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Research Article

Clinical and Histopathologic Efficiency of Sucralfate and Ursodeoxicolic Acid in Pediatric Duodenogastric Reflux Disease

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Abstract

Aim: The treatment approach, long-term consequences and surveillance protocols of duodenogastric reflux disease (DGRD) are not well established in the pediatric population. The aim of this study was to evaluate the histopathological and clinical responses to treatment with Ursodeoxicolic Acid (UDCA) and Sucralfate in children diagnosed with DGRD.

Material and Methods: This is a retrospective pre-post design study performed with children admitted to our clinic with reflux symptoms and diagnosed with duodenogastric reflux disease according to endoscopic and histopathologic evaluation. Patients were treated with Sucralfate 60mg/kg/day orally and UDCA at 10 mg/kg/day orally, for 6 months. We compared symptoms/findings, presence of Helicobacter pylori and histopathologic grade of disease before and after treatment.

Results: The presence of all symptoms statistically significantly decreased after treatment. The presence of Helicobacter pylori decreased from 43.8% to 21.9%. There was also statistically significantly histopathologic improvement after six-month treatment of Sucrafate and UDCA.

Conclusion: Six-month treatment of Sucralfate and UDCA provided valuable improvements in clinical and histopathologic features in pediatric patients with DGRD.

Keywords: Duodenogastric reflux disease, sucralfate, ursodeoxycholic acid

INTRODUCTION

While there is a consensus on the definition of GERD, there is limited guidance on the definition of duodenogastric reflux (DGR) and/or duodenogastric reflux disease (DGRD) in children. DGR is described as the reflux of duodenal contents into the stomach and it becomes a pathological entity when it is extreme and lasts for a long time (1). DGR is associated with gastric surgery in adults (2). However, the incidence and etiology in children is not clear. In a study with 1120 children, 92 (8.21%) had bile reflux on endoscopy (3). Primary DGR has not been documented in children and concluded that this was due to difficulties in diagnosis (4).

DGRD is important as the injuries can predispose to gastric ulcers and there is a possibility of malignant transformation (5,6). Gross anatomic and histopathologic changes in DGR are diverse. Gastric mucosa inflammation, ulceration, intestinal metaplasia can be seen (3). In a 2012 study, which investigated the histological features of DGR in children showed lymphatic follicles, intestinal metaplasia, foveolar hyperplasia, interstitial edema, vascular congestion and fibroproliferation (5).

The treatment of DGR is mainly symptomatic in children. There are treatments in children with sucralfate and cisapride (4). Sucralfate adheres to mucosal surface and promote healing and also protect the surface from peptic injury. However, sucralfate is not recommended for treatment of chronic GERD (7). In the past, some studies suggested ursodeoxycholic acid (UDCA) in the treatment of DGR (8,9).

MATERIAL AND METHOD

Study design and setting

The study was carried out in conformity with the Declaration of Helsinki after obtaining the approval of

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This is a retrospective before-after trial, in which we studied the efficiency of the treatment of UDCA and Sucralfate on clinical and histopathological findings of the DGRD in a pediatric population. Medical records of patients who admitted with reflux sign and symptoms between January 2014 and June 2017 who underwent upper GI endoscopy, were scanned. Data was obtained from the electronic medical records of the hospital. The hospital is a tertiary level university hospital with a bed capacity of 983, and has a pediatric gastroenterology clinic which offers diagnostic and treatment services, including pediatric endoscopy and biopsy, with experienced medical staff.

Sample size and patients

We did not estimate a priori minimum sample size, we intended to include all eligible patients according to inclusion and exclusion criteria. Inclusion criteria of the study were: (1) admission to our clinic with reflux signs and symptoms, and (2) undergoing esophagogastroduodenoscopy and being diagnosed with DGRD. We defined diagnosis of DGRD as the presence of bile in stomach in the esophagogastroduodenoscopy. Exclusion criteria of the study were: (1) having gastroenteritis or upper respiratory tract infection at the time of endoscopy, (2) receiving long-term NSAID treatment, (3) having received prior *Helicobacter (H) pylori* eradication therapy, and (4) missing patient data.

Endoscopic evaluation

Upper GI endoscopy was performed in all patients by an 12 year experienced pediatric gastroenterologist using EG-530WR endoscopic equipment (Fujifilm Co., Japan). Patients were fasted for 6 to 8 hours before endoscopy. The patients were sedated initially with 0.1mg/kg of midazolam and 1mg/kg of ketamine intravenously, during procedure, an additional dose of sedation was given as necessary. During endoscopy, esophagus, Z line, cardia, fundus, corpus, antrum, pylorus, bulbus and duodenum were examined, respectively. All patients were assessed for findings of endoscopic gastritis, such as erythema, hyperemia, atrophy, and mucosal nodularity following the criteria of the Houston-updated Sydney system. A minimum two histopathological sampling (one each from the antrum and the duodenum) were performed, and sent for the histopathological examination in Hollande solution.

Histopathologic evaluation

The histopathologic examinations were performed by a 25-year experienced pathologist using a light microscope (Olympus Corp., Tokyo, Japan) with 100X and 200X magnifications. Five-micrometer-thick sections were prepared from all obtained biopsy specimens, and the tissue sections were stained with hematoxylin and eosin and Diff-Quick stain for histopathological examination. Histopathologic evaluation included detection of *H. pylori* and histopathologic findings of inflammation. The biopsies were graded using the Houston-updated Sydney system: normal (Grade 0), mild inflammation (Grade 1), moderate inflammation (Grade 2), and severe inflammation (Grade 3).

Treatment and follow-up

All the patients were treated with sucralfate 60mg/kg/day (suspension or tablet) orally and UDCA 10mg/kg/day orally, for 6 months. Patients were followed-up with a planned visit once a month for the continuity of treatment, and for the presence of the reported signs and symptoms. At the end of the six-month treatment period, all patients underwent upper GI endoscopy, and control samples were taken for histopathologic evaluation.

Variables and outcomes

Patients' demographics, baseline characteristics, magnetic resonance cholangiopancreatography (MRCP) reports, endoscopic findings, and follow-up changes of these features, were recorded. We calculated body mass index (BMI) by dividing a patient's weight in kilograms by the square of height in meters, and then, we defined the weight status using age and sex specific percentiles for BMI which were defined for Turkish children (10). We categorized patients who were less than the 5th percentile as underweight, who were between 5th percentile and less than 85th percentile as normal weight, who were between 85th percentile and less than the 95th percentile as overweight, and who were 95th or greater percentile as obese. We reviewed the MRCP reports to determine the presence of any anatomic abnormality of biliary tract and pancreatic duct.

There were two primary outcomes in the study; changes in clinical features and histopathological changes. We defined the changes in clinical features as the changes in the prevalence of signs and symptoms (epigastric burning pain, dyspepsia, nausea, vomiting with bile, loss of appetite, and weight loss or inadequate weight gain), and the histopathological changes as the presence of *H. pylori* and histopathologic grade of disease. We categorized the histopathologic grade as normal, mild, moderate and severe based on the Houston-updated Sydney system (11).

Statistical analysis

Statistical analyses were run using SPSS version 20 (IBM Corp. in Armonk, NY). Descriptive data are displayed as frequency and percentage for categorical variables, and median with interquartile range for numerical variables. Related-Samples McNemar Test was used for comparing dichotomous variables, and Related-Samples Marginal Homogeneity Test was applied for comparing ordinal variables among pre and post treatment evaluations. A value of $p<0.05$ was considered statistically significant.

RESULTS

This retrospective study was performed with the patients admitted to our clinic with reflux signs and symptoms, underwent esophagogastroduodenoscopy and diagnosed with DGRD. 4000 patients who underwent endoscopy were scanned through archive scanning in digital media, 3958 of them admitted with reflux signs and symptoms and 186 patients diagnosed with DGRD according to the endoscopic and histopathologic evaluation. After excluding 154 patients, 32 patients were included in the study (Figure 1).

In the present study, a total of 32 pediatric patients with DGRD, all are in adolescence period, were included, treated and followed during 6 months. We discuss the effectiveness of a combined treatment with sucralfate 60mg/kg/day (suspension or tablet) orally and UDCA at 10mg/kg/day orally, for 6 months. We demonstrated the statistically significant improvement in every clinical signs and symptoms, including epigastric pain and nausea, dyspepsia, vomiting, weight loss and loss of appetite. Also, upper GIS endoscopy were repeated after the 6-months treatment period in all patients and we showed statistically significant decrease in the presence of *H. pylori* and statistically significant improvement in histologic features of gastric mucosa.

The median age of the children was 15.0 years(min:13.0-max:17.0), and girls were 81.3% of the study population. Ten patients were underweight, 14 had normal weight, 3 were overweight and 5 were obese. Six of the patients had kindredship between mother and father, and one patient had a family history for DGRD. Median age at the time of diagnosis was 13.5 years(min:10.3–max:15.0), while the median time from symptom onset to receiving the treatment was 15.0 months(min:12.0–max:33.0). We detected anatomic abnormality in three patients on MRCP (Table 1). One of these patients had prominence in the intrahepatic biliary tract, one underwent cholecystectomy, and one had biliary sludge and dilatation in the intrahepatic biliary tract (data not shown).

The signs and symptoms of the patients before and after treatment, are shown in Table 2. The two most common complaints were epigastric pain and nausea. Dyspepsia, vomiting, weight loss and loss of appetite were other complaints. The presence of all signs/symptoms statistically significantly decreased after treatment (Table 2).

The presence of *H. pylori* statistically significantly decreased from 43.8% to 21.9% (p=0.016). Before the treatment, three patients had normal histologic appearance, 21 patients had mild and 8 patients had moderate histopathological changes. However, the number of the histologically normal patients increased to 13, and the percentage of the mild and moderate histopathologic grades decreased. These changes were statistically significant (p=0.002) (Table 3).

Table 1. Demographics and baseline characteristics

Characteristics (n=32)	
Age (years), median (IQR)	15.0 (13.0-17.0)
Sex (female), n (%)	26 (81.3)
BMI, n (%)	
Underweight	10 (31.3)
Normal weight	14 (43.8)
Overweight	3 (9.4)
Obese	5 (15.6)
Kindredship between mother and father, n (%)	6 (18.8)
Family history, n (%)	1 (3.1)
Age of diagnosis (year), median (IQR)	13.5 (10.3-15.0)
Time from symptom onset to treatment (month), median (IQR)	15.0 (12.0-33.0)
Anatomic abnormality on MRCP, n (%)	3 (9.4)

Note: IQR: Interquartile range, BMI: Body mass index

Table 2. Comparison of signs and symptoms among pre and post treatment period

Signs and Symptoms (n=32)	Pre-treatment, n (%)	Post-treatment, n (%)	p*
Epigastric burning pain	28 (87.5)	6 (18.8)	<0.001
Dyspepsia	21 (65.6)	5 (15.6)	<0.001
Nausea	27 (84.4)	9 (28.1)	<0.001
Vomiting	20 (62.5)	7 (21.9)	<0.001
Loss of appetite	14 (43.8)	7 (21.9)	0.016
Weight loss or inadequate weight gain	15 (46.9)	1 (3.1)	<0.001

* Related-Samples McNemar Test was used

Table 3. Comparison of histopathologic features among pre and post treatment period

Features (n=32)	Pre-treatment, n (%)	Post-treatment, n (%)	p
Presence of Helicobacter pylori	14 (43.8)	7 (21.9)	0.016*
Histopathologic grade			
Normal	3 (9.4)	13 (40.6)	0.002**
Mild	21 (65.6)	17 (53.1)	
Moderate	8 (25.0)	2 (6.3)	

* Related-Samples McNemar Test was used.
** Related-Samples Marginal Homogeneity Test was used

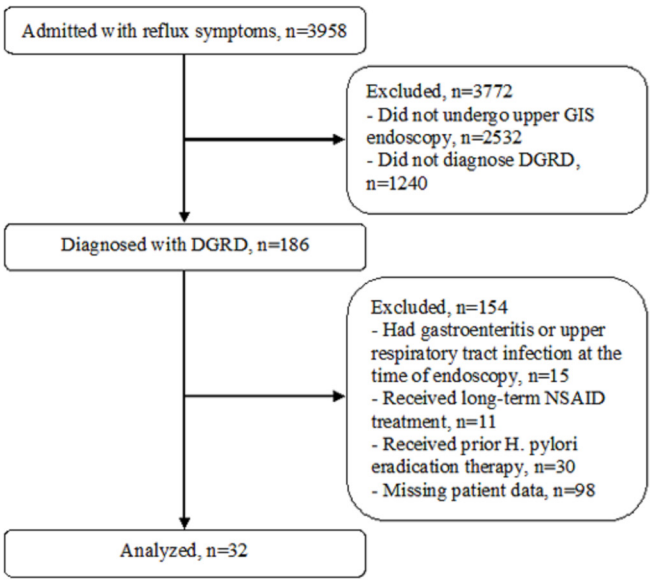

Figure 1. Flow diagram of the study

DISCUSSION

Frequency, clinical implications, treatment approach, long-term outcomes, and monitoring procedures of DGRD are incompletely understood in the pediatric population. In a study, UDCA relieved the symptoms, however, did not make change on histopathological changes, when compared to placebo (8). In our study we showed histopathological and clinical changes in patients. Based on this limited literature, the objective of this study was to investigate the histopathological and clinical responses to combined treatment of UDCA and sucralfate in children diagnosed with DGRD.

The primary medical therapeutic approach for the reflux disease is that proton pump inhibitors reduce acid reflux and relieve reflux symptoms such as epigastric pain (12). However, these drugs are not as good at alleviating all symptoms of patients with reflux disease (13). It was emphasized in a review, the belief that proton pump inhibitors could completely prevent metaplasia was inconsistent, since the proof was all secondary and not supported in randomized controlled trials (14). Therefore, novel therapeutic agents are required for treating reflux disease and prevent its long-term consequences such as metaplasia. Sucralfate is one of the commonly added agents to treat reflux disease because of its selective properties to form a protective antacid layer and its effectiveness against bile acids (4). Our study supports these studies and shows that sucralfate is effective.

Souza has investigated some possible new therapeutic approaches for reflux esophagitis and Barrett's esophagus (15). It was shown that patients with Barrett's esophagus have significant esophageal exposure to bile acids, and some bile acids are more harmful than others (2,16). In support of these studies, in our study, it was shown that the content of bilirubin in patients diagnosed with DGRD harms the stomach and esophagus. In a rat study, refluxed acid and toxic bile salts trigger the production of inflammatory cytokines and that induce cytokine mediated DNA damage in Barrett's cells, and likely contributing to carcinogenesis. Souza, demonstrated that altering bile acids composition with oral treatment of UDCA, which is a hydrophilic bile acid and is not genotoxic, reduces the esophageal DNA damage and cytokine activation resulting from toxic bile acids. (15). In our study, it was shown that UDCA is effective in the treatment of DGRD and plays an important role in both symptom relief and histopathological improvement. On the other hand, the author emphasized that preventing cytokine mediated inflammation -and not just controlling gastric acid- should be another therapeutic approach to relieve reflux induced symptoms and moreover. It was shown in other study that the pretreatment with UDCA decreases oxidative stress, DNA damage and cytokine activation in patients with Barrett's esophagus (17). In a meta-analysis, it was shown that UDCA had therapeutic feature for preventing the inflammatory bowel disease-associated colon cancer in patients with primary sclerosing cholangitis (18). In a way that both supports these studies and makes a new addition, In light of abovementioned fact, we added UDCA therapy to sucralfate as a new therapeutic agent to treat pediatric patients with DGRD.

DGRD is a common physiological process that is generally described as the transition of duodenal material from the duodenum to the stomach (19). Duodenal content leads to proliferation in inflammatory cells in the gastric mucosa, hyperplasia of gastric mucous cells and changes in glandular morphology. Therefore, DGRD has been involved in the pathogenesis of upper gastrointestinal

disorders such as esophagitis, gastritis, gastric ulcers, gastric adenocarcinoma and also intestinal metaplasia of the gastric mucosa (19,20). In adults, diagnostic approach, treatment and follow-up procedures are arranged and widely performed. We think that early diagnosis and effective treatment should be performed for all DGRD patients including pediatric patients. We believe that more comprehensive studies reporting pediatric patients with DGRD should be conducted so as to completely comprehend the natural course of this illness and its leading consequences.

The upper GI endoscopy is the primary method to evaluate the amount and depth of tissue damage of DGRD and it is performed routinely in our center. This process should be performed gently, especially for risk groups such as pediatric patients, as it can cause disturbance in gastric and duodenal motility and may cause undesirable side effects (19). All pediatric patients were sedated before the procedure, the experienced pediatric gastroenterologist performed the procedure, and no side effects were observed after procedure and during follow up period.

The frequency of *H. pylori* in pediatric populations is variable. (21-23). The age-related rise in the seroprevalence of *H. pylori* was shown by Wu et al. They demonstrated that the seroprevalence of *H. pylori* infection sharply elevated in young adolescence: 18.6% at age 15 years, 28.1% at age 16 years, 32.4% at age 17 years and 41.0% at age 18 years, respectively. The marked increase in social activities during school age was thought to be the main cause of *H. pylori* infection (14). In another study, it was demonstrated that an age-related increase *H. pylori* occurrence both in symptom free and in dyspeptic children, and a significantly higher rate in dyspeptic children aged 12-15 years, 38 % of children was found positive for *H. pylori* (14). In our study, similar to these studies the prevalence of *H. pylori* was found to be 43.8% and 21.9% in pre-treatment and post-treatment period, respectively. We think that the prevalence of *H. pylori* in our study group is compatible with literature and our combined treatment can be effective on *H. pylori* prevalence.

There were a number of limitations of the study. First of all, this study is a single-center study with a quite low sample number and the results concerning our study population cannot be generalized to other pediatric populations suffering reflux symptoms related the other health problems than DGRD. The clinical and histopathological improvements as the outcomes of the study are valid for short follow-up period, and may not reflect the long-term effects of the treatment. Also, another limitation is having no control group because of the nature of the pre-post design of the study. These limitations should be taken into account when interpreting the outcomes of the study.

If we look at the strengths of the study

1. In this study, imaging with MRCP to investigate gender, family history, parental consanguinity, and etiological anatomical pathologies in terms of risk factors that may cause DGRH.
2. Evaluation of DGRH together with the control group to investigate the effect of *H. pylori* infection.
3. Separate evaluation of symptoms before and after treatment.
4. Clinical staging of patients according to the presence of symptoms and evaluation of improvement in staging.
5. Performing histopathological evaluation together with the clinic.

CONCLUSION

UDCA and Sucralfate treatment with a six-month period, provides valuable histopathological and clinical improvements in patients with DGRD. Further clinical trials with a relatively large sample size and with a longer follow-up period using long-term outcomes, are needed to validate the results of our study.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The study was carried out in conformity with the Declaration of Helsinki after obtaining the approval of Akdeniz University Clinical Research Ethics Committee (Approval date: 01.11.2017, No:622).*

REFERENCES

1. Zhang Y, Yang X, Gu W, et al. Histological features of the gastric mucosa in children with primary bile reflux gastritis. World J Surg Oncol. 2012;10:27.
2. Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastric reflux in esophageal mucosal injury: a review of animal and human studies. Gastroenterology. 1995;108:1897-907.
3. Szarszewski A, Korzon M, Kamińska B, et al. Duodenogastric reflux: clinical and therapeutic aspects. Arch Dis Child. 1999;81:16-20.
4. Hermans D, Sokal EM, Collard JM, et al. Primary duodenogastric reflux in children and adolescents. Eur J Pediatr. 2003;162:598-602.
5. Burden WR, Hodges RP, Hsu M, O'Leary JP. Alkaline reflux gastritis. Surg Clin North Am. 1991;71:33-44.
6. Dalenbäck J, Abrahamson H, Björnson E, et al. Human duodenogastric reflux, retroperistalsis, and MMC. Am J Physiol. 1998;275:R762-9.
7. Rosen R, Vandenplas Y, Singendonk M, 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. Journal of Pediatric Gastroenterology and Nutrition. 2018;66:516-54.

8. Stefaniwsky AB, Tint GS, Speck J, et al. Ursodeoxycholic acid treatment of bile reflux gastritis. Gastroenterology. 1985;89:1000-4.

9. Rosman AS. Efficacy of UDCA in treating bile reflux gastritis. Gastroenterology. 1987;92:269.

10. Neyzi O, Bundak R, Gökçay G, et al. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015;7:280-93.

11. Dixon MF, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996;20:1161-81.

12. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology. 2008;135:1392-1413, 413.e1-5.

13. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-83.

14. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011;140:e18-52; quiz e13.

15. Souza RF. From Reflux Esophagitis to Esophageal Adenocarcinoma. Dig Dis. 2016;34:483-90.

16. Nehra D, Howell P, Williams CP, et al. Toxic bile acids in gastro-oesophageal reflux disease: influence of gastric acidity. Gut. 1999;44:598-602.

17. Peng S, Huo X, Rezaei D, et al. In Barrett's esophagus patients and Barrett's cell lines, ursodeoxycholic acid increases antioxidant expression and prevents DNA damage by bile acids. Am J Physiol Gastrointest Liver Physiol. 2014;307:G129-139.

18. Singh S, Khanna S, Pardi DS, et al. Effect of ursodeoxycholic acid use on the risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2013;19:1631-8.

19. Chen TF, Yadav PK, Wu RJ, et al. Comparative evaluation of intragastric bile acids and hepatobiliary scintigraphy in the diagnosis of duodenogastric reflux. World J Gastroenterol. 2013;19:2187-96.

20. Mittal BR, Ibrarullah M, Agarwal DK, et al. Comparative evaluation of scintigraphy and upper gastrointestinal tract endoscopy for detection of duodenogastric reflux. Ann Nucl Med. 1994;8:183-6.

21. Camacho-Gomez SM, Bernieh A, Saad AG, et al. Non-Helicobacter *pylori* Gastric Intestinal Metaplasia in Children: A Series of Cases and Review of the Literature. Case Rep Gastrointest Med. 2018;2018:5930415.

22. Riddell RH. Pathobiology of Helicobacter pylori infection in children. Can J Gastroenterol. 1999;13:599-603.

23. Oderda G, Vaira D, Holton J. Age-related increase of Helicobacter pylori frequency in symptom-free and in dyspeptic children. Lancet. 1992;340:671-2.

24. Wu TC, Chen LK, Hwang SJ. Seroprevalence of Helicobacter pylori in school-aged Chinese in Taipei City and relationship between ABO blood groups. World J Gastroenterol. 2003;9:1752-5.