O R I G I N A L   A R T I C L E

A preliminary report on the use of Midodrine in treating refractory gastroesophageal disease: Randomized Double-Blind Controlled Trial

Kamran Bagheri Lankarani[1], Gholam Reza Sivandzadeh[2]*, Marziyeh Zare[1], Mohammadali Nejati[2], Ramin Niknam[2], Ali Reza Taghavi[2], Fardad Ejtehadi[2], Mahvash Alizade Naini[2], Maryam Moini[2], Mohammad Hossein Anbardar[2], Payam Peymani[1]*

[1] Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Fars, Iran; [2] Department of Internal Medicine, Gastroenterohepatology Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Fars, Iran

Summary. *Background:* Gastroesophageal reflux disease (GERD) is a common disease with various clinical presentations. Acid suppression with proton pump inhibitors and lifestyle modification may not lead to satisfactory response in a substantial portion of patients. We investigated the possible effect of midodrine in patients with refractory GERD. *Methods:* Patients suffering from GERD and were refractory to one-month course of pantoprazole 40mg twice daily entered the study. This was a pilot, randomized, double-blind, and placebo-controlled study. After randomization, one group received Midodrine 5mg before meals for one month, and the other group received placebo for the same period. Meanwhile, pantoprazole was continued 40mg twice daily in both arms. The severity of symptoms was evaluated by the visual scoring system. Quality of life (QoL) in both groups was measured using a standardized version of Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD). *Results:* A total of twenty patients were enrolled in this study. There was a significant interaction between the groups and time on all measured scores based on QOLRAD questionnaire. All the markers in the Midodrine group had significant improvement over time, but the placebo group did not show any significant improvement. Both visual severity score and total QoL score in Midodrine arm showed a U shape change during 6 weeks. *Conclusions:* Midodrine before a meal could be useful in alleviating symptoms and improving QoL in the patients with refractory gastroesophageal disease. (www.actabiomedica.it)

Key words: gastroesophageal reflux, Midodrine-Hydrochloride, proton pump inhibitor

Introduction

Gastroesophageal reflux disease (GERD) is common with a variety of clinical presentations, imposing a considerable economic burden on patients and healthcare systems. Pathologic GERD occurs when reflux of stomach contents leads to heartburn, regurgitation, and/or complications due to chronic mucosal injury (1). Quality of life (QoL) of 40% of the population may be affected by this condition (2-5).

Despite good response to lifestyle modification and acid suppression with proton pump inhibitors (PPIs) in the majority of patients, there are still group of patients who are refractory to these measures. It is estimated that about 10-40% of patients do not show a satisfactory response to PPI. In addition to inad-

---

* Gholam Reza Sivandzadeh and Payam Peymani are co-Corresponding authors and have contributed equally to this work

equate dosing or improper timing of PPIs, there are other causes of refractory GERD including non-acid reflux, hypersensitivity, and eosinophilic esophagitis. The clinical definition of refractory GERD is controversial in the literature. Most experts consider refractory GERD in those who fail to show improvement in their symptoms, either partially or entirely, with PPIs twice daily (6-13).

The main pathogenesis of classical GERD, as well as refractory cases, are considered to be increased transient lower esophageal relaxations. A variety of medications might reduce this event including baclofen, lesogaberan, or acotiamide through various mechanisms (14-17).

These drugs have either significant side effects or in many cases, are not affordable. Midodrine is an alpha-1 adrenergic agonist with an excellent safety profile. Since alpha-adrenergic receptor stimulation causes lower esophageal sphincter contraction in physiologic studies, midodrine could theoretically reduce reflux episodes. For the first time, in this study, we investigated the possible effect of midodrine in managing patients with refractory GERD.

Patients and Methods

Patients

Patients who presumed to have refractory GERD referred to a special clinic affiliated to Shiraz University of Medical Sciences in 2015-2017. Before entering the study, all cases were given one-month course of pantoprazole 40 mg (ACTOVERCO Pharmaceutical Factory, Karaj-Iran under license of KRKA Company, Slovenia) twice daily. Those who completed this course of medication and their symptom failed to improve were considered for this study. Patients with the following criteria were deemed to be eligible: age 18-65 years, having had at least one symptom consistent with GERD (such as retrosternal burn or regurgitation), and lack of response to pantoprazole 40 mg twice daily for one-month. Exclusion criteria included prior abdominal surgery, dysphagia, significant co-morbid illnesses that could interfere with the study or compromise patients' safety such as malignancy, peptic ulcer disease, hypertension(HTN), urinary retention, heart disease, vascular insufficiency, renal failure, pheochromocytoma, severe respiratory disorders, cirrhosis, hypersensitivity to midodrine, use of other medications affecting LES pressure or relaxation (including beta- blockers, steroids, theophylline, inhalers, antihistamines), any mental or psychiatric illness, pregnancy or breastfeeding in women, and consuming alcohol. Twenty patients were included in this study based on the inclusion criteria. All the patients signed a written informed consent before entering the study.

The histologic diagnosis of GERD is based on papers written in the early days of endoscopic biopsies, and the criteria described are still in use today. The typical features of GERD are increased thickness of the basal cell layer (thickness of the basal layer exceeds 15%); increased length of the papillae with suprapapillary thinning (extension above the midportion of the squamous mucosa); intraepithelial inflammation, including eosinophils, neutrophils and lymphocytes; and intercellular edema (spongiosis) (18, 19). The endoscopic diagnosis of GERD is based on erosive picture and experts seen erosion for all cases and just the patients with typical symptoms alone were included.

Study design

This was a pilot, randomized, double-blind, and placebo-controlled study (20, 21). The study was approved by the local Ethics Committee of Shiraz University of Medical Sciences, code number CT-P-92-6683. The study design and protocol was approved by the Iranian Clinical Trial Registry (IRCT) with identification # IRCT201402274226N2.

All twenty qualified patients underwent upper endoscopy at the beginning and biopsy was taken from the distal and mid part of esophagus following standard protocols. The participants were randomized using a computer-generated scheme into two groups with 10 cases each. All cases completed the study period. Both arms of the study were given pantoprazole 40mg twice daily. One group received 5mg midodrine tablets (Takeda pharmaceutical company, Linz-Austria, purchased from local market) three times per day before meals, and the other group was given a placebo with similar shape, packaging, and instruction for consumption for

four weeks. After completing the treatment course, all cases were followed for another two weeks while continuing to consume pantoprazole 40mg twice per day. All the participants were asked to complete a visual score of their symptoms severity from 1 to 10 (with higher scores indicating higher severity) at the onset of study (before drugs consumption), and at weeks 2, 4, and 6 (two weeks after drug cessation), successively.

Furthermore, all the patient filled out the verified and standardized Persian version of QoL in Reflux and Dyspepsia (QOLRAD) questionnaire at the beginning of the study (22), visits on weeks 2, 4, and 6, successively. This questionnaire assesses five different dimensions in GERD including emotional distress, sleep disturbance, food problems, physical/social functioning, and vitality. Each question scores from 1 to 7. score one shows low QoL, and a higher score indicates a better QoL. During all visits, blood pressure was measured. All women in childbearing age had a serum HCG test before being enrolled into the study and were asked to practice some forms of contraception during their participation.

Statistical analysis

All statistical analyses were done using statistical package for social sciences (SPSS) version 25. The repeated measure analysis of variance (RM-ANOVA) was employed to compare the changes during time between the groups. Within and between groups comparisons were done through the paired *t*-test and independent *t*-test. Chi-square test and Fisher exact test were used to compare qualitative variables between the groups. Qualitative and quantitative variables were described using frequency (percent) and mean ± standard deviation (SD). *P*-value less than 0.05 was considered to be statistically significant. Overall observed power (partial eta-squared as effect size), through a multivariate test, was 99% (0.33) for time, 68% (0.64) for group, and 98% (0.25) for time*group (supplement 1).

Results

Figure1 shows the trial profile and patient flowchart, based on the CONSORT-statement (http://

www.consort-statement.org) guideline. A total of 20 patients were screened and divided into two groups of patients with refractory GERD. The mean age in the midodrine group (36.30 ± 11.44) and placebo group (37.50 ± 10.30) were not significantly different (P = 0.808). The mean duration of GERD symptoms was not significantly different between the groups (midodrine: 49.10 ± 46.90, Placebo: 50.80 ± 74.27 months; P = 0.952). Also, BMI, gender, ethnicity, smoking status, sign and symptom, endoscopic and pathologic findings were the same in either arm of the study. The demographic and clinical information of both groups are shown in Table 1.

Table 2 shows the detailed comparison of the measured scores between the groups over the time. Repeated measure ANOVA showed that there was a significant interaction effect between the group and time on all of the measured scores (Table 2). Although all the markers in the midodrine group had significant changes over the time, the placebo group did not show any significant changes. These changes with related confidence interval in each time point are shown in Figure 2. Visual severity score in midodrine shows a U shape change during the time. It had a significant decrease in week 2 (P = 0.001) and week 4 (P = 0.001) compared with the baseline and a significant increase in week 6 (P = 0.05). Emotional score, sleep score, food score, physical score, vitality score, and total QoL in Midodrine group showed an inverse U shape changes during the time. All of them had a significant increase in week 2 and week 4 compared with the baseline and a significant decrease in week 6.

In week 2, visual severity score in midodrine group had higher mean than placebo group (P = 0.004); and emotional score (P = 0.020), food score (P = 0.045), vitality score (P = 0.010), and total QoL (P = 0.040) in midodrine group had significantly higher mean than placebo group. In week 4, the same pattern in differences between the groups remained statistically significant only for visual severity score (P = 0.002), Emotional score (P = 0.049), and Vitality score (P = 0.028). There were not any significant differences between the groups in week 6. No significant adverse effect/change in blood pressure was observed in either case or control groups.
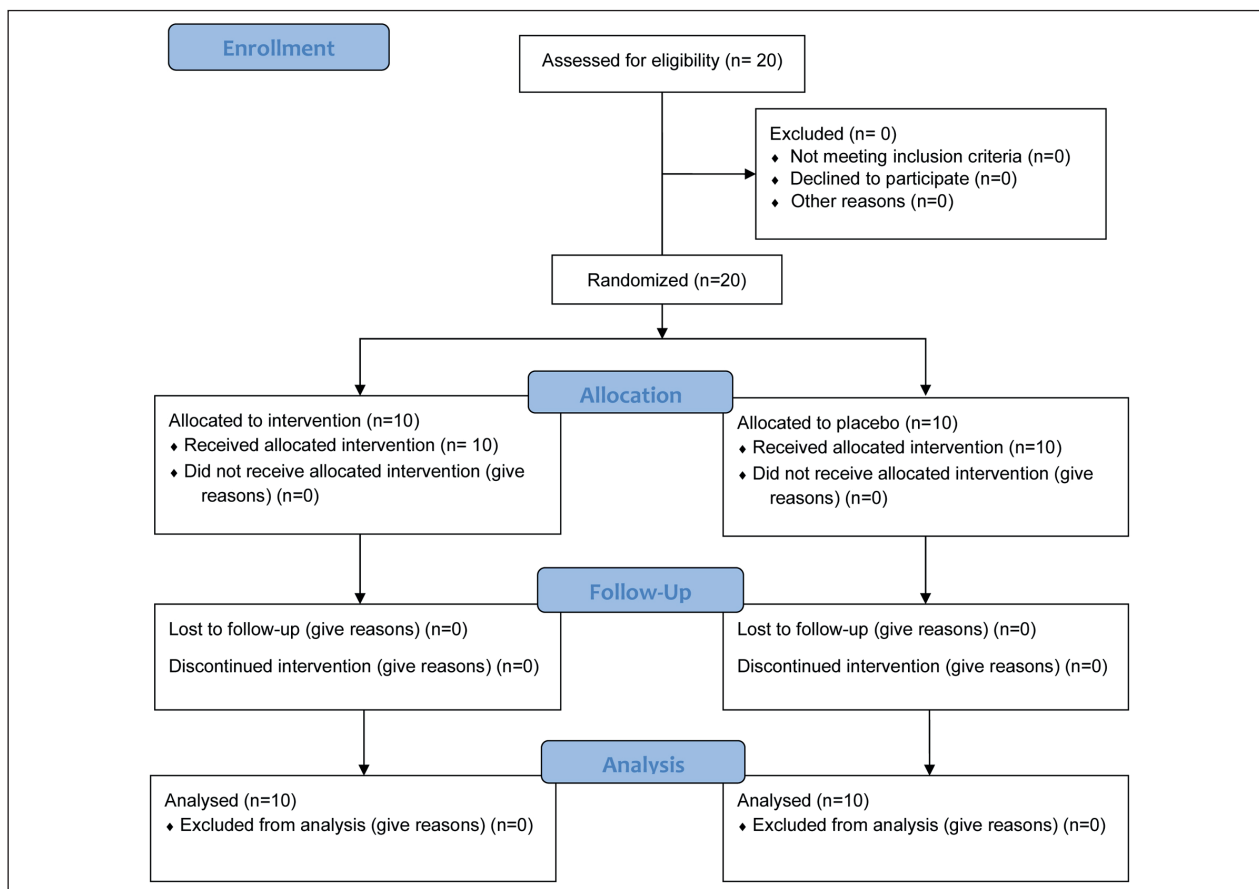
Figure 1. CONSORT Flow Diagram

Table 1. Demographic and clinical information of patients in midodrine and placebo groups

		Midordine	Placebo	P-value
Age		36.30±11.44	37.50±10.30	0.808
BMI		24.46±3.62	24.34±4.31	0.946
Duration of disease		49.10±46.90	50.80±74.27	0.952
Gender	Female	5(50)	6(60)	0.999
	Male	5(50)	4(40)	
Ethnicity	White	9(90)	10(100)	0.999
	Black	1(10)	0(0)	
Ex-Smoker	Yes	1(10)	1(10)	0.999
	No	9(90)	9(90)	
Gesture at symptom	Upright	2(20)	4(40)	0.536
	Supine	5(50)	2(20)	
	Both	3(30)	4(40)	
Endoscopic findings	Normal	5(50)	6(60)	0.999
	GERD	5(50)	4(40)	
Pathologic finding	Reflux esophagitis	8(80)	6(60)	0.628
	Reflux and Hpylori	2(20)	4(40)	

Table 2. Comparison of the measured scores according to QOLRAD[1] questionnaire between the groups over the study time

		Baseline	Week 2	Week 4	Week 6	P_{Time}	P_{Group}	$P_{Time*Group}$
Visual severity score	Midodrine	7.60±1.71a	4.70±2.58a	3.90±2.46a	6.60±2.11a	**0.001**	**0.011**	**0.001**
	Placebo	8.60±1.77	8.20±2.14	8.00±2.62	8.30±2.21			
	P	0.216	**0.004**	**0.002**	0.096			
Emotional score	Midodrine	19.90±7.89ab	27.80±9.50ac	27.20±9.50bd	20.10±8.53cd	**0.001**	0.138	**0.005**
	Placebo	17.11±8.76	18.44±6.65	18.44±8.32	18.33±9.27			
	P	0.482	**0.020**	**0.049**	0.671			
Sleep score	Midodrine	21.00±6.54ab	25.80±8.89ac	26.20±7.37bd	21.70±5.90cd	**0.003**	0.202	**0.007**
	Placebo	19.66±8.67	19.22±5.80	19.66±8.45	18.77±7.71			
	P	0.579	0.052	0.090	0.364			
Food score	Midodrine	19.60±8.11ab	27.40±9.14ac	26.20±8.70bd	19.00±8.31cd	**0.001**	0.442	**0.001**
	Placebo	20.55±7.89	20.11±5.96	21.00±7.82	19.55±7.65			
	P	0.821	**0.045**	0.191	0.882			
Physical score	Midodrine	21.00±6.35ab	26.50±8.56ac	27.20±8.23bd	20.80±7.91cd	**0.001**	0.696	**0.001**
	Placebo	23.77±5.56	22.66±5.72	22.88±6.11	21.33±6.18			
	P	0.281	0.254	0.217	0.873			
Vitality score	Midodrine	10.00±3.52ab	14.70±4.39ac	15.60±4.59bd	9.80±4.04cd	**0.001**	0.159	**0.002**
	Placebo	10.00±4.35	9.88±3.62	10.44±4.74	9.44±4.36			
	P	0.823	**0.01**	**0.028**	0.856			
Total quality of life score	Midodrine	91.50±30.22ab	122.30±39.67ac	122.40±36.93bd	91.40±32.18cd	**0.001**	0.266	**0.001**
	Placebo	91.22±32.01	90.33±25.38	92.44±32.65	87.44±33.02			
	P	0.936	**0.040**	0.080	0.795			

Within rows, the same lower letter indicates the significant difference between two time periods
[1] QOLRAD: Quality of Life in Reflux and Dyspepsia questionnaire

Discussion

Gastroesophageal reflux disease (GERD) is a prevalent disease, which can adversely affect several aspects of patients' lives including their productivity at work (23).

Although proton pump inhibitors (PPIs) are the mainstay in GERD medical management, around one third of these patients do not respond to PPIs once daily. Significant proportion of these patients show improvement in their symptoms after increasing the standard dose of PPIs twice (BID) daily. As a result, the use of PPIs in BID dosages is a common practice and standard of care in GERD patients who stay refractory to PPIs once daily. In this investigation, we studied this group of patients with refractory GERD who remained symptomatic despite being treated with PPI BID (8, 24-28).

Although gastric acid is the principal noxious agent in GERD, increased episodes of transient lower esophageal relaxations (TLESRs) has been considered as one of the major pathogenetic factors in GERD. TLESR occurs as a physiologic response to gastric distension through vagal stimulation in healthy individuals. Increased episodes of TLESRs accounts for 65% of reflux episodes. Based on these findings TLESR has been considered as an attractive target for treating GERD. Gamma-aminobutyric acid (GABA) receptor type B agonist such as baclofen and lesogaberan have been shown to reduce TLESRs and decrease acid reflux episodes and increase LES pressure in several clinical trials. These drugs have major side effects including somnolence, fatigue, and dizziness, which some patients cannot tolerate (14, 15, 29-40). Acotiamide has been recently introduced as an option for treating refractory GERD, which reduces TLESRs and enhances
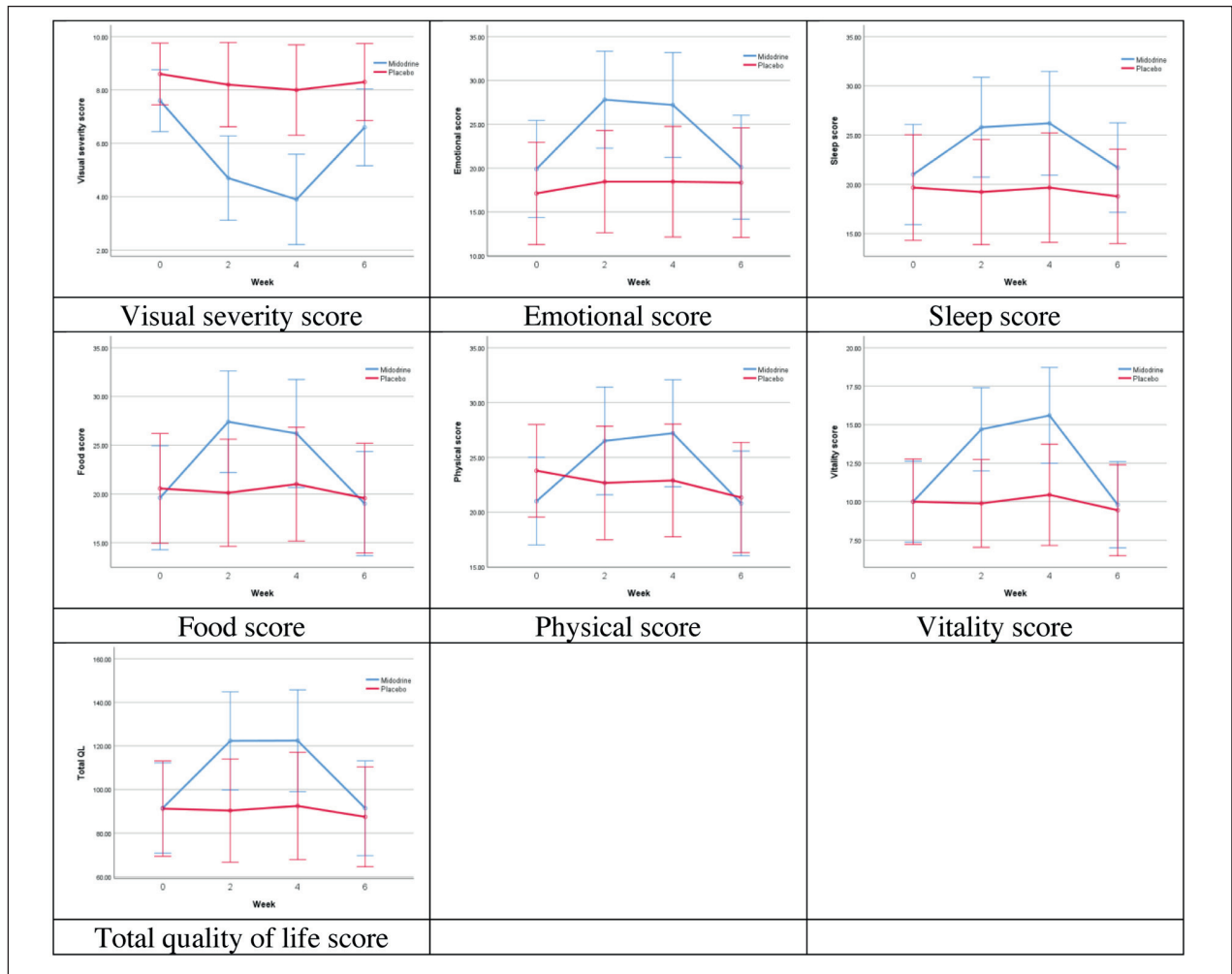
Figure 2. Comparison of the measured scores according to Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD) questionnaire between the groups over the study time

esophageal motility. However, its efficacy in improving symptom of refractory GERD remains to be elusive (16). Midodrine, an alpha-1 adrenergic agonist, in clinical practice is mainly used to treat orthostatic hypotension and hepatorenal syndrome. It is metabolized to its active metabolite, desglymidodrine, with peak blood levels reaching within 30-60 minutes after oral intake. The drug has good oral bioavailability and safe side effect profile (41, 42). In this double-blind, randomized controlled study on patients with refractory GERD midodrine 5mg 30 minutes before meal significantly improved symptom severity based on visual scorings. The beneficial effect increased during treatment for four weeks, but was aborted two weeks after discontin-

uation of treatment. Through QOLGAD, the standardized and validated questionnaire for measuring the QoL in patients suffering from GERD, we were able to show a significant improvement in both overall QoL score and all other aspects after midodrine usage. As with severity score, changes in QOLGAD parameters had a time pattern. The scores improved in the second and fourth week while being on midodrine and then decreased to baseline two weeks after discontinuation of midodrine. No adverse event was reported. For the first time in this study, we showed that midodrine could be useful in managing refractory GERD.

Maybe, some patients suffering from functional heartburn rather than acid-based reflux. But at this

group, midodrine had efficacy and in this group, they also benefit from taking medication. Finally, Even in this group using midodrine is better in compare to use Common treatment such as anti-depressant.

This study used rigorous inclusion criteria to avoid the effect of confounders. Since this is a pilot study, it has several limitations. Small sample size (supplement 1) and lack of pH-metric and impedance results are amongst the major weaknesses of our study. However, this is the first study on the effect of midodrine in refractory GERD patients and in future studies these limitations should be acknowledged.

In conclusion, midodrine before a meal could be effective in alleviating symptoms and improving QoL in patients with refractory GERD. We recommend larger trials with adequate sample size; in addition to pH-metric and impedance to unravel the probable midodrine mechanism of action.

Key Points

- A proportion of patients with gastroesophageal disease are refractory to potent anti-acid agents including proton pump inhibitors. This study evaluated the role of midodrine in the management of refractory patients.
- Use of midodrine lead to significant improvement in both severity of symptoms and quality of life of refractory reflux patients.
- Midodrine could be an upcoming safe medication in the management of reflux disease in refractory patient.

Acknowledgements

References

1. Lankarani KB, Akbari M, Tabrizi R. Association of Gastrointestinal Functional Disorders and Migraine Headache: a Population Base Study. Middle East journal of digestive diseases. 2017;9(3):139.

2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. The American journal of gastroenterology. 2006;101(8):1900-20; quiz 43. Epub 2006/08/25.

3. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005;54(5):710-7. Epub 2005/04/16.

4. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. Journal of neurogastroenterology and motility. 2011;17(1):14-27. Epub 2011/03/04.

5. Delavari A, Moradi G, Birjandi F, et al. The Prevalence of Gastroesophageal Reflux Disease (GERD) in the Islamic Republic of Iran: A Systematic Review. Middle East journal of digestive diseases. 2012;4(1):5-15. Epub 2012/01/01.

6. Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. Gastroenterology report. 2015;3(1):41-53. Epub 2014/10/03.

7. Moraes-Filho JP. Refractory gastroesophageal reflux disease. Arquivos de gastroenterologia. 2012;49(4):296-301. Epub 2013/01/19.

8. Fass R, Gasiorowska A. Refractory GERD: what is it? Current gastroenterology reports. 2008;10(3):252-7. Epub 2008/07/16.

9. Mermelstein J, Chait Mermelstein A, Chait MM. Proton pump inhibitor-refractory gastroesophageal reflux disease: challenges and solutions. Clinical and experimental gastroenterology. 2018;11:119-34. Epub 2018/04/03.

10. Hillman L, Yadlapati R, Whitsett M, et al. Review of antireflux procedures for proton pump inhibitor nonresponsive gastroesophageal reflux disease. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 2017;30(9):1-14. Epub 2017/09/02.

11. Foroutan M, Norouzi A, Molaei M, et al. Eosinophilic esophagitis in patients with refractory gastroesophageal reflux

disease. Digestive diseases and sciences. 2010;55(1):28-31. Epub 2009/02/26.

12. Sa CC, Kishi HS, Silva-Werneck AL, et al. Eosinophilic esophagitis in patients with typical gastroesophageal reflux disease symptoms refractory to proton pump inhibitor. Clinics (Sao Paulo, Brazil). 2011;66(4):557-61. Epub 2011/06/10.

13. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. Best practice & research Clinical gastroenterology. 2010;24(6):923-36.

14. Zhang Q, Lehmann A, Rigda R, et al. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. Gut. 2002;50(1):19-24. Epub 2002/01/05.

15. Boeckxstaens GE, Rydholm H, Lei A, et al. Effect of lesogaberan, a novel GABA(B)-receptor agonist, on transient lower oesophageal sphincter relaxations in male subjects. Alimentary pharmacology & therapeutics. 2010;31(11):1208-17.

16. Yamashita H, Kanamori A, Fukuchi T, et al. Novel Prokinetic Acotiamide Reduces Transient Lower Esophageal Sphincter Relaxation in Healthy Subjects. Digestion. 2015;92(2):90-8. Epub 2015/08/19.

17. Fass R. Therapeutic options for refractory gastroesophageal reflux disease. Journal of gastroenterology and hepatology. 2012;27 Suppl 3:3-7.

18. Grin A, Streutker CJ. Esophagitis: old histologic concepts and new thoughts. Archives of Pathology and Laboratory Medicine. 2015;139(6):723-9.

19. Krugmann J, Neumann H, Vieth M, et al. What is the role of endoscopy and oesophageal biopsies in the management of GERD? Best practice & research Clinical gastroenterology. 2013;27(3):373-85.

20. Peymani P, Ghavami S, Yeganeh B, et al. Effect of chloroquine on some clinical and biochemical parameters in non-response chronic hepatitis C virus infection patients: pilot clinical trial. Acta Bio Medica Atenei Parmensis. 2016;87(1):46-53.

21. Peymani P, Yeganeh B, Sabour S, et al. New use of an old drug: chloroquine reduces viral and ALT levels in HCV non-responders (a randomized, triple-blind, placebo-controlled pilot trial). Canadian journal of physiology and pharmacology. 2016;94(6):613-9.

22. Tofangchiha S, Razjouyan H, Nasseri-Moghaddam S. Quality of life in reflux and dyspepsia (QOLRAD) questionnaire in Iranian patients with GERD: A validation study. Middle East journal of digestive diseases. 2010;2(2):84.

23. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871-80. Epub 2013/07/16.

24. Dellon ES, Shaheen NJ. Persistent reflux symptoms in the proton pump inhibitor era: the changing face of gastroesophageal reflux disease. Gastroenterology. 2010;139(1):7-13.e3. Epub 2010/05/25.

25. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut. 2012;61(9):1340-54. Epub 2012/06/12.

26. Kahrilas PJ, Keefer L, Pandolfino JE. Patients with refractory reflux symptoms: What do they have and how should they be managed? Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2015;27(9):1195-201. Epub 2015/08/26.

27. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. The American journal of gastroenterology. 2005;100(2):283-9. Epub 2005/01/26.

28. Bajbouj M, Becker V, Phillip V, et al. High-dose esomeprazole for treatment of symptomatic refractory gastroesophageal reflux disease--a prospective pH-metry/impedance-controlled study. Digestion. 2009;80(2):112-8. Epub 2009/07/31.

29. Blondeau K. Treatment of gastro-esophageal reflux disease: the new kids to block. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2010;22(8):836-40.

30. Piche T, Galmiche JP. Pharmacological targets in gastro-oesophageal reflux disease. Basic & clinical pharmacology & toxicology. 2005;97(6):333-41. Epub 2005/12/21.

31. Lehmann A, Jensen JM, Boeckxstaens GE. GABAB Receptor Agonism as a Novel Therapeutic Modality in the Treatment of Gastroesophageal Reflux Disease. 2010;58:287-313.

32. Koek GH, Sifrim D, Lerut T, et al. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut. 2003;52(10):1397-402. Epub 2003/09/13.

33. Galmiche JP, Zerbib F, des Varannes SB. Treatment of GORD: Three decades of progress and disappointments. United European gastroenterology journal. 2013;1(3):140-50. Epub 2014/06/12.

34. Cossentino MJ, Mann K, Armbruster SP, et al. Randomised clinical trial: the effect of baclofen in patients with gastro-oesophageal reflux--a randomised prospective study. Alimentary pharmacology & therapeutics. 2012;35(9):1036-44.

35. Miner PB, Jr., Silberg DG, Ruth M, et al. Dose-dependent effects of lesogaberan on reflux measures in patients with refractory gastroesophageal reflux disease: a randomized, placebo-controlled study. BMC gastroenterology. 2014;14:188. Epub 2014/11/20.

36. van Herwaarden MA, Samsom M, Rydholm H, et al. The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. Alimentary pharmacology & therapeutics. 2002;16(9):1655-62. Epub 2002/08/29.

37. Cange L, Johnsson E, Rydholm H, et al. Baclofen-mediated gastro-oesophageal acid reflux control in patients with established reflux disease. Alimentary pharmacology & therapeutics. 2002;16(5):869-73. Epub 2002/04/23.

38. Vela MF, Tutuian R, Katz PO, et al. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux

measured by combined multichannel intraluminal imped-
ance and pH. Alimentary Pharmacology and Therapeutics.
2003;17(2):243-51.

39. Grossi L, Spezzaferro M, Sacco LF, et al. Effect of baclofen
on oesophageal motility and transient lower oesophageal
sphincter relaxations in GORD patients: a 48-h manomet-
ric study. Neurogastroenterology and motility : the official
journal of the European Gastrointestinal Motility Society.
2008;20(7):760-6.

40. Sharma N, Anderson SHC. The relevance of transient
lower oesophageal sphincter relaxations in the pathophysi-
ology and treatment of GORD. Frontline gastroenterology.
2013;4(3):171-4. Epub 2013/07/01.

41. Anstey MH, Wibrow B, Thevathasan T, et al. Midodrine
as adjunctive support for treatment of refractory hypoten-
sion in the intensive care unit: a multicenter, randomized,
placebo controlled trial (the MIDAS trial). 2017;17(1):47.

42. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus
albumin versus midodrine and octreotide plus albumin in
the treatment of hepatorenal syndrome: A randomized trial.
Hepatology (Baltimore, Md). 2015;62(2):567-74. Epub
2015/02/04.