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Effect of Locust Bean Gum in Anti-regurgitant Milk on the Regurgitation in Uncomplicated Gastroesophageal Reflux

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ABSTRACT

Objectives: To evaluate the efficacy of anti-regurgitant milk (AR milk) with reduced concentration of locust bean gum (LBG) compared with the usual commercially available concentration of this thickener.

Methods: Thirty infants with daily regurgitation but no other medical problems were randomly assigned to one of two groups. Infants in group A (n = 16) were fed either HL-450, an AR milk thickened with a commonly used concentration of LBG (0.45 g/100 mL) or control milk (HL-00; no LBG) in a crossover manner for periods of 1 week. The order of milk was randomly chosen for each subject. Infants in group B (n = 14) were fed HL-350, an AR milk with a reduced LBG concentration (0.35 g/100 mL), or HL-00 in the same crossover fashion. The number of episodes of regurgitation, feeding time, and body weight gain were recorded. Three infants in group B did not complete the protocol and were excluded.

Results: Both AR formulas decreased the number of regurgitation episodes by approximately 50% compared with control. Five mothers who gave their infants HL-450 and no mothers who fed their children HL-350 reported that the infants had difficulty sucking the formula through the nipple. Thirteen (81.3%) mothers who used HL-450 and 9 (81.8%) mothers who used HL-350 preferred the AR milk to the control milk.

Conclusions: An AR milk with reduced LBG was as effective in reducing regurgitation as one with the usually available concentration of LBG. ***JPGN 38:479–483, 2004.*** **Key Words:** Anti-regurgitant milk—Gastroesophageal reflux disease—Infant—Locust bean gum—Regurgitation. © 2004 Lippincott Williams & Wilkins

Regurgitation is common in infants (1–4). Approximately half of infants aged 4 months regurgitate at least once a day (5,6). According to the guidelines of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (2,6,7) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) (3) the conservative treatment for uncomplicated infant regurgitation consists of parental reassurance and thickening the formula,

In European countries, locust bean gum (LBG) is the agent most frequently used to thicken milk, while rice cereal is used predominantly in the United States (8). The viscosities of commercially available anti-regurgitant milks (AR milks) with LBG range from 320 to 530 mPa · s at pH 5. Concentrations of LBG of 0.4 to 0.45 g per 100 mL in the formula provide this viscosity. The viscosity of rice cereal-added AR milk is also approximately 400 mPa · s at pH 5.

Previous studies have shown that a thickened formula significantly decreases the number of episodes of regurgitation (9–11) and improves other symptoms of gastroesophageal reflux (GER), such as crying and sleep disturbances (12). However, some infants have difficulty sucking and swallowing thickened formula, and an increase in coughing has been reported in infants receiving formula thickened with rice cereal (13). The optimal viscosity of infant formulas for decreasing regurgitation and for comfortable feeding have not been well investigated.

We studied the number and the volume of regurgitations, the feeding time and the volume consumed, weight gain, and bowel movement frequency in infants fed formula thickened with different concentrations of LBG.

PATIENTS AND METHODS

Patients

Study patients were recruited during routine well-baby check-ups in two public health centers (Kasagake Health Center and Haramachi Health Center) and one local hospital (Tone Central Hospital) in Gunma Prefecture from August 2000 to

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August 2001. Infant check-ups are conducted by the local government, and most infants in these regions visit one of these facilities several times during infancy. In addition to routine physical examination and measurement of weight, questionnaires were distributed to the mothers of all 458 infants 3 to 5 months old. Questions included gender, birth weight, method of feeding, breast milk or formula, the number of episodes of regurgitation per day, and the number of bowel movements. The answers were checked by one pediatrician (H.K.), who was conducting the check-up.

If the infant regurgitated once a day or more (n = 132; 28.8%), additional questions were asked by another physician (R.M.). These questions included whether the infant was irritable, had hematemesis, passed black stools, had a chronic cough, was occasionally cyanotic, or had any other medical problem. The mothers also were asked whether the infant was fed mainly with infant formula or breast milk. Thirty-eight of these 458 (8.3%) infants had three or more episodes of regurgitation per day but had no symptoms indicating GER-related complications and were fed mainly with formula. We excluded infants who were neurologically handicapped or had a known organic or metabolic cause of GER or a major medical problem, including birth weight less than 2000 g, prematurity (less than 35 weeks gestation), jaundice, or any other gastrointestinal symptoms, such as diarrhea, constipation, or abdominal distention, or previous drug treatment for GER.

The mothers of 30 of 38 infants (14 boys, 16 girls) with three or more episodes of regurgitation per day agreed to participate in the study. They were randomly separated to two groups: group A was fed with HL-450 and HL-00 (n = 16) and group B was fed with HL-350 and HL-00 (n = 14). Three infants who had been assigned to group B were excluded after the enrollment because they experienced viral infections during the study. Gender, age, body weight, and the number of infants receiving supplemental breast feeding were similar in groups A and B (Table 1).

Test Formulas

We used three infant formulas that were identical except for the concentration of LBG. The concentrations of LBG in HL-450, HL-350, and HL-00 were 0.45 g/100 mL, 0.35 g/100 mL, and 0.0 g/100 mL, respectively. The control milk, HL-00, was identical with one of the common infant formulas in Japan (Hagukumi, Morinaga, Tokyo).

The formula per 100 mL contained 67 kcal, 1.64 g of protein (casein 32% and whey 68%), 7.2 g of carbohydrate, and 3.51 g of lipid. The osmolarity was 288 mOsm/kg · H_2O. All formulas were provided to the mothers with in identical cans and with identical labels applied by the manufacturer. However, it was not difficult to notice the difference between thickened formula and control milk by the difference in viscosity. Therefore, blinding was presumably valid only as to the concentration of LBG.

Measurement of Formula Viscosity

HL-450, HL-350, and HL-00 were dissolved in hot water (50°C) at their recommended concentration. Formula thickened with pregelatinized rice starch (2.3 g rice starch per 100 mL of 13% HL-00) was prepared at a final concentration of 15.3% (w/v). After the pH of formulas was adjusted from 6 to 4 with 1 mol/L HCl and from 4 to 1 with 6 mol/L HCl, the formulas were kept at 37°C in a water bath for 20 minutes, and the viscosity was measured at 37°C, at 60 rpm by the Brookfield viscometer (Tokyo Keiki Co., Tokyo, Japan).

Protocol

Each infant in group A was fed with HL-450 or HL-00 for 1 week each. The order of the test formulas was chosen at random for each subject. Seven infants were fed HL-450 for the first week. Each infant in group B was fed with HL-350 or HL-00 for 1 week each. Six infants were fed HL-350 first. The number of regurgitation episodes per day and the estimate of the volume regurgitated, the feeding time, the volume fed and the number of bowel movements per day were recorded by the mother in a study diary. We excluded three infants in group B who experienced apparent viral illnesses during the 2-week study period.

The volume of formula regurgitated was estimated visually in a semiquantitative manner using the following scoring system proposed by Orenstein et al. (12): 0: no regurgitation; 1: minimal regurgitation (approximately 2 mL or less); 2: about 1 teaspoonful (2 to 5 mL); 3: 2 to 3 teaspoonfuls (5 to 15 mL); and 4: 4 teaspoonfuls or more. Body weight was measured on days 1, 8, and 15 of the study. After the 2-week test period, each mother was interviewed to find which milk she preferred: AR milk or control milk. Whichever she chose, that formula

TABLE 1. *Clinical features of subjects*

	Group A (n = 16)* (fed with HL-450 and HL-00)	Group B (n = 11)† (fed with HL-350 and HL-00)	*P* value
Sex (% of female)	56.3	36.4	0.480‡
Age (d)	130.9 ± 20.8	124.5 ± 17.7	0.413§
Body weight (g)	6,726.3 ± 720.5	6,815.0 ± 636.4	0.745§
Number of infants receiving supplemental breast feeding	2	5	NS‡

NS: not significant.

* Seven infants in group A were fed HL-450 for the first week and HL-00 for the second week. Nine infants were fed HL-00 for the first week and HL-450 for the second week.

† Six infants in group B were fed HL-350 for the first week and HL-00 for the second week. Five infants were fed HL-00 for the first week and HL-350 for the second week.

‡ Chi square test.

§ Unpaired Student *t* test.

was supplied for 2 months, and body weight was measured when the infant was 7 and 12 months old.

Ethical Consideration

Informed consent was obtained from the mother of each subject. This study was approved by the Human Investigation Committee of Gunma University on January 25, 2001.

Statistical Analysis

Patient age and body weight and viscosities of each formula are shown as the mean ± SD. Percentage of the number of regurgitation episodes for each regurgitated-volume score is shown as the mean ± SE. Others are represented as the median and interquartile range. The statistical significance of differences was tested by either the χ^2 test, unpaired Student *t* test, or Wilcoxon signed rank test, whichever was appropriate. *P* values of less than 0.05 were regarded as significant. All analyses were performed using Stat View computer software (Stat View, version 5.0, Tokyo, Japan).

RESULTS

The viscosities of the three formulas used in this study and that of milk thickened by rice cereal are shown in Table 2. In each formula, viscosities were greatest when the pH was between 4 and 5. At pH 5, the viscosity of HL-450 and HL-350 was greater than that of HL-00 by approximately 20-fold and 10-fold, respectively.

The average number of regurgitation episodes occurring each day while the infants were fed different formulas is shown in Figure 1. In all 16 infants fed with HL-450 (group A), the number of regurgitation episodes was less when the infants were fed HL-450 than when they were fed HL-00. The median value was approximately half (1.6; 0.8–2.0: median; interquartile range) that seen with HL-00 (3.5; 2.3–4.9). Similarly, in 10 of 11 infants in group B, the number of regurgitation episodes was less when they were fed HL-350 (1.3; 0.6–2.3) than when they were fed HL-00 (2.9; 2.0–3.2), and the median value was decreased by approximately 50%. The estimated volume of milk in each regurgitation episode did not differ significantly between HL-450 and HL-00

TABLE 2. *Viscosities of each formula at various pH levels*

	mPa · s			
	HL-450	HL-350	HL-00	Added-rice starch*
pH 1	216.0 ± 7.1	144.2 ± 19.0	5.2 ± 0.3	102.2 ± 4.4
pH 2	143.8 ± 9.8	86.3 ± 7.2	4.2 ± 0.1	47.6 ± 1.0
pH 3	162.2 ± 4.6	80.8 ± 5.9	4.6 ± 0.1	57.7 ± 0.7
pH 4	227.7 ± 11.7	169.3 ± 3.7	33.9 ± 1.2	308.5 ± 4.3
pH 5	334.5 ± 16.0	192.0 ± 6.5	16.0 ± 0.5	426.8 ± 9.3
pH 6	108.2 ± 2.8	68.2 ± 1.6	4.3 ± 0.1	57.0 ± 4.5
pH 6.8	113.8 ± 2.0	65.8 ± 1.7†	4.1 ± 0.1	48.6 ± 0.6

* 2.3 g rice starch is added to 100 mL formula.
† Measured at pH 6.7.

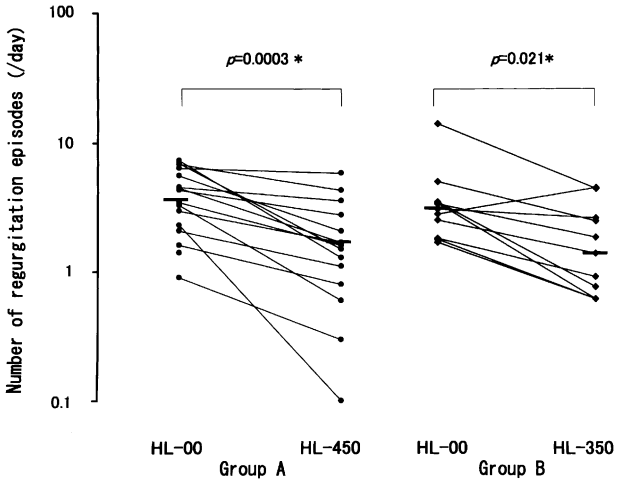

FIG. 1. The average number of regurgitation episodes when patients were fed with HL-450 (left panel) or HL-350 (right panel) compared with HL-00. *Wilcoxon signed rank test.

or HL-350 and HL-00, except that the proportion of minimal regurgitation was slightly less with HL-450 than with HL-00 (Fig. 2).

Table 3 shows the feeding volume and time, weight gain, and the number of bowel movements per day. There was no significant difference in the feeding volume between HL-450 and HL-00 or between HL-350 and HL-00. The median feeding time was longer when the infants were fed HL-450 than when fed HL-00. Similarly, the feeding time was greater with HL-350 than with HL-00. However, the difference was statistically significant only with HL-450 and HL-00 because of a relatively wide variation of values with HL-350 and HL-00. The 1-week weight gain with HL-450 was similar to that with HL-00, whereas that with HL-350 was slightly, but significantly, greater than that with HL-00. The number of bowel movements was similar with HL-450 and HL-00, whereas the number with HL-350 was slightly, but significantly, greater than that with HL-00.

No infants had any complications during the study. Five of 16 mothers who gave their infants HL-450 and none of the 11 mothers who fed their infants HL-350 reported that their infants seemed to have difficulty sucking the formula. Long-term weight gain after giving each formula is shown in Table 4. After 2 weeks, 13 of 16 (81.3%) mothers who used HL-450 and 9 of 11 (81.8%) mothers who used HL-350 preferred the thickened formula to control milk and wanted to continue to use AR milk.

DISCUSSION

Thickening of formula has been recommended as one treatment for GER (1–3), and the efficacy of this therapy has been proven in previous studies (9–11). LBG is a popular milk-thickening agent used mainly in Europe

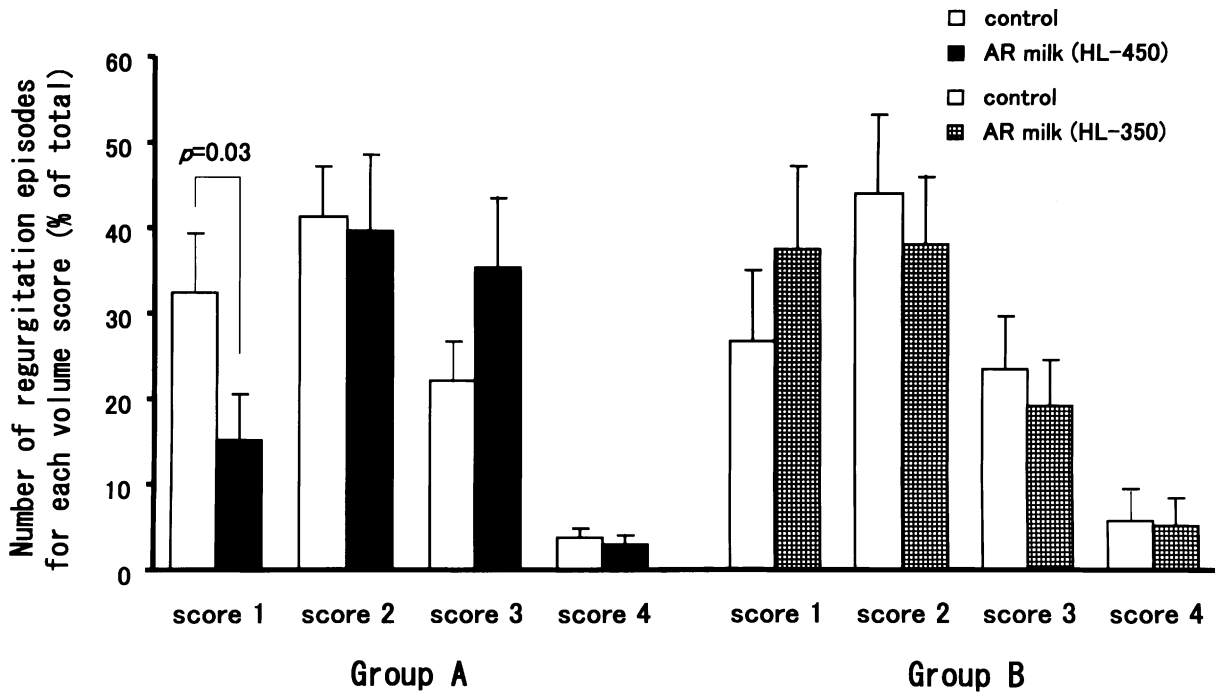

FIG. 2. The number of regurgitation episodes for each volume score. Each bar indicates the number of regurgitation episodes for each regurgitated-volume score expressed as the percentage of total regurgitation episodes. 0 = no regurgitation; 1 = minimal regurgitation (approximately 2 mL or less); 2 = about 1 teaspoonful (2 to 5 mL); 3 = 2 to 3 teaspoonfuls (5 to 15 mL); and 4 = 4 teaspoonfuls or more.

that has been demonstrated to reduce episodes of regurgitation. The concentration of LBG in most LBG milks ranges from 0.4 to 0.5 g/mL. However, no studies have been performed to determine the effect of different LBG concentrations on regurgitation. The current study compared two AR milks with different concentrations of LBG. HL-450, a formula with the concentration of LBG used in most commercial LBG milks, and HL-350, a formula with reduced LBG. Both formulas reduced the frequency of regurgitation when compared with unthickened formula. However, more mothers noted increased difficulty with feeding the HL-450 compared with the control formula. This likely represents a difference in the effort to suck the HL-450 formula because there was no difference in feeding time or long-term weight gain with the different formulas administered to otherwise healthy infants. The infants in this study were healthy infants. It is likely that differences in formula viscosity would have a greater impact on the ability of infants with feeding disorders to ingest adequate amounts of formula for growth.

Short-term weight gain was better with HL-350 than with control milk, whereas weight gains with control milk and HL-450 were similar. However, the long-term weight gains in infants fed with HL-450, HL-350, and regular formula were similar at 7 and 12 months of age.

TABLE 3. *Feeding characteristics, weight gain, and bowel movement frequency in control versus formulas with different concentrations of locust bean gum*

	Group A (n = 16)			Group B (n = 11)		
	HL-00	HL-450	*P* value*	HL-00	HL-350	*P* value*
Feeding volume (mL/d)	779 (695.0–833.6)	840 (687.7–859.7)	0.30	778 (678.6–940.6)	809 (745.5–917.9)	0.50
Feeding time (min)	11.3 (9.9–12.1)	12.8 (10.5–16.2)	0.04	12.5 (10.9–16.0)	15.6 (10.7–17.2)	0.69
Weight gain (g/d)	20.7 (10.5–31.0)	20.7 (14.3–26.1)	0.76	13.2 (7.9–21.5)	29.3 (23.2–32.8)	0.03
Bowel movement (d)	1.4 (1.0–1.5)	1.4 (1.1–1.6)	0.48	1.4 (0.8–1.6)	1.6 (1.1–2.3)	0.02

All values are expressed as the median and the interquartile range.
* Wilcoxon's signed rank test.

TABLE 4. *Weight gain during the first year of life with administration of formula with different concentrations of locus bean gum*

Age	HL-450	HL-350	HL-00
4 months old (g)	6,935 ± 687	7,156 ± 452	6,096 ± 594
7 months old (g)	7,912 ± 774	8,139 ± 619	7,387 ± 740
12 months old (g)	8,934 ± 700	9,136 ± 454	8,649 ± 846

Therefore, this difference is unlikely to be of clinical importance.

No serious adverse effects of LBG have been reported, and we did not notice any symptoms that might be related to the milk in this study. One adverse effect that we anticipated was a change in bowel movements because LBG is, unlike rice cereal, not absorbed from the gastrointestinal tract. Our results showed that the number of bowel movements was greater in children fed HL-350 than in those fed HL-00. However, the difference was small, so the change in the stool frequency probably is of no clinical importance.

The results of this study performed in infants with uncomplicated GER might not be immediately applicable to infants with severe GER, who have complications such as failure to thrive, esophagitis, or respiratory disorders. However, most patients with GER who are given an AR milk have only uncomplicated regurgitation, so a thinner AR milk would adequately treat most of these infants.

There have been no data published previously to show the viscosity of milk at a pH below 5. Our data showed that the viscosity of milk was greatest at pH 4 to 5 and then decreased below 4. This decrease in viscosity in milk with a pH lower than 4 may be explained by the pH dependence of casein coagulation, which is greatest at pH 4 to 5. Thus, these milk thickeners may be more effective when combined with antisecretory therapy that raises intragastric pH from fasting values of less than 2. However, this may not be important because gastric pH is often greater than 4 after feeding, when most episodes of regurgitation occur (14,15).

In conclusion, our results indicate that thinner AR milk reduces the number of episodes of regurgitation and is well tolerated in infants with uncomplicated regurgitation. We suggest that additional studies should be done to determine the usefulness of AR milks containing less thickener than do current AR milks.

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