

Clinical Article

Nutritional Management of Children with Gastroesophageal Reflux: A Comparison of Two Different Formulas

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Abstract

Preferred treatment for uncomplicated infant gastroesophageal reflux (GER) is thickening of infant feedings either by adding rice cereal to infant formula or using a pre-thickened commercial infant formula. This study compares the effectiveness of rice cereal-thickened formula versus an anti-regurgitation formula pre-thickened with cornstarch (AR) on clinical symptoms and distal esophageal pH in infants diagnosed with uncomplicated GER. Fifty-two infants (15-120 days old) diagnosed with GER and averaging at least three episodes of vomiting/regurgitation per 24-hours over a 2-week period, were fed either infant formula thickened with 5% rice cereal (RC) or formula pre-thickened with pre-gelatinized cornstarch (AR). Esophageal pH was monitored for 24-hours at baseline and following three weeks of feedings. There was a significant decrease in vomiting episodes in the AR group, and a significant decrease in regurgitations in both groups. There was also significant improvement in measures associated with pH monitoring (longest reflux episode, reflux index, reflux episodes per hour) in the AR group alone. A commercial anti-regurgitation formula (AR) was more effective than standard formula thickened with 5% rice cereal (RC) in reducing the incidence of regurgitation and improving esophageal pH in infants being treated for GER. *Int Pediatr.* 2003;18(2):78-83.

Key words: Gastroesophageal reflux in infancy, pre-thickened formulas, esophageal pH monitoring study

Introduction

Gastroesophageal reflux (GER) is defined as the involuntary passage of stomach contents into the esophagus and is associated with a lowering of esophageal pH. Virtually all infants experience some degree of GER with symptoms ranging from a simple burp to persistent vomiting.¹ Incidence peaks at 3

months of age and usually resolves by 6-12 month^{2,3} coincident with maturation of the esophageal sphincter and the ability to sit upright. In the absence of complicating factors such as esophagitis, failure to thrive, and respiratory symptoms, GER can be diagnosed and treated without further testing.⁴

A standard first approach for treatment of GER includes the long-accepted practice of thickening infant feedings, either with rice cereal, bean gum starch or, more recently, commercial formulas pre-thickened with rice or pre-gelatinized (pre-cooked) cornstarch.^{4,7}

Previous studies have shown that thickened feeds are effective in reducing episodes of regurgitation in infants with GER.^{3,5-8} However, in these studies the reflux index (percentage of time distal esophagus is less than pH 4) remained unchanged, which can result in episodes of occult reflux. Therefore, children presenting with esophagitis should be carefully monitored.

Monitoring distal esophageal pH is considered the "gold standard" for assessing infant GER.⁹⁻¹³ A continuous 24-hour pH probe is relatively safe and provides a reproducible method for measuring acid reflux in infants.¹⁴⁻¹⁸

The aim of this study was to compare the effects of a traditional whey-based infant formula thickened with 5% rice cereal to a casein-predominant infant formula pre-thickened with pre-gelatinized cornstarch on clinical symptoms in children with GER and evaluation of esophageal pH over 24-hours.

Case Report

In this single blind (investigator blinded) study, 52 infants, 15-120 days of age, were randomized into two groups, using a computer-generated randomization schedule, with assignments in balanced block technique. One group was fed a traditional infant formula thickened by the addition of 5% (5 g/100 ml) rice cereal (RC). The alternate group was fed a commercial anti-

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regurgitation formula (AR) containing pre-gelatinized cornstarch.¹⁹ Mothers were instructed to feed their infant with their assigned formula every 3 hours. Both formulas were manufactured by Wyeth Nutrition. The protocol was approved by the Research and Ethical committee of the Instituto Nacional de Pediatría SS. Parents of participating infants signed a written informed consent form.

Infants included in this study had been experiencing a minimum of 3 regurgitations and/or vomiting episodes within a 24-hour period, for at least two weeks. Vomiting is defined as the forceful expulsion of upper gastrointestinal contents, and regurgitation as an effortless, oral expulsion without contraction of the diaphragm.²⁰ For ethical reasons, children with respiratory symptoms were not included in this study, since these children are at risk of respiratory complications such as pneumonia.

At the initial (baseline) visit, study personnel recorded infant gender, birth date, and date of enrollment. Infants were weighed (grams) using a calibrated scale and infant length (cm) was measured using a recumbent length board. Each week, infants returned to a medical clinic where weight and length were recorded and the parent was interviewed for the number of regurgitation and/or vomiting episodes during the previous 24-hours. None of the subjects received any additional medical or non-pharmacological treatment. Patient visits took place at the Gastroenterology and Nutrition Department of Instituto Nacional de Pediatría SS, a level III facility, in Mexico City, Mexico between February 1999 and January 2000.

Of the 31 subjects in the AR group, 3 dropped out for economic reasons leaving 28 infants with a mean

age of 2.52 ± 1.62 months, 18 males and 10 females (Table 1). The RC group lost 4 subjects for the same economic reasons leaving 24 infants with a mean age of 1.93 ± 2.23 mo, 13 males and 9 females. Notably, none of the dropouts were related to GER disease or difficulties with the test formulas. There were no significant differences between the AR group and the RC group in any of the clinical variables recorded at the initiation of the study (Table 1).

The frequency of vomiting decreased significantly in the AR group over the course of the study, but not in the RC group. The number of regurgitation episodes decreased in both feeding groups with no significant difference between them (Table 2). There were no reports of cough or irritability among subjects in either feeding group over the study period. There were three reports of constipation - all were in the RC group.

To conduct the 24-hour continuous pH monitoring of the distal esophagus, a Mark-III (Medtronic) antimony catheter, calibrated using commercially available standards, was placed 3 cm above the lower esophageal sphincter, at the baseline appointment and following three weeks of treatment. Data were used to calculate reflux index (percentage of time distal esophagus is $< \text{pH } 4$), longest reflux episode, number of reflux episodes per hr, and esophageal clearance (time for esophagus to return to $\text{pH} > 4$ following a period of reflux).

Results of the pH monitoring studies are presented in Table 3. Infants in the AR group experienced a significant reduction in duration of the longest reflux episode, reflux index, and number of reflux episodes per hour. There were no changes in these variables between baseline and study end-point for infants in the RC group. Esophageal clearance did not change

Table 1 - Baseline Clinical Characteristics

Characteristic	AR formula ¹	RC Formula ²	Significance $p \leq$
Age, mo	2.52 ± 1.62	1.93 ± 2.23	0.18
Gender, % male	64.3	54.2	0.46
Weight, kg (mean \pm sd)	4.95 ± 1.3	4.67 ± 1.5	0.32
Height, cm (mean \pm sd)	56.9 ± 4.6	56.3 ± 5.4	0.59
Regurgitations/24 hr (mean \pm sd)	4.3 ± 2.8	4.9 ± 2.5	0.32
No. vomits (mean \pm sd)	2.8 ± 2.6	3.7 ± 2.2	0.16
Longest reflux episode, min (mean \pm sd)	29.2 ± 28.8	13.5 ± 9.0	0.12
Reflux index, %	7.33 ± 7.7	3.4 ± 3.2	0.24
Reflux / hr (mean \pm sd)	2.0 ± 3.0	1.6 ± 1.0	0.64
Esophageal clearance (x \pm sd)	1.8 ± 2.8	1.7 ± 0.98	0.17

P values determined using the Chi square or U-Mann Whitney test.

¹Formula pre-thickened with pre-gelatinized cornstarch

²Formula thickened by adding 5% rice cereal (5 g/100 ml)

Table 2 - Vomit and Regurgitation Evolution

Variable ¹	Baseline		Week 1		Week 2		Final		p ≤
Vomit									
AR group ²	2.8	2.6	2.2	5.4	1.9	4.2	1.5	7.4	0.04
RC group ³	3.7	2.2	4.4	7.4	7.2	9.8	5.4	8.3	NS
Regurgitation									
AR group	4.3	2.8	3.1	5.3	2.4	4.1	2.5	4.6	0.03
RC group	4.9	2.5	2.9	4.1	2.3	1.9	3.4	6.0	0.027

P values were determined using the Friedman repeated measures analysis and refer to the difference between the basal and final measurements.

¹Episodes/24 hr

²Formula pre-thickened with pre-gelatinized cornstarch

³Formula thickened by adding 5% rice cereal (5 g/100 ml)

Table 3 - pH Monitoring Reflux Parameters

P values were determined using the Friedman repeated measures analysis.

¹Formula pre-thickened with pre-gelatinized cornstarch

²Formula thickened by adding 5% rice cereal (5 g/100 ml)

over the duration of the study for infants in either group.

Discussion

Good nutrition is essential for the normal growth and development of newborns; therefore, providing adequate nutrition while infants are experiencing GER has been problematic and recommended treatments have been controversial.²⁰ Most physicians recommend dietary management with thickened formulas for one to two weeks as the first step in the treatment for these infants.^{4,6,17} It is believed that this conservative therapy

has little or no risk in simple regurgitation, and it is the initial treatment currently recommended by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).^{4,21,22} Positional therapy, once recommended to be used in conjunction with dietary treatment, has been reconsidered in light of the correlation of the prone position with sudden infant death syndrome.²¹ ESPGHAN also emphasizes that parental reassurance should be central to the initial treatment of all children with GER.

Refinement of the 24-hour pH monitoring technique, (a thin, flexible probe used to monitor pH

in the distal esophagus), has resulted in an inexpensive and reproducible method for measuring esophageal acid reflux. With the development of a portable recording device, children can now be monitored outside of the clinical setting,^{23,24} allowing for a broader use of these diagnostic studies than was previously feasible. A 24-hour pH monitoring study measures the frequency of esophageal efflux, the duration of each episode, and the esophageal clearance (time for esophageal pH to go above 4). These data may be interpreted as reflecting the severity of the GER. By measuring 24-hour esophageal pH both at baseline and following three weeks of treatment, temporal changes associated with each feeding group may be elucidated.

In this study we observed a significant decrease in the frequency of vomiting episodes, the duration of the longest reflux episode, the reflux index, and number of reflux episodes per hour in the group fed AR formula compared to the group fed RC formula (Table 2). It is notable to report that use of a pre-thickened formula resulted in both decreased duration of reflux, as reflected by pH monitoring, as well as decreased number of regurgitations (clinical symptom).

Previous work by Vandenplas showed a positive effect in newborns six to eight weeks old fed a casein-predominant formula thickened with carob bean gum.⁷ These infants had fewer episodes of regurgitation than those fed regular infant formula. Orenstein found that infants fed dry rice cereal had a decreased volume as well as a decreased frequency of regurgitation compared to infants fed thickened formula.¹⁸ However, in neither study were there any changes in the reflux index. This raised the concern that dietary treatment which alleviates the symptoms of reflux without eliminating the underlying cause may be inappropriate for subjects with esophagitis or severe GER disease.²⁵

There were two major differences in formula composition between the two feeding groups (Table 4). One was the use of starch as a thickening agent in the commercial formula and the second was the relative composition of casein and whey in the protein component of the formulas. The lipid content of the two formulas is comparable.^{4,7,17-19} Historically, rice starch has been most widely used to thicken milk. Lifschitz first demonstrated the digestibility of rice starch in 2-4 month old infants both during acute diarrhea and following recovery.²⁶ However, a known disadvantage of rice is its association with

constipation,¹⁸ a side effect that occurred in 3 of 24 infants in the RC group.

Pre-gelatinized cornstarch is an appropriate carbohydrate to add to formula as a thickening agent for several reasons. Cornstarch can be digested by children less than 6 months of age.^{27,28} Cornstarch also provides a source of calories, and it does not interfere with the absorption of other nutrients. For these reasons it has been approved for use in infant formulas in Europe and additional countries of Asia and Latin America. Other starches which have been used as milk thickeners include locust or carob bean gum. However, these starches are not absorbed and furthermore, fermentation of these gums in the gastrointestinal tract may cause abdominal distension and discomfort. It is also known that diets containing 1-10% carob bean gum can interfere with the absorption of minerals such as zinc, copper, calcium, and iron.²⁹

The decrease in reflux index, and improvement in other reflux parameters observed in the AR group may stem from the higher proportion of casein in the AR formula. The theory behind use of a casein-predominant formula is that the larger curds formed by casein in the stomach are thought to result in fewer episodes of reflux.^{30,31} Illustrative of the controversies in this area of research, Khoshoo reported a higher incidence of GER among infants fed a standard casein-predominant formula compared to those fed a standard whey-based formula,³² and attributes this difference to slower gastric emptying associated with higher casein content.^{34,33} Thus it is possible that the inclusion of the pre-gelatinized cornstarch alone is the effective component of the AR formula. Additional investigations are needed to continue to study these variables.

It is conceivable that some of the improvements in clinical symptoms observed in this study were due to the natural amelioration of GER symptoms over time; however, we do see a difference in the degree of improvement between the groups, and a lack of any significant improvement in pH monitoring results among infants fed formulas thickened with rice cereal (RC). Furthermore, previous studies have shown that the symptoms of GER resolve gradually over a period of several months, not 2-3 weeks as in our study.⁴

The significant improvement in reflux parameters, as well as the amelioration of clinical symptoms, in infants fed AR formula represents a new finding. An additional benefit of pre-thickened AR formula is the

Table 4 - Difference in Macronutrients of Two Treatment Groups

RC Formula¹ (before rice cereal)	AR Formula
Protein:60/40 Whey to Casein	20/80 Whey to Casein
Carbohydrate:100% Lactose	71% Lactose; 26% Cornstarch; 3% Maltodextrin
Osmolality:280 mOsm/kg	230 mOsm/kg

¹Formula thickened by adding 5% rice cereal (5 g/100 ml). Table reflects composition prior to addition of rice cereal.

²Formula pre-thickened with pre-gelatinized cornstarch

quality control exercised during formula preparation. Thickening of individual feedings in the home environment can result in inconsistencies in formula composition; therefore, the clinical use of commercially prepared pre-thickened AR formula adds reliability both for the physician prescribing this treatment and the parent.

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