ORIGINAL ARTICLE

The effect of adding duloxetine to lansoprazole on symptom and quality of life improvement in patients with gastroesophageal reflux diseases: A randomized double-blind clinical trial

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Background: Gastroesophageal reflux disease (GERD) is a common upper gastrointestinal disorder with a negative impact on the quality of life. This study was aimed to assess the effect of adding duloxetine to lansoprazole on the symptom and quality of life improvement in GERD patients. **Materials and Methods:** Seventy adult patients with a complaint of heartburn and regurgitation were enrolled in this randomized trial. Patients with a history of atypical symptoms, advanced systemic disease, medication-induced symptom, structural lesion in endoscopy, allergy to the medication, and unco-operative were excluded. The patients randomly (computer generated table) assigned in Groups A who received lansoprazole 30 mg plus placebo daily and Group B, in which duloxetine 30 mg daily replaced by placebo during 4 weeks. All of participants, care-givers, and outcomes assessors were blinded. Basic demographic data, symptom severity score, depression and anxiety Beck score, and quality of life questionnaire were recorded at the starting and ending of treatment. **Results:** Fifty-four patients have completed the study. The mean difference of Anxiety Beck score (13, 95% confidence interval [CI] [10–16], $P = 0.001$) and total raw score of quality of life (7, 95% CI [3.89–10.11], $P = 0.043$) were significantly improved in Group B. Complete and overall heartburn improvement rates were significantly better in Group B (odds ratio [OR] Adj: 2.01, 95% CI [1.06–2.97] and OR Adj: 1.31, 95% CI [1.05–1.57], respectively). **Conclusion:** We found that the combination of duloxetine and lansoprazole is a safe and tolerable regimen, and it can significantly improve anxiety, heartburn, coffee consumption, the quality of sleep, and life in patients who suffer from the symptoms of GERD.

Key words: Anxiety, duloxetine, gastro-esophageal reflux disease, heartburn, quality of life

How to cite this article: Mokhtare M, Chaharmahali A, Bahardoust M, Ghanbari A, Sarveazad A, Naghshin R, *et al*. The effect of adding duloxetine to lansoprazole on symptom and quality of life improvement in patients with gastroesophageal reflux diseases: A randomized double-blind clinical trial. J Res Med Sci 2021;26:4.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic recurrent disease with mucosal damage due to bringing up of stomach contents through the lower esophageal sphincter (LES) into the esophagus or beyond that into the larynx and lung. The prevalence of GERD varies between 2.5%–25% with the highest and lowest prevalence rates in American and Asian countries, respectively.[1]

Regurgitation and heartburn are considered as typical clinical manifestations in GERD patients and other

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_300_19

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Submitted: 18-May-2019; **Revised:** 13-Apr-2020; **Accepted:** 18-Aug-2020; **Published:** 28-Jan-2021

manifestations such as dyspepsia, bloating, nausea, chest pain, belching, laryngitis, asthma, and a chronic cough defined as atypical or extra-esophageal clinical symptoms.[2] GERD is diagnosed with weekly heartburn and regurgitation. It is a chronic disease with multi-factorial etiology and has a negative impact on the quality of life. Typical manifestations were more specific for diagnosis, especially in the absence of any alarm sign (history of dysphagia, hematemesis, anemia, cancer in family, and lymphadenopathy and/or mass detection in a physical examination), and the good response to an empiric proton-pump inhibitors (PPIs) therapy. This diagnostic empiric PPIs therapy is cost-saving, noninvasive with acceptable specificity (89% and 95%), and low sensitivity (38% and 6%) regarding well-taken history of heartburn and regurgitation, respectively. Other diagnostic methods must be considered in a special situation such as refractory or complicated reflux disease to confirm the other diagnosis.[3]

The aggravating factors of GERD are different concerning the aging process. Male gender, smoking, coffee consumption, and body mass index ≥25 are the major aggravating factor among young adults. *Helicobacter pylori* are considered a positive and negative aggravating factor in old age and young adult patients, respectively.[4]

Other aggravating factors are psychosocial factors (anxiety, depression, and sleep quality). The increased acid secretion has been marked as a main worsening factor for GERD symptoms in patients who already have a loose LES.[5-8]

Lifestyle modification (lowering the weight, elimination of the psychosocial factors, reducing alcohol, chocolate, coffee and tea consumption, and considering at least 2 h between meal and time to bed and elevation the head part of the bed), medical treatment, and even in some cases, endoscopic, or surgical treatment might be considered in management of the patients.[3] The key point in the medical treatment of GERD is acid suppression; such as anti-acids, histamine-receptor antagonists, and PPIs.[3]

Previous studies found that PPIs are more effective than the other agents. It seems that heartburn and regurgitation have 64.1% and 69.5% of improvement rate to PPIs, respectively.[9]

Symptom improvement rates was assessed on 450 GERD patients in Asia Pacific Survey. They established that 45% of patients had good daily response to PPI with restricted improvement in nocturnal complaints. Moreover, 49% of patients had persistent symptoms and need to the additional therapy.[10]

GERD patients may remained symptomatic despite proper use of PPIs. It might be related to the different in-built pharmacokinetic and pharmacodynamic profiles of conventional first-generation PPIs. New PPI isomers with a unique dual delayed-release delivery system has been designed to overcome to this problem in patients with nonerosive esophageal reflux disease (NERD), nocturnal heartburn and GERD-related sleep disruption, and regurgitation. PPI therapy can improve esophageal mucosal inflammation much more predictable than symptoms in GERD patients.[10]

The causes of PPI-refractory GERD are low patients' adherence to treatment, sustain acid secretion, functional disorders, nonacid reflux, and PPI bioavailability. A number of medications, alternative and complementary therapies with potential benefit also considered.[11]

The association between GERD and depression was shown in some studies.[12,13] It seems that patients with anxiety and depression have lower visceral pain sensitivity threshold and have experienced more GERD symptoms. On the other side, depression and anxiety are more common in patients with GERD. The result of some studies showed that anti-anxiety and anti-depressant medication alone or in combination to PPIs can eliminate the symptoms and improve quality of life in these patients.[3] Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor. Duloxetine letdowns chemicals (serotonin and norepinephrine) in the brain and treats depression and anxiety disorders in an adult. It may improve the mood, sleep, desire for food, and energy level of patients, and decrease anxiety.[14]

The adverse effect of duloxetine consists of nausea, dry mouth, constipation, anorexia, drowsiness, fatigue, and increased sweating.[15]

The main aim of GERD treatment are to get rid of symptoms, heal and keep up remission of erosions, reduce complications, and increase health-associated quality of life. Pain modulators, or visceral analgesics, have been shown to significantly improve the symptoms related to esophageal hypersensitivity, functional heartburn, and refractory GERD by acting at the central nervous system level and/or peripherally at the sensory afferent level.[10]

Because of the low response rate of conventional PPI on daily/nocturnal symptoms and sleep and quality of life in GERD patients, some studies recommend the combination of PPI with another medications or if available using of new isomer of lanzoprazole, dex-lanzoprazole MR, to achieve better improvement rates. Regarding the effect of duloxetine as an anti-anxiety/depressant besides modulating the esophageal sensitivity, we design this study to evaluate the effect of combined therapy on symptom, and quality of sleep and life improvement.

MATERIALS AND METHODS

Study design and setting

This study is a randomized, double-blind, placebo control clinical trial. Our study was approved in the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC1396.9311160007), and the study protocol was registered in the Iranian Registry of Clinical Trials (IRCT20141201020178N6). All the researchers of this study were believed in Helsinki Ethical principles. All patients entered the study after receiving a complete explanation of the study and providing written consent.

All of naive GERD patients with typical symptoms, including heartburn and regurgitation and age range, between 18 and 65 years who referred to the gastroenterology clinic of Rasoul-e-Akram Hospital during December 2017 and September 2018, were included. Upper endoscopy was done for patients with a history of any coexisting alarm signs. The patients who defined as NERD regarding LA classification were included. Upper endoscopy was done for patients with a history of any alarm signs and who defined as NERD regarding LA classification was included. Eligible patients were randomly assigned into two treatment groups. The patients with a chief complaint of atypical symptoms, history of anti-depressant or-anxiety medication, nonsteroid anti-inflammatory drugs, MAO inhibitors, alcohol, methylxanthine, betamimetics, nitrate, calcium-channel blockers and sildenafil (among recent 6 months), progressive systematic disease (heart, lung, kidney and liver disease, uncontrolled hypertension), glaucoma, cancer, seizure, myopathy and scleroderma, and gastrointestinal tract surgery, peptic ulcer disease, pregnancy and lactation, history of allergy to prescribed medication and noncooperative patients, were excluded.

Group A: Received lansoprazole (Lanzo, Abidi Pharmaceuticals, Iran) 30 mg about half an hour before breakfast with one capsule of placebo (Dr. Abidi Pharmaceuticals, Iran) about 2 h after breakfast per day.

Group B: Received lansoprazole (Lanzo, Dr. Abidi Pharmaceuticals, Iran) 30 mg half an hour before breakfast plus one capsule duloxetine (Dr. Abidi Pharmaceuticals, Iran) 30 mg, 2 h after breakfast per day for 4 weeks.

Patients and grouping

The random allocation sequence was produced by CENCEC, which provided a computer-generated randomization table. The random allocation, enroll participants and assigned participants to intervention groups were performed by the methodologist. Seventy eligible patients were included and randomly assigned in one of the treatment groups (ratio 1:1). All of participants, caregivers, and outcomes assessors were blinded.

Patients follow-up

Basic demographic data were recorded at the beginning of treatment. Depression and anxiety Beck score, symptom severity score, and quality of life questionnaire[16,17] were recorded as a paper format for all patients at the starting and ending of the treatment regimen.

In order to assess symptom severity in clinical trials, a combination of the severity and frequency of symptom has often been used based on either the investigator's assessment every 2 weeks and patient daily data-gathering sheets. The four-graded severity scale is defined as:[17] none (0) = no symptoms, mild (1) = awareness of symptom, but easily tolerated, moderate (2) = discomfort sufficient to cause interference with normal activities, and severe (3) = incapacitating, with the inability to perform normal activities. Treatment comparisons were sometimes performed based on a difference in mean severity score, but more often they were based on a difference in treatment success rates.

The treatment success rate is defined as both the severity and frequency scales. The treatment success rate in this study was defined as the complete resolution of symptom (no symptom during the previous 7 days and if remembered for instance 1 month), and partial as adequate relief of symptom (at most 1 day of mild heartburn during the previous 7 days), before a certain clinical visit.[17] The patients who consumed at least 80% of prescribed medications during 80% of the treatment time were enrolled. Drug adverse effects and patient's adherence to the treatment were recorded by patient-recorded daily sheet and pill count in each visit by a physician, respectively, at the middle (week 2) and end (week 4) of the treatment.

Sample size calculation

Based on the results of previous studies, the average difference in improving heartburn rates between the two regimens was 43%,[3,18] with an effect size of 0.8 obtained from the difference in improving heartburn rates between the two study groups, at a power of 80%, and significance level of 5%, Using G Power software version 3.1(Heinrich Heine University, Düsseldorf,Germany) the sample size for each group was calculated to be 35 patients.

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation (SD) for quantitative variables and numbers and percentages for categorical variables. The assumptions were that the variables were normal and that the variance

was equal in the two groups. The normality of continuous variables was checked using the Kolmogorov–Smirnov test. A comparative evaluation for the mean score reduction between the two groups was performed by Mann–Whitney U-test. The Chi-square test was used to assess the relationship between the categorical variables. The comparison of the mean scores of treatment assessment results was performed by the Mann–Whitney U-test. We performed an intention-to-treat analysis for binary endpoints according to the randomization allocation. In this study, we used the odds ratio (OR) and its 95% confidence interval (CI) to compare primary and secondary efficacy of end points, treatment compliance, and adverse effects. Randomization was used to control the confounders in the design stage of the study. All significant variables achieved from univariate analysis were included in a multivariate logistic regression model with the forward method to control the confounders in the data analysis stage. $P < 0.05$ was considered statistically significant. Data were analyzed using the IBM SPSS Statistics for Windows (version 22; SPSS Inc., Chicago, IL, USA).

RESULTS

Seventy patients were eligible. Totally, 16 patients excluded, and 54 patients with the mean age of 37 ± 11.74 (mean ± SD) years have completed the study [Figure 1]. The majority of the patients were male 30 (54%), single 41 (73%) and educated above diploma 43 (77%). There was no significant difference between the two treatment groups regarding baseline demographic data [Table 1].

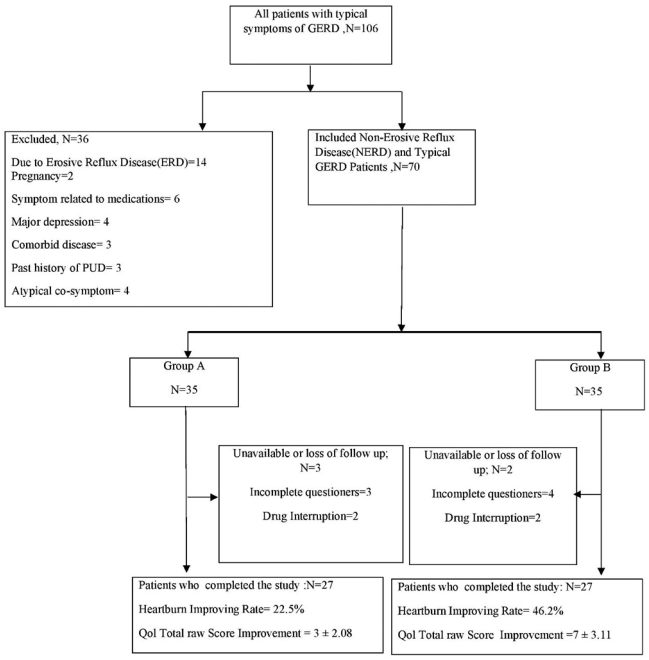

Figure 1: Flow chart of the method of follow-up and treatment efficacy

There were no significant statistical differences between the two treatment groups regarding the anxiety and depression score, basically and in the depression score at the end of treatment. However, there was a significant improvement of anxiety score between two groups at the end of the treatment (mean anxiety score = 22 ± 4 and = 9 ± 3 in Group A and Group B, respectively ($P = 0.001$) [Table 2].

The complete and overall heartburn improvement rates were significantly better in Group B compared Group A (complete improvement rate; 6 [22.5%] vs. 12 [46.2%], [OR: 2.09, 95% CI (1.09–3.07)]) and (overall improvement rate; 18 [66.66%] vs. 23/[88.46%], [OR: 1.3, 95% CI (1.03–1.62)]) in Group A and B. There was no significant differences in the partial heartburn improvement rate between treatment groups (partial improvement rate; 12 [44.44%] vs. 11 [42.30%], [OR: 1.3, 95% CI (1.03–1.62)]) in Group A and B, respectively ($P = 0.44$).

Table 1: Comparison of the baseline demographic data of the patients between two groups

Demographic variables	Group A	Group B	Total	*P*
Age	37±12.038	37±11	37±11.74	0.85
Gender				
Male	14 (50)	16 (57)	30 (54)	0.44
Female	14 (50)	12 (43)	26 (46)	
Marital status				
Married	7 (25)	8 (29)	15 (27)	0.25
Unmarried	21 (75)	20 (71)	41 (73)	
Education status				
<diploma	6 (22)	7 (26)	13 (23)	
Diploma	10 (35)	10 (35)	20 (35)	
Bachelor	8 (28)	9 (36)	17 (30)	0.77
Master	3 (11)	2 (7)	5 (10)	
PhD	1 (4)	0	1 (2)	
Body mass index				
Before intervention	25.4±4.75	25.87±3.58	25.68±4.25	0.8
After intervention	25.3±4.77	25.84±3.53	25.62±4.48	
Current smoking (positive)	4 (16)	5 (20)	9 (16)	0.18
Symptom severity in preceding 7 days Heartburn*				
None	0	0	0	0.9
Mild	10/27 (37)	11/26 (42)	21/53 (40)	0.25
Moderate	14/27 (52)	13/26 (50)	27/53 (51)	0.78
Severe	3/27 (11)	2/26 (8)	5/53 (9)	0.89
Regurgitation*				
None	0	0	0	0.99
Mild	9/24 (37)	9/26 (35)	18/50 (36)	0.96
Moderate	13/24 (54)	15/26 (58)	28/50 (56)	0.83
Severe	2/24 (8)	2/26 (7)	4/50 (8)	0.9

Statistical tests: A comparative evaluation for the mean score reduction between the two groups was performed by the Mann-Whitney U-test. The Chi-square test was used to assess the relationship between the categorical variables and in instances of small sample sizes (i.e. fewer than 5), the Fisher's exact test was considered

Table 2: The comparison of the anxiety, depression, symptoms, and sleep improvement between two groups (ITT analysis)

Variables	Group A (%)	Group B (%)	OR (95% CI)	*P*
Depression score				
Before	14±4	14±3	–	0.4
After	13±2	12±2	–	0.082
Anxiety score				
Before	23±5	22±3	–	0.23
After	22±4	9±3	–	0.001
Heartburn				
Before	27 (96)	26 (93)	0.96 (0.72-1.21)	0.32
After	21 (75)	14 (50)	0.67 (0.46-0.88)	0.009
Treatment success rate				
Complete	6 (22.22)	12 (46)	2.09 (1.09-3.07)	0.009
Partial	12 (44.44)	11 (42.30)	0.95 (0.74-1.16)	0.44
Overall	18 (66.66)	23 (88.46)	1.32 (1.03-1.62)	0.001
Regurgitation				
Before	24 (85)	26 (93)	1.09 (0.84-1.35)	0.068
After	19 (67)	20 (71)	1.06 (0.81-1.32)	0.097
Treatment success rate				
Complete	5 (21)	6 (23)	1.09 (0.84-1.35)	0.17
Partial	6 (25)	8 (30.79)	1.2 (0.92-1.49)	0.21
Overall	11 (46)	14 (53.79)	1.15 (0.9-1.41)	0.11
The proximal extension of burning pain sensation				
Before	24 (85)	22 (78)	0.91 (0.551.27)	0.087
After	20 (71)	14 (50)	0.7 (0.49-0.91)	0.033
Waking up due to heartburn				
Before	19 (67)	20 (71)	1.06 (0.8-1.32)	0.3
After	16 (57)	11 (39)	0.68 (0.43-0.93)	0.023
Waking up due to Regurgitation				
Before	16 (57)	15 (54)	0.94 (0.75-1.13)	0.19
After	13 (46)	12 (43)	0.93 (0.73-1.14)	0.15
Symptoms worsen by drinking tea (positive)				
Before	17 (61)	16 (57)	0.93 (0.71-1.15)	0.081
After	14 (52)	14 (50)	0.96 (0.75-1.19)	0.097
Symptoms worsen by drinking coffee (positive)				
Before	5 (18)	6 (22)	1.22 (0.80-1.68)	0.12
After	4 (16)	1 (4)	0.25 (0.11-0.40)	0.0001

*Statistical tests: The comparison of the mean scores of treatment assessment results was performed by the Mann-Whitney U-test. OR and its 95% CI to compare primary and secondary efficacy end points. CI=Confidence interval; OR=Odds ratio; ITT: Intention to Treat analysis

There were no significant differences in the complete, partial, and overall improvement rates for regurgitation between treatment groups (complete improvement rate; 5 [21%] vs. 6 [23%], [OR: 1.09, 95% CI (0.84–1.35)] in two group, respectively, *P* = 0.097) (partial improvement rate; 6 [25%] vs. 8 [30.79%], [OR: 1.2, 95% CI (0.92–1.49)] in Group A and B, respectively, *P* = 0.21) (overall improvement rate; 11 [46%] vs. 14 [53.79%], [OR: 1.15, 95% CI (0.9–1.41)] in Group A and B, respectively, *P* = 0.11). The proximal extension of burning pain sensation was significantly comforted in Group B (*P* = 0.033) [Table 2].

At the end of the treatment, there was a significant statistical improvement in the number of cases who woke up because of heartburn (symptom improvement rate Group A = 3 [15.7%] vs. Group B = 9 [45%], [OR: 2.8, 95% CI (1.62–3.98)]). There was no significant improvement in the number of cases who had woken up because of regurgitation (symptom improvement rate Group A = 3 [19%] and Group B = 3 [20%] in two group (*P* = 0.15) [Table 2].

At the end of the treatment, there was the significant improvement in the number of symptomatic cases who could drink coffee in Group B. Symptom improvement rates were in Group A = 1 (20%) and B = 5 (83.5%), (OR: 4.11, 95% CI [1.98–6.24]) (*P* = 0.001). However, there was no significant improvement in the number of symptomatic cases who could drink tea. Symptom improvement rates were in Group A = 3 (17.5%) and B = 2 (12.5%), (OR: 0.96, 95% CI [0.75–1.19]) (*P* = 0.097) [Table 2].

The improvement of quality of life in Group B was significantly better compared Group A. Mean score differences were 3 CI 95% (0.92–5.09 and 7 CI 95% [3.88–10.12] in Group A and B, respectively ($P = 0.026$) [Table 3].

All significant variables achieved from the univariate analysis were included in a multivariate logistic regression. Based on these variables, further multivariate analysis using the forward method was performed, and we found that the complete and overall heartburn improvement rates (OR Adj: 2.01, 95% CI [1.06–2.97] and OR Adj: 1.31, 95% CI [1.05–1.57]), improvement of anxiety score (OR Adj: 1.81, 95% CI [1.13–2.48]), symptom improvement rate (OR Adj: 3.80, 95% CI [1.76–5.91]) and the improvement of quality of life (OR Adj: 1.42, 95% CI [1.06–1.79]) were significantly better in Group B compared to the Group A.

The patient's adherence to treatment was excellent. Drug adverse reaction was recorded in 3/27 (11%) of Group A and 4/27 (15%) of Group B, without any significant differences between them ($P = 0.23$). Adverse effects consist of headache, constipation, and dizziness in Group A and headache, dizziness, nausea, and fatigue in Group B which were mild, transient and tolerable. The most common was nausea 3 (11.1%) in Group B.

DISCUSSION

Heartburn and regurgitation are the cardinal manifestations of GERD.[19] The diagnosis of GERD is made by a history of typical clinical manifestations. The symptoms impair the quality of sleep and life in these patients.[20,21] Anxiety and depression may have a significant role in the existence of the symptom presentations of GERD and a negative impact on the quality of life in these patients.[22]

In previous studies, the symptoms of GERD patients were more prevalent in whom with higher education and unmarried.[18,19] We found the same result in this study.

Lansoprazole has acceptable bioavailability and efficacy in controlling the secretion of gastric acid. Heartburn relief was seen in 37% of patients that received a single dose of PPIs per each day for 28 days.[23] Studies have shown that heartburn relief with PPIs occurs 5.9% per week.[4] We found the same results in this study.

Table 3: Comparison the improvement rate in the quality of life between two groups

A total raw score of quality of life	Group A	Group B	*P*
Before	33±13.8	34±12	0.062
After	30±11	27±10.2	0.043
Differences before and after	3±2.08	7±3.11	0.026

*Statistical tests: The comparison of the mean scores of treatment assessment results was performed by the Mann-Whitney U-test

A placebo control systematic review found that the standard dose of PPI can relieve heartburn in 30%–35% of patients sufficiently and in 25%–30% of patients completely.[10]

In this study, the complete improving rates were 22.5% and 46.2% in Group A and B, respectively ($P = 0.001$). Our improving rates in this study were similar to the average rate of previous studies. The proximal extension of burning pain sensation was significantly better in Group B ($P = 0.033$).

Interrupted sleep does not directly induce GERD symptoms. However, it can cause visceral hyperalgesia and consequently high sensitivity in the mucosa of the esophagus in response to acid.[24] In our study, nocturnal heartburn and sleep disruption were significantly improved in Group B ($P = 0.023$).

In general, using anti-depression drugs to improving the GERD manifestations are controversial.

The first view is that both depression and anti-depressant medications could worsen the symptoms of GERD. It has been proved that using anti-depressant for reasons except depression would increase the symptoms of GERD. The patients with depression without anti-depressant consumption showed less GERD symptoms in comparison to those who were using anti-depressant medication. It seems that using anti-depressants might have a negative impact on the symptoms of patients with GERD.[8] The tricyclic antidepressants with anticholinergic effects can reduce LES tone, delay in gastric emptying, lower esophageal peristalsis, reduce in salivation, and esophageal clearance and finally lead to worsening the GERD manifestations.[19]

The second view is that depression and using anti-depressant might have a positive impact on the symptoms of patients with GERD. The anti-depressant can modulate the esophageal hypersensitivity.[25]

While the SSRIs, can modulate the esophageal hypersensitivity by lowering chemical sensitivity and improve GERD symptom.[18] Duloxetine inhibits both serotonin and norepinephrine transporter with different proportions between their effects on the two-neurotransmitter systems.[26] The results of our study were the same to this study with the positive impact on heartburn and the esophageal hypersensitivity by adding of duloxetine 30 mg to PPI regimen.

We had some limitations in this study: First of all, the sample size is small. Second, the majority of data were qualitative and descriptive, that depends on how the patients can remind them. Third, our results can be interpreted about heartburn and regurgitation symptoms that might be a presentation of

a wide range of esophageal disorders including ERD, NERD, hypersensitivity in the esophagus, and functional esophageal disorders. A good patient/physician relationship and tight following of symptom and psychosocial improvement in GERD patients were the strength of this study.

As a suggestion, further study with a large sample size and a definite diagnosis of underlying esophageal disorders should be considered. As well as, sleep apnea is associated with GERD. More studies may demonstrate the effect for this medication in GERD-associated sleep apnea.

CONCLUSION

We found that the combination of duloxetine and lansoprazole is a safe and tolerable regimen and it can significantly improve anxiety, heartburn, coffee consumption amusement, the quality of sleep, and life in patients who suffer from the symptoms of GERD.

Acknowledgments

The authors sincerely appreciate of all From Rasoul-e-Akram Hospital's medical records department, we provided patients' files and information. Our study was approved in the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC1396.9311160007).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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