

Gastro-oesophageal reflux in infants: optimizing behavioural and pharmacological therapy

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The aim was to investigate the prevalence of gastro-oesophageal reflux (GOR) in newborns and unweaned because of its possible overestimation or underestimation due to parent's disposition. The main purposes of this study were to evaluate the effectiveness of behavioural therapy to limit the use of drug, and the correlation between GOR and type of feeding, since there is evidence in the literature that breastfeeding could have a protective role. This prospective observational study was carried out in paediatric patients from June 2015 to December 2017. We enrolled 180 children aged between one and six months. Patients were classified in two groups, as follows: group 1 (without GOR) and group 2 (with GOR). Inclusion criteria in group 2 were the presence of at least one of the following symptoms: early sense of satiety, nausea, aversion to food, vomiting and/or regurgitation, rumination, poor growth, wheezing, and cry. History exploration and clinical investigation were conducted to analyse the main characteristics of reflux episodes and the possible correlation with breastfeeding. Behavioural treatment based on postural measures and dietary advice was prescribed to group 2 infants. In case of non-response to therapy, histamine H2 receptor antagonists (H2RAs) were prescribed at a dosage of 5 mg/kg/day in two doses. The presence of GOR was excluded in 140/180 (77.8%) children, yielding a reflux prevalence index equal to 22.2% of the sample (40/180). Regarding the symptoms, 95% of the group with reflux showed vomiting, regurgitation, rumination and poor growth; 2.5% also showed wheezing, and the remaining 2.5% showed inconsolable crying too. No statistically significant correlation was found between the type of feeding and the onset of reflux. In group 2 (with GOR), 97.5% of the infants responded to behavioural therapy, while the condition failed to improve in only 2.5% and drug therapy with H2RAs was started. GOR is a common clinical condition in infants. Conservative approach is more required in children than in adults, especially considering both regression of GOR within the first year of life in most cases and side effects of pharmacological treatment. Breastfeeding did not appear to have a significant role.

Key words: CHILD; GASTROESOPHAGEAL REFLUX; BREAST FEEDING; THERAPY

INTRODUCTION

Gastro-oesophageal reflux (GOR) is a common condition in infancy occurring several times a day and resolving spontaneously in most cases (1, 2). According to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Guidelines, GOR is defined as the passage of gastric

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contents into the oesophagus with or without regurgitation and vomiting, and gastro-oesophageal reflux disease (GORD) as troublesome symptoms that affect daily functioning and/or complications (3). GOR without any warning signs does not need other evaluations in addition to history and physical examination, above all if the feeding, growth and acquisition of developmental milestones are not affected, with no impact on the quality of life (3-5). Most cases of GOR can be treated conservatively with parental education, lifestyle and dietary advice, such as positional therapy and feeding modification (using thickened food, avoiding overfeeding, continuing breastfeeding if possible, or using a hydrolysate formula) (3).

If the non-pharmacological treatment fails, proton pump inhibitors (PPIs) are used as first-line therapy, and if PPIs are not available or are contraindicated, H₂ receptor antagonists (H₂RAs) can be considered despite their side effects, but evaluating treatment efficacy after 4-8 weeks (3).

The primary outcome of our study was to assess the effectiveness of non-pharmacological treatments and the real need for drug therapy, used only in clinical situations that really require it.

Secondary outcomes included investigation of the actual prevalence of GOR in newborns and unweaned, and the correlation between GOR and feeding type.

PATIENTS AND METHODS

At the Paediatric Unit of Campus Bio-Medico University Hospital of Rome, a total of 180 children (99 males and 81 females) aged between one and six months with reported suspicion of GOR by parents were enrolled from June 2015 until December 2017. This prospective observational study was conducted in accordance with regulatory standards of the Good Clinical Practice and the Declaration of Helsinki. History evaluation was conducted first to investigate the presence and main characteristics of reflux episodes such as age at onset, frequency, duration, associated symptoms and signs, and type of feeding. This assessment was performed since it has been shown in the literature that partially breastfed infants may suffer from regurgitation more frequently than exclusively breastfed infants, especially between two and six months of age (6). Subsequently, clinical examination was performed, integrated with the use of the Orenstein questionnaire as support to the diagnosis of reflux in paediatric age (7). The Orenstein questionnaire is made up of a series of questions addressed to parents investigating both the presence of certain symptoms such as vomiting, regurgitation, cough, apnoea, hiccups, and any family history of reflux or allergies. The Orenstein questionnaire has 47% sensitivity and 81% specificity when the re-

flux index is >10%. However, when the reflux index is <5%, it has 65% sensitivity and 63% specificity. Reflux index refers to the time during which the oesophageal pH is <4.32 (8). After this preliminary evaluation, patients were classified in two groups, as follows: children without at least one of symptom suggestive of GOR (early sense of satiety, nausea, aversion to food, vomiting and/or regurgitation, rumination, poor growth, wheezing and cry) were excluded from the study (group 1), while children with GOR (group 2) were included and subjected to therapeutic measures. Behavioural treatment based on postural measures and dietary advice was prescribed to group 2 patients. In fact, for infants who were breastfed, it was recommended to prefer shorter and more frequent feeding. On the other hand, in bottle-fed patients, we prescribed replacement of artificial milk 1 with anti-reflux milk, and in addition, anti-reflux syrup (magnesium alginate) and thickened formulas. Concerning postural measures, we recommended vertical position in the cradle and in the wheelchair (supine reversed-Trendelenburg sleeping position); prone sleeping position was not recommended due to the risk of sudden infant death syndrome. In case of non-response to therapy, H₂RAs were prescribed.

Finally, parents had to note, before and during treatment, the characteristics of reflux episodes to evaluate the effectiveness of the therapy proposed.

In our study, a dual analysis was conducted, i.e., descriptive analysis for data evaluation and calculation of the main summary indices; in particular, two prevalence indices were evaluated by calculating the proportion of prevalence and the relative 95% confidence interval (95% CI). Subsequently, the inferential analysis was conducted to assess the possible correlation between the onset of symptoms and the main variable of interest (breastfeeding); regression analysis was performed for this purpose. A dedicated software package (Stata, StataCorp LLC, USA) was used for both statistical analyses (descriptive and inferential).

RESULTS

In the enrolled sample, the presence of reflux episodes was excluded in 140 children (77.8% of the total, group 1), yield-

TABLE 1. Characteristics of all study patients

	Total	Patients without GOR (Group 1)	Patients with GOR (Group 2)
	n (%)	n (%)	n (%)
Total	180	140 (7.8)	40 (22.2)
Male	99 (55)	75 (53.6)	24 (60)
Female	81 (45)	65 (46.4)	16 (40)

GOR = gastro-oesophageal reflux

TABLE 2. Treatment of gastro-oesophageal reflux

	Vomiting, regurgitation, rumination and poor growth and/or wheezing		Vomiting, regurgitation, rumination, poor growth and inconsolable crying
	n (%)		n (%)
Type of feeding	Breastfed patients 21(53.8)	Bottle-fed patients 18 (46.1)	Bottle-fed patients 1 (100)
Type of therapy	Behavioural therapy (vertical position; shorter and more frequent feedings)		Behavioural therapy; replacement of artificial milk 1 with anti-reflux milk and in addition, anti-reflux syrup (magnesium alginate) and thickened formulas
	Behavioural therapy and replacement of artificial milk 1 with anti-reflux milk and in addition, anti-reflux syrup (magnesium alginate) and thickened formulas		Behavioural therapy; replacement of artificial milk 1 with anti-reflux milk and in addition, anti-reflux syrup (magnesium alginate) and thickened formulas; drug therapy with H2RAs

H2RAs = H2 receptor antagonists

TABLE 3. Clinical features of patients with gastro-oesophageal reflux

Group 2 (with GOR)	
	n (%)
Vomiting, regurgitation, rumination and poor growth	38 (95)
Vomiting, regurgitation, rumination and poor growth, wheezing	1 (2.5)
Vomiting, regurgitation, rumination and poor growth, inconsolable crying	1 (2.5)

GOR = gastro-oesophageal reflux

ing a reflux prevalence index equal to 22.2% of the sample (95% confidence interval (95% CI) 16.4%-29.1%). Of these 40 little patients recruited (group 2), there were 24 (60%) males and 16 (40%) females (Table 1). Group 2 patients were at first subjected to behavioural therapy and 97.5% (95% CI 86.8%-99.9%) showed marked improvement in symptoms. This group included children who presented vomiting, regurgitation, rumination, poor growth and/or wheezing. In group 2, 2.5% of patients (95% CI 0.1%-13.1%) did not respond to behavioural therapy. In particular, we noted that inconsolable crying was present only in these unresponsive children. In this case, drug therapy with a H2RA was started (Table 2). Interestingly, 2.5% of group 2 patients unresponsive to behavioural therapy were bottle-fed. Both behavioural and pharmacological treatments adopted to our study patients had favourable effect on resolution of the GOR symptoms, and pharmacological therapy had to be administered to only one patient (2.5% of the sample). Regarding symptoms, 38 (95%) group 2 children showed vomiting, regurgitation, rumination, and poor growth (95% CI 86.8%-99.9%); one child (2.5%) showed vomiting, regurgitation, rumination, poor growth, and wheezing (95% CI 0.1%-13.1%); and another one (2.5%) showed vomiting, regurgitation, rumination, poor growth, and inconsolable crying (95% CI 0.1%-13.1%) (Table 3).

Using regression analysis, no statistically significant correlation was demonstrated between the type of feeding (breastfeeding, artificial feeding) and the onset of reflux at the mean age of 3.2 months. In our study, 21/40 (52.5%) children were breastfed, while 19/40 (47.5%) children were bottle-fed.

DISCUSSION

Gastro-oesophageal reflux is a condition frequently encountered in infants, which resolves within the first year of life in 90% of cases (1). In our sample, the reflux prevalence index, globally understood at the clinical level, was equal to 22.2% (95% CI 16.4%-29.1%), reflecting the observations reported in the literature (9). According to the latest guidelines, the first treatment of children with GOR should always focus on behavioural therapy consisting of education, reassurance and support of parents, along with feeding techniques and positioning (3, 10). Our study demonstrated that conservative therapeutic approach was efficient in most cases, i.e., 97.5% of children responded to behavioural therapy alone, whereas only 2.5% showing inconsolable crying required drug therapy with H2RAs.

Children are a category at a higher risk of GOR, probably exacerbated by the type of feeding, maintenance of prone position, and the relative structural and functional immaturity of the oesophagus-gastric junction (9). Generally, infants experience reflux most commonly after meals because of the passage of air in the stomach during feeding. There also are other factors that can predispose to GOR, such as excessive crying and increased intra-abdominal pressure, due to exertion, coughing or sitting (11).

We recommended to parents a position as vertical as possible and to place infants on the right side for the first hour after feeding to promote gastric emptying, and then on the left side to decrease the frequency of reflux (12). Although some studies demonstrated that left lateral positioning reduced the reflux episodes and vomiting, additional studies are required to investigate the effectiveness of this approach (3).

Dietary advice was also prescribed. We suggested shorter and more frequent feedings, maintaining an appropriate total daily amount because there is evidence in the literature that large feedings could worsen GOR, causing an increase in transient releases of the lower oesophageal sphincter (13).

Treatment with thickened formulas was also adopted, since in several studies it was found that their use significantly in-

creased daily percentage of newborns without regurgitation and vomiting and symptoms such as crying and irritability, noting that the thickened rice cream formula reduced the frequency of regurgitation more effectively (3, 14, 15). However, clinical results of some trials failed to show improvement in pH-metric parameters, maybe because thickened feeding reduces postprandial reflux, which is typically non-acid (3). Finally, in the bottle-fed patients we substituted milk 1 with anti-reflux milk and in addition, we proposed an anti-reflux syrup at a dosage of 3 mL/kg/day after meals. The anti-reflux syrup has, in fact, the purpose of reducing the symptoms related to GOR, such as cough, esophagitis, dysphonia, and nasopharyngeal inflammation.

Despite behavioural measures undertaken, 2.5% of the children continued to have symptoms and needed drug therapy. According to the literature, PPIs are the first-line therapy, but it is uncertain whether their use reduces the symptoms of GORD, improves histology/macroscopy, or leads to less side effects compared with H2RAs (3). Because of the small number of studies in the literature, we decided to evaluate the effectiveness of H2RAs, administering them to unresponsive children, and we obtained complete resolution of GORD. The NASPGHAN and ESPGHAN Guidelines suggest to use these drugs for 4-8 weeks for typical symptoms in children with GORD but not for visible regurgitation in otherwise healthy infants (3). In fact, various side effects of H2RAs are reported, e.g., an increased rate of intestinal infections, irritability, headache, drowsiness, impaired liver and leukocyte function, and pneumonia (16-18). It is important to evaluate the real need for drug therapy and above all the situations in which we have to consult a gastroenterologist. There are some alarm features, so called 'red flags', that should warrant further investigation by other healthcare professionals to rule out complications of GORD and to uncover underlying disorders presenting with signs or symptoms of GOR. Some red flags can suggest systemic infections, such as weight loss, lethargy, fever, excessive irritability; others can be indicative of a neurological underlying condition, such as bulging fontanel, seizures, macro/microcephaly; finally, biliary vomit, hematemesis, and chronic diarrhoea can suggest a gastrointestinal condition (hypertrophic pyloric stenosis, intestinal obstruction) (3).

Unfortunately, this study had some limitations, such as the small sample. Thus, future investigations are required to expand the cohort of children and to analyse the real need for pharmacological therapy, even if we can assert that uncomplicated regurgitation of the infant does not justify the use of drugs. Furthermore, in bottle-fed infants with reflux, there is often the hypothesis of intolerance to milk proteins, which can be solved by switching to hydrolysed formula. Future studies could evaluate the role of hydrolysate for-

mula in GOR/GORD, considering in particular infants with atopic familiarity and those in which non-pharmacological conservative approach has been ineffective.

CONCLUSION

Our findings confirm that GOR is a common heterogeneous condition in infants. Although being a benign condition, it is possible to intervene, in particular if symptoms are presented. As observed in the field survey conducted in this study, the first approach suggested is to change lifestyle, nutrition and posture, and only then, if it is not enough, drug therapy could be used. In fact, parental education, guidance and support are always necessary and often sufficient in the management of healthy infants with physiological GOR symptoms (19, 20).

In conclusion, a more conservative approach is required in children than in adults, especially considering regression within the first year of life in most cases, the benign nature of the condition, and the potential collateral effects of drugs (16, 18, 21).

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SAŽETAK

Gastroezofagusni refluks u dojenčadi: optimiziranje ponašajne i farmakološke terapije

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Cilj je bio ispitati učestalost gastroezofagusnog refluksa (GER) u novorođenčadi i dojene dojenčadi zbog moguće precijenjenosti ili podcijenjenosti ovoga poremećaja uvjetovane stavom roditelja. Osnovna namjera bila je procijeniti učinkovitost terapije promjenom ponašanja kako bi se ograničila primjena lijekova, kao i korelaciju GER-a s načinom hranjenja, jer postoje dokazi u literaturi da bi dojenje moglo imati zaštitnu ulogu. Ova prospektivna opservacijska studija provedena je na pedijatrijskim bolesnicima od lipnja 2015. do prosinca 2017. godine, a uključila je 180 djece u dobi od jednog do šest mjeseci. Bolesnici su podijeljeni u dvije skupine: 1. skupina (bez GER-a) i 2. skupina (s GER-om). U 2. skupini kriteriji za uključivanje bili su prisutnost najmanje jednog od sljedećih simptoma: rani osjećaj sitosti, mučnina, averzija prema hrani, povraćanje i/ili regurgitacija, „preživavanje“, slab rast, wheezing i plač. Proučena je anamneza i provedeno je kliničko ispitivanje kako bi se analizirale glavne značajke epizoda refluksa i moguća korelacija s dojenjem. Dojenčadi iz 2. skupine propisana je terapija promjene ponašanja zasnovana na položaju tijela te savjeti o prehrani. U slučaju izostanka odgovora na ovu terapiju propisani su antagonisti receptora H₂ (H₂RA), 5 mg/kg/dan u dvije doze na dan. Prisutnost GER-a isključena je u 140/180 (77,8%) djece, uz indeks učestalosti refluksa od 22,2% ispitnog uzorka (40/180). S obzirom na simptome, povraćanje, regurgitacija, „preživavanje“ i slab rast zabilježeni su u 95% našega uzorka s refluksom; 2,5% ih je također pokazivalo wheezing, a preostalih 2,5% je neutješno plakalo. Nije nađena statistički značajna korelacija između načina hranjenja i nastupa refluksa. U 2. skupini (s GER-om) 97,5% dojenčadi odgovorilo je na terapiju promjenom ponašanja, dok se u 2,5% njih stanje nije popravilo pa je trebalo uvesti terapiju pomoću H₂RA. GER je često kliničko stanje u dojenčadi. Konzervativni pristup potrebniji je u djece nego kod odraslih, osobito uzimajući u obzir regresiju GER-a unutar prve godine života u većini slučajeva, kao i nuspojave farmakološke terapije. Nije se pokazalo da bi dojenje imalo neku značajnu ulogu.

Ključne riječi: DJECA; GASTROEZOFAGUSNI REFLUKS; DOJENJE; LIJEČENJE