Pediatric Gastroenterology, Hepatology & Nutrition

pghn

Original Article

Check for updates

Is the Diagnostic Trial with Proton Pump Inhibitors Reasonable for School Age Children with Gastroesophageal Reflux Symptoms?

Jaeeun Yang ⓘD, **Jieon Lee** ⓘD, **Hyunju Lee** ⓘD, **Juyeon Lee** ⓘD, **Young Mi Yoon** ⓘD, **Jae Hong Choi** ⓘD, **Yoon-Joo Kim** ⓘD, **Hyun Sik Kang** ⓘD, **Kyoung Hee Han** ⓘD, **Seung Hyo Kim** ⓘD, **and Ki-Soo Kang** ⓘD

Department of Pediatrics, Jeju National University School of Medicine, Jeju, Korea

OPEN ACCESS

ORCID iDs
Jaeeun Yang ⓘD
https://orcid.org/0000-0002-6765-4071
Jieon Lee ⓘD
https://orcid.org/0000-0002-8051-302X
Hyunju Lee ⓘD
https://orcid.org/0000-0003-0457-635X
Juyeon Lee ⓘD
https://orcid.org/0000-0003-4172-2766
Young Mi Yoon ⓘD
https://orcid.org/0000-0003-3819-8668
Jae Hong Choi ⓘD
https://orcid.org/0000-0003-3284-9407
Yoon-Joo Kim ⓘD
https://orcid.org/0000-0002-2832-036X
Hyun Sik Kang ⓘD
https://orcid.org/0000-0002-7495-7871

ABSTRACT

Purpose: On the basis of evidence, we aimed to reevaluate the necessity of the empirical proton pump inhibitor (PPI) trial for children with suspected gastroesophageal reflux disease (GERD).
Methods: We analyzed the frequency of GERD in 85 school-age children with gastroesophageal reflux (GER) symptoms, who received 24-hour esophageal pH monitoring and/or upper endoscopy. According to the reflux index (RI), the children were classified into normal (RI <5%), intermediate (5%≤ RI <10%), or abnormal (RI ≥10%) groups.
Results: Fifty six were female and 29 were male. Their mean age was 12.6±0.5 (±standard deviation) years (range: 6.8–18.6). The RI analysis showed that the normal group included 76 patients (89.4%), the intermediate group included 6 patients (7.1%), and the abnormal group included 3 patients (3.5%). The DeMeester score was 5.93±4.65, 14.68±7.86 and 40.37±12.96 for the normal, intermediate and abnormal group, respectively (p=0.001). The longest reflux time was 5.56±6.00 minutes, 9.53±7.84 minutes, and 19.46±8.35 minutes in the normal, intermediate, and abnormal group, respectively (p=0.031). Endoscopic findings showed reflux esophagitis in 7 patients. On the basis of the Los Angeles Classification of Esophagitis, 5 of these patients were included in group A, 1 patient, in group B and 1 patient, in group C.
Conclusion: The incidence of GERD was very low in school-age children with GER symptoms. Therefore, injudicious diagnostic PPI trials would be postponed until the actual prevalence of GERD is verified in future prospective studies.

Keywords: Gastroesophageal reflux; Proton pump inhibitor; Child; Empirical

INTRODUCTION

Recently, a new pediatric gastroesophageal reflux (GER) clinical practice guideline recommended an empirical trial with proton pump inhibitors (PPI) as a diagnostic approach in children with GER symptoms [1]. The guideline was a joint recommendation by the North American Society of Pediatric Gastroenterology and the European Society for Paediatric Gastroenterology Hepatology and Nutrition. The inclusion of a PPI trial is an important difference from the organizations' 2009 version [2]. The new guideline is also similar to an

Kyoung Hee Han (iD)
https://orcid.org/0000-0002-6830-7311
Seung Hyo Kim (iD)
https://orcid.org/0000-0001-7277-3748
Ki-Soo Kang (iD)
https://orcid.org/0000-0001-6374-8356

Conflict of Interest
The authors have no financial conflicts of interest.

older recommendation for the diagnosis of gastroesophageal reflux disease (GERD) in adults with GER symptoms [3]. The PPI trial for adults had a moderate sensitivity to GERD ranging from 78 to 83% [4,5]; however, the new guideline for children had fewer reference studies, and the grade of recommendation was weak because of the lower strength of the evidence [1].

Although the new guideline suggests PPI trials in children with suspected GERD in whom diet and lifestyle modification had failed [1], it can result in the abuse of PPIs [6]. In Belgian children, the prescribed volume of PPIs increased from 3,472 daily doses per month in January 1997 to 103,926 daily doses per month in June 2009 [7]. Although PPI use had not been definitely correlated with adverse effects, it can cause various side effects and complications [6,8].

The authors found a very low prevalence of GERD in children with GER symptoms who had visited a pediatric gastroenterology center and tried to analyze the actual prevalence in a pediatric gastroenterology motility center. On the basis of the evidence obtained from this study, we question whether PPI trials are justified for the diagnosis of GERD in school-age children with GER symptoms without other underlying diseases.

MATERIALS AND METHODS

Inclusion and exclusion criteria

We retrospectively enrolled 104 children who had GER symptoms and who were tested using ambulatory 24-hour esophageal pH monitoring (Orion II; Medical Measurement System, Enschede, Netherlands) and/or upper endoscopy at Jeju National University Hospital, South Korea, between September 2006 and June 2018. GER symptoms included vomiting, nausea, regurgitation, dyspepsia, chest discomfort, and chronic cough. Dyspepsia was defined as a symptom complex that included nausea, vomiting, regurgitation, epigastric bloating or epigastric pain, and chest discomfort. We could not define the typical GERD symptoms in the school-age children. Patients with underlying diseases, such as cerebral palsy, and younger children (infants, toddlers, and preschool age children attending kindergarten) were excluded. Ultimately, 85 school-age children were included in this study. Most of these children had already undertaken management with lifestyle change and dietary education in the primary or secondary medical organization.

Demographic data collection

Clinical data collected included demographic information, GER symptoms, endoscopic findings, and the results of the ambulatory 24-hour esophageal pH monitoring. Grading reflux esophagitis by endoscopy was based on the Los Angeles Classification of Esophagitis [9]. Most patients began esophageal pH monitoring in the late afternoon following their morning endoscopy. The pH probe was placed at a level 3 vertebrae above the diaphragm. Reflux index (RI), DeMeester score, and the duration of the longest reflux were included as pH monitoring parameters. Other parameters including symptom index, symptom sensitivity index, and symptom association probability were not included. These are parameters that show the coincidence or relationship between symptoms and reflux episodes on the machine. The RI was defined as the percentage of time with pHs below 4.0 over the course of the entire monitoring [10]. According to the RI, patients were classified into the three groups: normal (RI <5%), intermediate (5%≤ RI <10%), and abnormal (RI ≥10%) [11]. The DeMeester score is a complex scoring system and consists of: (1) the total number of reflux episodes, (2) the %

Table 1. Demographic and clinical characteristics of 85 school-age children with GER symptoms and without other underlying diseases according to the reflux index (RI) during ambulatory 24-hour esophageal pH monitoring

Variable	Reflux index (RI)[*]		
	Normal (RI <5%)	Intermediate (5%≤ RI <10%)	Abnormal (RI ≥10%)
Total patients (n=85)	76 (89.4)	6 (7.1)	3 (3.5)
Sex			
Female	50	5	2
Male	26	1	1
Age (yr)	12.80±2.91	12.26±4.46	12.02±4.83
Duration of symptoms (mo)	7.45±11.07	4.29±4.26	5.00±3.61
Patients with GER symptoms			
Dyspepsia	32	1	2
Vomiting	26	1	2
Nausea	41	3	1
Chest discomfort	41	2	2
Regurgitation	30	2	2
Chronic cough	2	0	0
Endoscopy (n=66)	58	6	2
Reflux esophagitis[†] (n=7)			
Group A/B/C/D 5 (5.8%)/1 (1.2%)/1 (1.2%)/0	3/1/0/0	2/0/0/0	0/0/1/0

Values are presented as number (%), number only, or mean±standard deviation.
GER: gastroesophageal reflux, RI: reflux index.
[*]The percentage of time with pHs below 4.0 over the total monitoring time [10,11]. [†]Los Angeles classifications. Includes Group A defined as one (or more) mucosal breaks with length <5 mm; Group B defined as two and one (or more) mucosal breaks with length >5 mm, Group C defined as fusions of adjacent ulcers and not circumferential, and Group D defined as circumferential ulcers [9].

total time that the esophageal pH was <4, (3) the % upright time that the esophageal pH was <4, (4) the supine time that the esophageal pH was <4, (5) the number of reflux episodes ≥5 minutes, and (6) the longest reflux episode (minutes) [12].

Statistical analysis

This study was a cross-sectional study with a high numeric difference among the three groups (**Table 1**) [9-11]. The Kruskal-Wallis test was used for statistical analyses. A p-value<0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

Among the 85 school-age children with GER symptoms, 57 patients were female and 28 were male, with a mean age of 12.6±0.5 (±standard deviation [SD]) years (range: 6.8–18.6). A few patients who had been taking histamine-2 receptor antagonists or PPIs when they visited our hospital stopped taking the medication at least 7 days before the endoscopy and esophageal pH monitoring. Authors did not performed any diagnostic PPI trial in all patients. The most common GER symtoms were dyspepsia, vomiting, nausea, chest discomfort, and regurgitation. Heartburn was not found in any of the cases (**Table 1**) [9-11].

Reflux index

The RI analysis showed that the normal group (RI <5%) included 76 patients (89.4%), the intermediate group (5%≤ RI <10%) included 6 patients (7.1%), and the abnormal group (RI ≥10%) included 3 patients (3.5%) (**Table 1**) [9-11]. The patients' ages (mean±SD) were 12.80±2.91, 12.26±4.46, and 12.02±4.83 years in the normal, intermediate, and abnormal groups, respectively.

Table 2. DeMeester scores and longest reflux times of 85 children with GER symptoms without other underlying diseases according to reflux indices during ambulatory 24-hour esophageal pH monitoring

Variable	Reflux index (RI)[*]			p-value[†]
	Normal (RI <5%)	Intermediate (5%≤ RI <10%)	Abnormal (RI ≥10%)	
DeMeester score[‡]	5.93±4.65	14.68±7.86	40.37±12.96	0.001
Longest reflux time (min)	5.56±6.00	9.53±7.84	19.46±8.35	0.031

Values are presented as mean±standard deviation.
GER: gastroesophageal reflux, RI: reflux index.
[*]The percentage of time with pHs below 4.0 over the total monitoring time [10,11]. [†]Kruskal-Wallis test. [‡]The parameters that constitute the DeMeester score include: (1) the total number of reflux episodes, (2) the % total time that the esophageal pH was <4, (3) the % upright time that the esophageal pH was <4, (4) the supine time that the esophageal pH was <4, (5) the number of reflux episodes ≥5 minutes, and (6) the longest reflux episode (minutes) [12].

Endoscopic findings

Endoscopy was performed in 66 (77.6%) of the 85 patients. Endoscopic findings showed that reflux esophagitis was detected in 7 patients (8.2%). On the basis of the Los Angeles Classification of Esophagitis, 5 of these patients were included in group A (5.8%), 1 patient, in group B (1.2%) and 1 patient, in group C (1.2%) (**Table 1**) [9-11]. The patient in Los Angeles Group C had been complaining about recurrent rumination after bullying by classmates at his school.

Symtom index, symtom sensitivity index, and symtom association probability

These three parameters could not be analyzed because of the many missed recordings by the patients.

DeMeester score and longest reflux time

The DeMeester score was 5.93±4.65 (mean±SD) for the normal group, 14.68±7.86 for the intermediate group, and 40.37±12.96 for the abnormal group (p=0.001, Kruskal-Wallis test) (**Table 2**) [10-12]. The longest reflux time was 5.56±6.00 minutes (mean±SD) in the normal group, 9.53±7.84 minutes in the intermediate group, and 19.46±8.35 minutes in the abnormal group (p=0.031, Kruskal-Wallis test; **Table 2**) [10-12].

DISCUSSION

This study enrolled school-age children only. We excluded infants, toddlers, and preschool-age children, because endoscopy and esophageal pH monitoring are more invasive in these children than in school-age children. Most patients were transferred to a single tertiary center from a primary or secondary medical organization. Eighty-five school-age children were enrolled for 12 years. This study included only 7 children per year at a single tertiary center. Most of these children had already undertaken management with lifestyle change and dietary education in the primary or secondary medical organization. Most children with functional dyspepsia, which is prevalent and needed to be differentiated from GERD, were excluded as they had no further problems after reassurance or lifestyle change and dietary education. PPI trials can be abused in the management of functional dyspepsia. Esophageal pH monitoring was not performed in most patients with functional dyspepsia. In this study, the prevalence of GERD was low in the strictly selected children with GER symptoms. Thus, we suggest that diagnostic PPI trials must be postponed until the actual prevalence of GERD is verified in future well-designed prospective studies for children with GER symptoms.

This study revealed a very low GERD prevalence (3%) in the abnormal group (or 10% when combining the intermediate and abnormal groups) among school-age children with GER symptoms without other underlying diseases. Most patients were tested using endoscopy and ambulatory 24-hour esophageal pH monitoring. Despite many studies in adults [4,5], there have been no studies regarding the prevalence of GERD in children with GER symptoms without other underlying diseases in pediatric gastrointestinal motility centers. This prevalence is very important evidence to help determine whether PPI trials for the diagnosis of GERD are justified.

When comparing cost with effectiveness, the new guideline for children may be acceptable only in selected cases, such as cases of developed countries, where the costs for tests is extremely high. Patients in the USA spend $3,870 for an upper endoscopy [13], whereas those in Korea spend only $40, and the cost of Bravo 48 hour pH monitoring for patients in the USA is $1,569 [14], whereas in Korea the cost of 24-hour pH monitoring is only $88. Despite the cost-effectiveness issues, PPI abuse can still occur. The diagnostic PPI trial for children with suspected GERD can infrequently cause serious adverse effects and PPI abuse [6,15,16].

DeMeester scores were significantly different between groups in this study (p=0.001) (**Table 2**) [10-12]. The cutoff value for DeMeester scores indicates that GERD has been well defined in adults [17]; however, it has not been well defined in children [18].

In this study, the prevalence of reflux esophagitis by endoscopy (8.2%) was very low in school-age children with GER symptoms without other underlying diseases. In contrast to this study, Yang et al. [19], reported a higher prevalence (37.7%) of reflux esophagitis in Korean children who underwent esophagogastroduodenoscopy for diagnostic reasons. There was no information regarding the distribution of reflux esophagitis grades in that study. In our study, four children showed reflux esophagitis in group A, even though they had a normal RI in the pH monitoring (**Table 1**) [9-11]. This might be overdiagnosis by endoscopy because the reflux esophagitis in group A can be confused with normal findings. Otherwise, this might be underdiagnosis by pH monitoring because the test can restrict the lifestyle and dietary habits of patients.

Endoscopy has a lower sensitivity for the diagnosis of GERD in adults and children, because the test cannot detect non-erosive reflux disease of GERD [1,20,21]. Nonetheless, 24-hour esophageal pH monitoring is the gold standard for establishing the presence of pathologic acid reflux even though the absolute cutoff value of acid reflux had not been completely defined in children with the exception of infants [11,22].

In children, typical GERD symptoms are difficult to differentiate from other symptoms even at the tertiary center. Heartburn was not detected in the children with GER symptoms in this study. The PPI trial for 4–8 weeks can cause PPI abuse and delayed diagnosis. According to the guideline, PPI trials can be abused in primary and secondary medical organizations. In adults, PPI trials can be acceptable for patients with GERD symptoms because of easy recognition of GERD symptoms and the prevalence of true GERD of >80% in the esophageal pH monitoring in these patients. The new guideline did not provide evidence of the effectiveness of PPI trials because of the absence of reports on the prevalence of true GERD in children with GER symptoms. The guideline does not indicate whether the recommendation of PPI trial without evidence was based on the issue of safety or extremely high costs of endoscopy and esophageal pH monitoring. In view of the safety during endoscopy, infants

and preschool-age children were excluded in this study. Even in childen with GER sypmtoms that are unresponsive to lifestyle change and dietary education, accurate diagnosis could be preferred to PPI trial.

This study has a few limitations as a retrospective and single-center study. First, the definition of RI might be incomplete, because the absolute cutoff value of acid reflux for esophageal pH monitoring had not been reported in children [1,10]. However, the prevalence in both the intermediate and abnormal acid reflux groups was very low, and an underdiagnosis of GERD might not occur. Second, the rate of diagnosis of GERD by esophageal pH monitoring might decrease as the test can be uncomfortable and restrict the patients' usual lifestyle. Third, other parameters such as symptom index, symptom sensitivity index, and symptomassociation probability could not be analyzed because of the many missed recordings by the patients, which is a general problem when studying GERD in children [1,2], in contrast to studying GERD in adults [23]. Fourth, as impedance monitoring was not performed in this study, we could not analyze weak acid and alkali refluxes in the patients.

In conclusion, the real prevalence of GERD in school-age children with GER symptoms might be low. This study has a limitation due to its retrospective nature. To avoid PPI abuse, diagnostic PPI trials must be postponed until the actual prevalence of GERD is verified in future well-designed prospective studies for children with GER symptoms.

REFERENCES

1. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the north american society for pediatric gastroenterology, hepatology, and nutrition and the european society for pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr 2018;63:516-54.
   PUBMED | CROSSREF

2. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al.; North American Society for Pediatric Gastroenterology Hepatology and Nutrition; European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498-547.
   PUBMED

3. Fass R. Empirical trials in treatment of gastroesophageal reflux disease. Dig Dis 2000;18:20-6.
   PUBMED | CROSSREF

4. Bautista J, Fullerton H, Briseno M, Cui H, Fass R. The effect of an empirical trial of high-dose lansoprazole on symptom response of patients with non-cardiac chest pain--a randomized, double-blind, placebo-controlled, crossover trial. Aliment Pharmacol Ther 2004;19:1123-30.
   PUBMED | CROSSREF

5. Fass R, Fennerty MB, Ofman JJ, Gralnek IM, Johnson C, Camargo E, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. Gastroenterology 1998;115:42-9.
   PUBMED | CROSSREF

6. Stark CM, Nylund CM. Side effects and complications of proton pump inhibitors: a pediatric perspective. J Pediatr 2016;168:16-22.
   PUBMED | CROSSREF

7. De Bruyne P, Christiaens T, Vander Stichele R, Van Winckel M. Changes in prescription patterns of acid-suppressant medications by Belgian pediatricians: analysis of the national database, [1997-2009]. J Pediatr Gastroenterol Nutr 2014;58:220-5.
   PUBMED | CROSSREF

8. Kinoshita Y, Ishimura N, Ishihara S. Advantages and disadvantages of long-term proton pump inhibitor use. J Neurogastroenterol Motil 2018;24:182-96.
   PUBMED | CROSSREF

9. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-80.
   PUBMED | **CROSSREF**

10. Johnsson F, Joelsson B, Isberg PE. Ambulatory 24 hour intraesophageal pH-monitoring in the diagnosis of gastroesophageal reflux disease. Gut 1987;28:1145-50.
    PUBMED | **CROSSREF**

11. Bagucka B, Badriul H, Vandemaele K, Troch E, Vandenplas Y. Normal ranges of continuous pH monitoring in the proximal esophagus. J Pediatr Gastroenterol Nutr 2000;31:244-7.
    PUBMED | **CROSSREF**

12. Neto RML, Herbella FAM, Schlottmann F, Patti MG. Does DeMeester score still define GERD? Dis Esophagus 2019;32:doy118.
    PUBMED | **CROSSREF**

13. MD save. Bravo 48 hour pH monitor [Internet]. San Francisco: MD saves; 2019 [cited 2019 May 7]. Available from: https://www.mdsave.com/procedures/bravo-48-hour-ph-monitor/d784fecc

14. MD save. Upper endoscopy [Internet]. San Francisco: MD saves; 2019 [cited 2019 May 7]. Available from: https://www.mdsave.com/procedures/upper-endoscopy-egd/d782ffc5

15. Benmassaoud A, McDonald EG, Lee TC. Potential harms of proton pump inhibitor therapy: rare adverse effects of commonly used drugs. CMAJ 2016;188:657-62.
    PUBMED | **CROSSREF**

16. Hassall E. Over-prescription of acid-suppressing medications in infants: how it came about, why it's wrong, and what to do about it. J Pediatr 2012;160:193-8.
    PUBMED | **CROSSREF**

17. Streets CG, DeMeester TR. Ambulatory 24-hour esophageal pH monitoring: why, when, and what to do. J Clin Gastroenterol 2003;37:14-22.
    PUBMED | **CROSSREF**

18. Lupu VV, Ignat A, Paduraru G, Ciubara A, Moscalu M, Marginean CO, et al. Correlation between the different pH-metry scores in gastroesophageal reflux disease in children. Medicine (Baltimore) 2016;95:e3804.
    PUBMED | **CROSSREF**

19. Yang A, Kang B, Choe JY, Kim HS, Kim K, Choe YH. Prevalence and epidemiological characteristics of endoscopically proven reflux esophagitis in children in Korea. Pediatr Gastroenterol Hepatol Nutr 2017;20:160-6.
    PUBMED | **CROSSREF**

20. Jung HK, Choi MG, Baek MK, Wu JCY. Development and psychometric assessment of a self-evaluation questionnaire for gastroesophageal reflux disease. J Neurogastroenterol Motil 2018;24:584-92.
    PUBMED | **CROSSREF**

21. Gonzalez Ayerbe JI, Hauser B, Salvatore S, Vandenplas Y. Diagnosis and management of gastroesophageal reflux disease in infants and children: from guidelines to clinical practice. Pediatr Gastroenterol Hepatol Nutr 2019;22:107-21.
    PUBMED | **CROSSREF**

22. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics 1991;88:834-40.
    PUBMED

23. Taghavi SA, Ghasedi M, Saberi-Firoozi M, Alizadeh-Naeeni M, Bagheri-Lankarani K, Kaviani MJ, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. Gut 2005;54:1067-71.
    PUBMED | **CROSSREF**