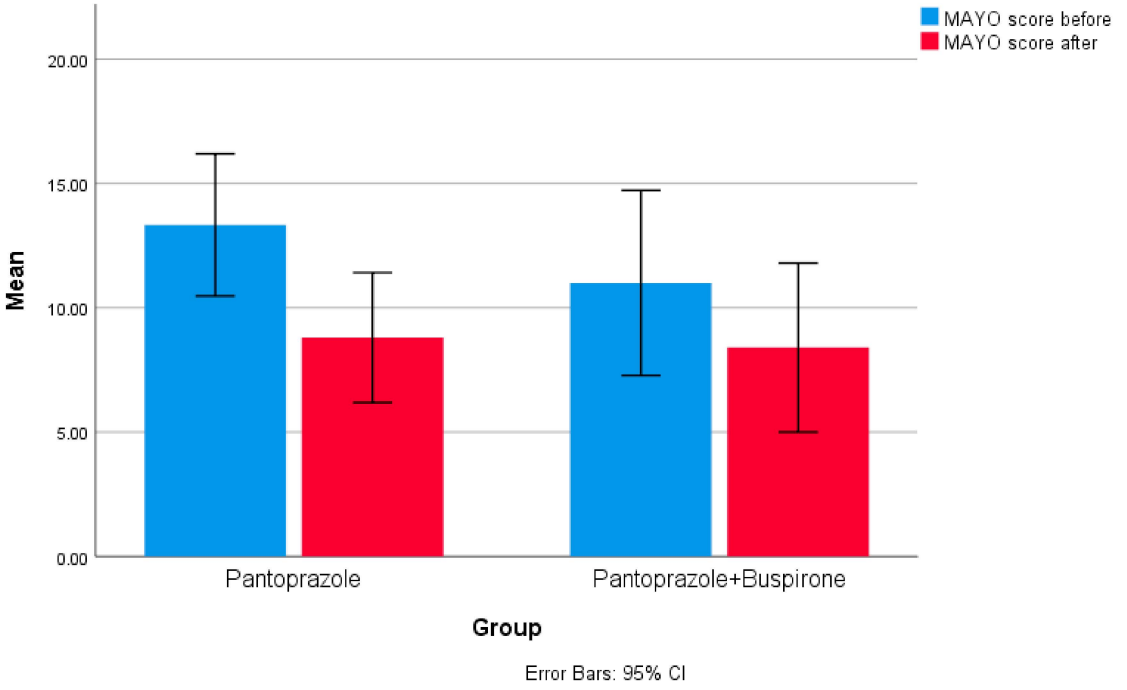

Figure 4. Clustered Bar Mean of MAYO score before and after by group of treatment.

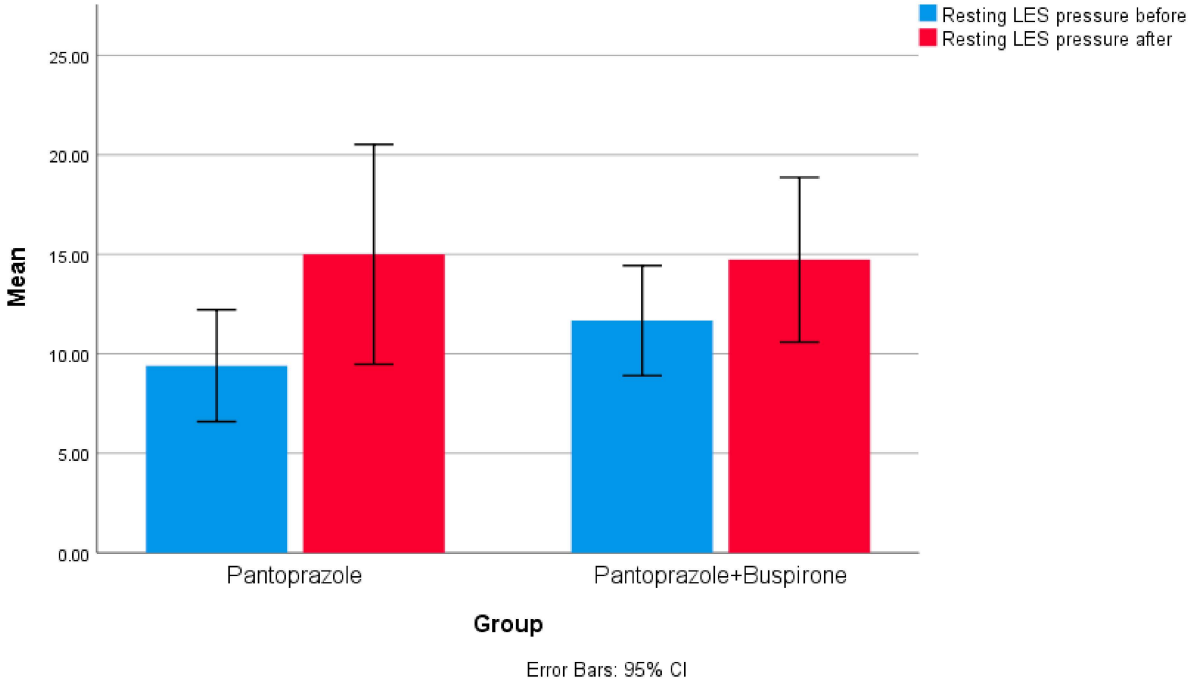

Figure 5. Clustered Bar Mean Resting LES pressure before and after by group of treatment.

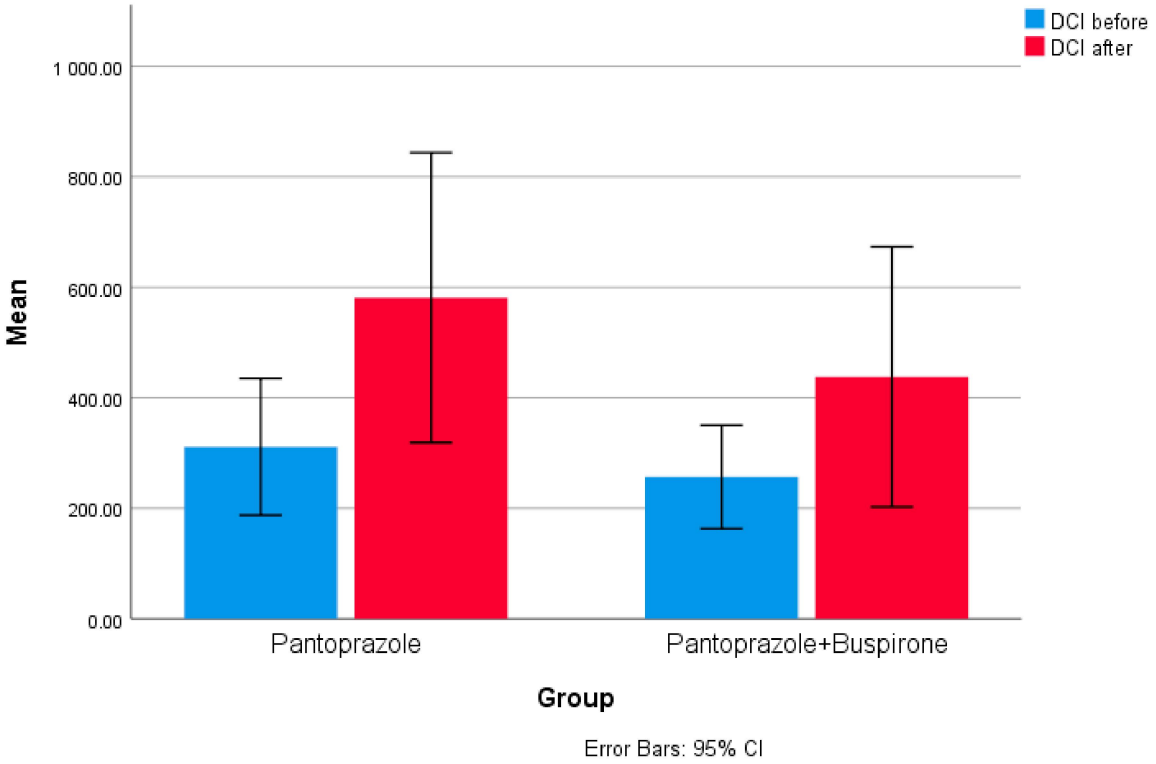

Figure 6. Clustered Bar Mean DCI before and after by group of treatment.

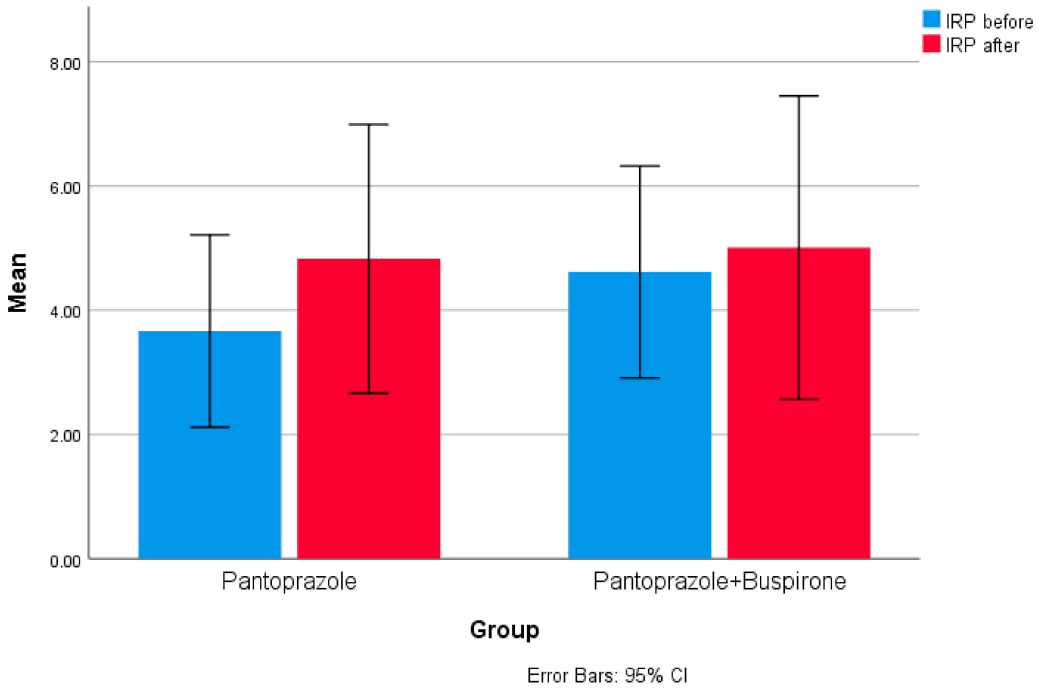

Figure 7. Clustered Bar Mean IRP before and after by group of treatment.

4. Discussion

According to the Chicago Classification for primary esophageal motility disorders, ineffective esophageal motility disorder is the most common disorder that is found on manometry in patients who are referred for evaluation of dysphagia [15]. This disorder leads to a significant number of referrals to gastroenterologists. It has been shown that

some disorders are related to this disorder, such as amyloidosis, diabetes, and eosinophilic esophagitis, but the most common disorder attributed to this disorder is GERD.

The balance between neurotransmitters, including acetylcholine, VIP, and nitric oxide, is crucial in the pathophysiology of esophageal motility. Activation of 5HT1A leads to an increase in acetylcholine, which is a positive mediator for smooth muscle activation in the esophagus. Theoretically, buspirone, which is a partial agonist for 5-HT (hydroxytryptamine) 1A receptors, and has a weak agonistic effect on 5-HT2 receptors, could be effective in the treatment of IEM [16,17].

In the present study, we investigated the therapeutic effects of two drug regimens (pantoprazole monotherapy and pantoprazole plus buspirone) on patients' symptom scores and manometric findings of IEM in patients with GERD disease. The results of our study showed that pharmacologic treatment with PPI improves the clinical condition and quality of life of patients. The therapeutic intervention caused a statistically significant improvement in manometric and clinical parameters. The Mayo score, and swallowing score decreased, and the resting pressure of LES and DCI increased after the treatment, which all were statistically significant.

Although the parameters studied in this study responded to treatment, the combination with buspirone did not make a significant difference. In fact, the addition of buspirone to the treatment regimen does not seem to have a significant effect on either clinical or manometric variables. To our knowledge, at least five different research centers have studied the effects of buspirone on IEM. In two studies, 20 mg of buspirone was administered to healthy adults, and esophageal motility was measured by conventional manometry within 60 min of administration in a blind, placebo-controlled trial. The results showed that the mean amplitude and duration of contraction in the distal esophagus increased in both studies after a single dose of buspirone [8,18]. This was against our findings. This study was conducted by Di Estefano et al. His study revealed that buspirone overcame the placebo in increasing LES tone and distal esophagus smooth muscle amplitude. The difference in the results of this study and ours could be due to differences in the study population. In addition, they have reached these results only after the administration of a single dose of buspirone and not continuous use [18]. Karamanolis et al. investigated buspirone in two different studies, including patients suffering from scleroderma and dysphagia. In the first study, buspirone was compared with domperidone and showed a beneficial effect in the manometric criteria conducted 30 min after ingestion. The second study examined the effect of buspirone on a four-week trial, and the only manometric value that showed a significant change was LES pressure [19,20]. Aggarwal et al. also examined buspirone against a placebo in the United States. As buspirone and the placebo both had a 30% increase in manometric variables, they did not consider buspirone superior to the placebo [21]. Nitin Aggarwal et al. conducted a cross-over study in 10 patients with functional dysphagia and IEM with six weeks of buspirone and a placebo. Similar to our study, they showed no improvement in a patient's symptom score and manometric findings after four weeks of use of this drug [21].

Studies by Wang et al. [22], and Shetler et al. [23] showed that IEM is accompanied by the severity of GERD disease, and interestingly, our study showed that treatment with PPI improves patient distal contractile integral, which could be an indicator of esophageal motility improvement.

A recent study by Taghavi et al. [24] examined the effectiveness of buspirone in patients with functional dyspepsia. The first group received buspirone 5 mg three times daily for the first month and 10 mg three times daily for the second month. During the course of treatment, patients were advised to report any adverse reactions. This study shows that there was no significant difference between the two groups of buspirone and placebo in terms of quality of life (p = 58.0), anxiety and depression (p = 36.0), and severity and frequency of functional dyspepsia symptoms (p = 0.22) before and after the intervention. They suggested that further studies are needed to introduce effective treatments based

on the pathophysiology of functional dyspepsia. However, some previous studies have suggested that buspirone may improve the therapeutic response.

Recent limited data has shown the role of acetylcholine and 5HT1A on esophageal smooth muscle and a single use of 10 mg buspirone was effective in increasing LES pressure and DCI, but the main effect of this drug was seen in single and short-term use of this drug. Our study showed that using 10 mg buspirone for four weeks was not superior to using PPI for improving symptoms and manometric findings. Interestingly, PPIs themselves could increase DCI and LES resting pressure, which indicates that the most important treatment in patients with GERD and ineffective esophageal motility could be an early and effective dose of PPIs. However, it should be noted that the sample size of this study is small and this result cannot be considered definitive, and to confirm or reject these findings, large clinical trials with a larger sample size are needed. In addition, the proper dose of buspirone for inducing acetylcholine release, increasing DCI, and augmenting smooth muscle strength thereafter has not been determined yet. We could not use more doses of this drug due to its severe sedative effect. Other detailed studies with different doses of buspirone will overcome this limitation.

Limitations: During the COVID-19 pandemic, fewer patients sought medical care for non-emergent problems such as dysphagia or heartburn, leading to a smaller sample size in the study than predicted. This study was also conducted in a single center; multicenter studies could be considered for future studies. Finally, we did not have any placebos in this study.

5. Conclusions

Treatment of concomitant GERD and IEM using proton pump inhibitors (such as pantoprazole) improves patients' clinical condition and quality of life. However, adding buspirone to the treatment regimen does not appear to make a significant difference in patient treatment.

Author Contributions: Conceptualization, F.A.A., E.B., N.A., F.A. and M.T.; methodology, H.A.V., N.F. and E.B.; software, H.A.V.; validation, F.A., E.B., N.A., F.A. and M.T.; formal analysis, H.A.V.; investigation, F.A.A., E.B. and N.F.; writing—original draft preparation, E.B., H.A.V. and F.A.; writing—review and editing, E.B. and F.A.A.; visualization, H.A.V.; supervision, F.A.A., E.B., N.A., F.A. and M.T.; project administration, F.A.A.; funding acquisition, F.A. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Tehran University of Medical Sciences (protocol code IR.TUMS.IKHC.REC.1399.181).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: Authors declare no conflict of interest.

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