

Original Article



Effectiveness and Tolerance of a Locust Bean Gum-Thickened Formula: A Real-Life Study

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ABSTRACT

Purpose: Thickened infant formulas reduce regurgitation frequency and volume. Because the digestive tolerance of locust bean gum-containing formulas is controversial, the effectiveness and tolerance of a locust bean gum-thickened formula in infants presenting with regurgitation was evaluated. No other interventions were allowed during the 1 month follow-up period.

Methods: We conducted an open, prospective, observational study of a locust bean gum-thickened formula administered to infants presenting with moderate to severe regurgitation according to parents during 1 month. Effectiveness and tolerance were assessed by evaluating gastrointestinal symptoms and quality of life indicators.

Results: A total of 2,604 infants with an average age of 9.3±4.3 weeks were included in this 1 month trial. Regurgitation frequency and estimated volume decreased significantly ($p<0.001$) and the episodes were resolved completely in 48% of the infants. A significant decrease in duration of crying and episodes of gas ($p<0.001$), with improvement in quality of life parameters, was observed. Stool frequency increased and stool consistency softened ($p<0.001$) to levels within the physiologic range, consistent with the increased fiber load (0.42 g/100 mL).

Conclusion: Locust bean gum-thickened formula decreased infant regurgitation, was well tolerated, and improved parental quality of life. Stool composition and frequency of the infants remained within the physiologic range.

Keywords: Locust bean gum; Quality of life; Gastro-esophageal reflux; Infant formula; Defecation; Diarrhea; Crying

INTRODUCTION

Infantile regurgitation is a frequent functional gastrointestinal disorder, requiring medical assistance in approximately 25% of infants [1,2]. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend parental reassurance and thickened formulas as the first-line approach for the management of regurgitation in formula-fed

Conflicts of Interest

Raish Oozeer and Leo Meunier are employees of the Danone Group (whose affiliate Laboratoires Gallia funded this study and editing services). Patrick Tounian received fees for participating in the scientific committee of the study. Gerrit Speijers and Yvan Vandenplas have no conflict of interest to declare.

infants [1]. Infant formula can be thickened with different agents such as locust bean gum (LBG), starch, pectin, or mixtures of various substances [3].

All thickening substances reduce the number of regurgitation episodes and the associated volume of regurgitation [1,3]. LBG has unique characteristics such as a pH-independent thickening effect resulting in more in vitro viscosity than other thickening agents [3-5]. LBG is not susceptible to degradation by salivary amylase in contrast to starch thickeners [3]. However, the gastrointestinal adverse effects of formulas thickened with LBG have been debated because they increase defecation frequency and stool softening [6-8]. Therefore, this observational study aimed to evaluate the efficacy and tolerance of an LBG-thickened infant formula in infants presenting with moderate to severe regurgitation.

MATERIALS AND METHODS

Study design and setting

This observational, open, prospective, nationwide multicenter study was conducted by French community pediatricians between January 2015 and December 2016. Each practitioner included between 1 and 10 infants over a maximum period of 3 months. Two visits were planned: one at inclusion and a second after 1 month at the end of the intervention period. A questionnaire was administered to collect the required information at both consultations (**Table 1**), during which the pediatrician discussed the required information with the parents.

Study participants

This study was performed with exclusively formula-fed, full-term born infants presenting with symptoms of moderate to severe regurgitation according to parental perception. The frequency of regurgitation was at least one episode per day. The study inclusion and exclusion criteria are listed in **Table 2**. The medical intervention consisted of reassurance and anticipatory guidance regarding infant regurgitation, in combination with a thickened anti-regurgitation formula, in accordance with the guidelines [1].

LBG-thickened formula (Gallia AR1; Danone Nutricia, Steenvoorde, France) was exclusively administered to all infants during the 1 month observation period, during which no other therapeutic intervention was allowed. Supplementation of probiotics or other remedies for reflux or colicky babies was excluded. The formula was thickened with 3% LBG (0.42 g/100 mL of reconstituted formula at 14.3%), containing postbiotics derived from the *Lactofidus* (Danone Nutricia) fermentation process with two bacterial strains, *Bifidobacterium breve* C50 and *Streptococcus thermophilus* O65, that generated bioactive compounds [9].

The formula had a whey/casein ratio of 40/60. The full composition of the study formula is provided in **Table 3**. In this study, data on the diagnosis and management of regurgitation was collected using the existing evidence-based guidelines [1]. The French Ethical Board, which coordinated the study, did not consider it necessary to collect signed, informed consent from the parents. Parents received detailed information on the study and had to orally declare their agreement to participate.

Table 1. Questionnaire

Regurgitation
Frequency
Absence
1–2 d
3–4 d
5–6 d
>6 d
Volume
None
Small
Significant
Excessive
Crying
Absent
<1 hr/d
1–3 hr/d
>3 hr/d
Defecation
Frequency
<1 d
1 d
2–3 d
3–4 d
>4 d
Consistency
Hard
Formed
Soft/mushy
Loose/watery
Transit time
Not changed
Faster
Slower
Flatulence frequency
None
1–2 d
3–4 d
>4 d
Sleep quality
Poor-good: 0–10
Parental anxiety
Poor-good: 0–10
Parental satisfaction
Poor-good: 0–10

Table 2. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Term birth (≥ 37 –42 wk)	Preterm birth (<37 wk gestation)
Birth weight between 2,500 g and 4,200 g	Prior treatment with thickening agents such as Gelopectose, Gumilk, and Magic Mix
Infants with moderate to severe regurgitation according to parental perception	Prior drug treatment for gastroesophageal reflux.
Exclusively formula-fed infants or those fed with standard starter formula or starch-thickened formula.	Prior administration of locust bean gum-thickened infant formula.
	Prior feeding with extensive hydrolysate or a formula containing probiotics or prebiotics.
	Prior treatment that could alter gastrointestinal transit
	Infants with acute or chronic disease.

Table 3. Composition of study formula

Item	Per 100 g	Per 100 kcal
Energy		
kJ	2,024	420
kcal	482	100
Protein (g), consisting of:	10.1	2.1
Casein	6.1	1.3
Whey	4.0	0.5
Carbohydrates (g), consisting of:	60.2	12.5
Sugar, consisting of:	38.0	7.9
Lactose	36.6	7.6
Fats (g), of which:	21.7	4.5
Saturated fatty acids	10.2	2.1
Linoleic acids	3.86	0.800
α -linoleic acid	0.328	0.068
Fiber (g)	2.7	0.57
Vitamins		
A (μ g-retinol equivalent)	406	84
D (μ g)	6.9	1.4
E (mg α -tocopherol equivalent)	5.9	1.2
K (μ g)	49	10
C (mg)	49	10
B1 (μ g)	368	76
B2 (μ g)	1,100	228
Niacin (μ g)	4,000	830
B6 (μ g)	315	65
Folic acid (μ g)	56	12
B12 (μ g)	1.20	0.26
Biotin (μ g)	18	3.7
Pantothenic acid (μ g)	2,470	511

Study outcomes and assessments

The following characteristics of the study population were collected at inclusion: sex, age, weight, height, and whether they were the first infant of the mother. In addition, the number of patients withdrawing from the study and the reason as well as all reported adverse events were recorded. All data were collected by the pediatrician at inclusion and after the 1 month intervention, based on the information provided by the parents.

The efficacy of the formula in reducing regurgitation was measured by estimating the change in the following variables between the two visits: regurgitation frequency and volume, expressed as excessive, significant, small, and none. Indicators for gastrointestinal tolerance of LBG were the change in defecation frequency and consistency, frequency of episodes of gas production, and quality of life parameters of crying duration, sleep quality, behavior of the infant (quiet/agitated or distressed), and anxiety level of the parents (**Table 1**).

Stool frequency was classified as “less than one,” “one,” “two or three,” or “four or more” defecations per day. Stool consistency was evaluated according to the Bristol stool scale [10], which we adapted from a seven-point scale to a four-point stool consistency scale: hard (covering Bristol scores 1 and 2), formed (covering Bristol scores 3 and 4), soft/mushy (covering Bristol score 5 and 6), and loose/watery (covering Bristol score 7) [11]. Data on the frequency of episodes of gas and crying, and quality of life indicators were obtained from information collected using the questionnaire filled in by the parents. Behavior, sleeping problems, and parental anxiety were assessed using a scale ranging from 0 (normal) to 10 (severely abnormal).

Statistical analyses

Statistical analyses were performed using the Statistical Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC, USA). To assess the efficacy and tolerability of the intervention, an ordinal logistics regression was used [12]. If an odds ratio (OR) was greater than one, the risk of severity decreasing from inclusion to the end of the study was multiplied by the OR value. If the OR was less than one, the risk of increasing severity from inclusion to the end of the study was divided by the OR value.

RESULTS

Of the 2,705 patients recruited, 101 did not meet the inclusion criteria and were excluded. At inclusion, mean weight was $5,007 \pm 1,136$ g (median 4,900 g), mean height was 57 ± 2 cm (median 56 cm), and mean age was 9.3 ± 4.3 weeks. Further information on the characteristics of the study population at inclusion are provided in **Table 4**. Over the course of the study, 183/2,604 (7.0%) participants dropped out (**Table 5**). At inclusion, 2,505/2,604 (96.2%)

Table 4. Characteristics of study population

Characteristics	Value (n=2,705)
Age at inclusion (wk)	9.3±4.3
Sex (n=2,701)	
Male	1,329 (49.2)
Female	1,372 (50.8)
First born (n=1,222)	
Yes	52 (4.3)
No	1,170 (95.7)
Feeding methods prior to inclusion	
Partially breastfed (n=1,188)	
1 mo	749 (63.0)
2 mo	312 (26.3)
3 mo	127 (10.7)
Starter infant formula (n=2,001)	
Yes	2,000 (99.9)
No	1 (0.1)
Starch-thickened infant formula (n=488)	
Yes	487 (99.80)
No	1 (0.20)

Values are presented as mean±standard deviation or number (%).

Table 5. Adverse events and reasons for dropping out of the study

Parameter	Value (n=2,604)
Participant dropout	183 (7.0)
Reason for dropout	
Intercurrent disease	12 (0.5)
Ineffectiveness of thickened formula	50 (1.9)
Intolerance/non-acceptance	77 (3.0)
None	44 (1.7)
In case of intolerance/non-acceptance*	
Refusal to drink	9 (0.4)
Allergy	8 (0.3)
Continuous crying	38 (1.5)
Constipation	14 (0.5)
Diarrhea	31 (1.2)
Parental decision	27 (1.0)
Other	7 (0.3)

Values are presented as number (%).

*Parents may have provided multiple reasons for leaving the study.

infants were younger than 4 months old. Intolerance of the formula was the most frequent (77/2,604, 3.0%) reason provided for study withdrawal, including refusal to drink the formula (n=9), suspected allergy to cow milk protein (n=8), or both.

Gastrointestinal intolerance-related parameters, i.e., crying without obvious cause (n=38/2,604, 1.5%), hard stools (n=14/2,604, 0.5%), and loose or watery stools (n=31/2,604, 1.2%) accounted for study withdrawal of 3.2% of the total number of infants included. One infant was lost to follow up. After 1 month of intervention, regurgitation frequency and volume decreased significantly ($p<0.001$, **Table 6**). Nearly half of the infants (48.6%, n=1,145/2,358) were no longer regurgitating after 1 month. Additionally, after 1 month of intervention, defecation frequency was higher and stools had become softer than they were before the intervention, as defined as change in at least one stool composition parameter ($p<0.001$, **Table 7**).

The number of patients with a stool frequency less than one per day decreased significantly from 16.1% (n=390/2413) at inclusion to 5.7% (n=137/2,397) after 1 month ($p<0.001$). In addition, the number of infants with a stool frequency of four or more per day also decreased

Table 6. Regurgitation parameters at inclusion and after 1 month of treatment in patients completing the study (n=2,421)

Parameter	At inclusion	After 1 month	OR (95% CI)	p-value
Regurgitation frequency	n=2,415	n=2,358	105.70 (88.01–126.94)	<0.001
None	-	1,145 (48.6)		
1–2 per day	139 (5.8)	906 (38.4)		
3–4 per day	995 (41.2)	266 (11.3)		
5–6 per day	939 (38.9)	33 (1.4)		
>6 per day	342 (14.2)	8 (0.3)		
Regurgitation volume	n=2,416	n=2,345	146.25 (119.42–179.12)	<0.001
None	-	1,114 (47.5)		
Insignificant	268 (11.1)	1,097 (46.8)		
Significant	1,401 (58.0)	121 (5.2)		
Excessive	747 (30.9)	13 (0.6)		

Values are presented as number (%).

OR: odds ratio, CI: confidence interval.

Table 7. Stool characteristics and gas episodes at inclusion and after 1 month of feeding with locust bean gum-thickened formula in patients completing the study (n=2,421)

Parameter	At inclusion	After 1 month	OR (95% CI)	p-value
Stool frequency	n=2,413	n=2,397	0.76 (0.69–0.84)	<0.001
<1 per day	390 (16.1)	137 (5.7)		
1 per day	713 (29.5)	820 (34.2)		
2–3 per day	1,111 (46.0)	1,311 (54.7)		
≥4 per day	199 (8.2)	129 (5.4)		
Stool consistency	n=2,415	n=2,387	2.25 (2.05–2.48)	<0.001
Liquid/watery	781 (32.3)	1,171 (49.0)		
Soft/mushy	553 (22.9)	572 (24.0)		
Formed	734 (30.4)	581 (24.3)		
Hard	347 (14.4)	63 (2.6)		
Frequency of gas episodes	n=2,350	n=2,390	12.67 (11.22–14.31)	<0.001
None	0 (0)	907 (37.9)		
1–2 per day	949 (40.4)	1,132 (47.4)		
3–4 per day	1,037 (44.1)	293 (12.3)		
>4 per day	364 (15.5)	58 (2.43)		

Values are presented as number (%).

OR: odds ratio, CI: confidence interval.

OR (95% CI): OR indicates progression of symptoms after 1 month. When OR >1, the risk of decreasing severity after 1 month is multiplied by OR (e.g., 12.67 less risk of having frequent gas). When OR <1, risk of increasing severity is divided by OR (e.g., 1/0.76=1.3 higher risk of having frequent stool).

Table 8. Endpoint assessment of indicators of gastrointestinal tolerance

Parameter	Value (n=2,421)
Decreased intestinal transit (n=2,368)	
Yes	274 (11.6)
No	2,094 (88.4)
Increased intestinal transit (n=2,364)	
Yes	813 (34.4)
No	1,551 (65.6)

Values are presented as number (%).

Table 9. Occurrence of crying at inclusion and after 1 month of feeding with locust bean gum-thickened formula in patients completing the study (n=2,421)

Parameter	Inclusion	After 1 month	OR (95% CI)	p-value
Total duration of crying				
None	232 (9.6)	911 (37.0)	9.15 (8.18–10.22)	<0.001
<1 hour per day	859 (35.5)	1,279 (53.3)		
1–2 hours per day	801 (33.1)	172 (7.2)		
2–3 hours per day	387 (16.0)	23 (1.0)		
>3 hours per day	139 (5.7)	13 (0.5)		
Duration of crying episodes				
<30 min	1,254 (54.9)	1,707 (90.0)	7.46 (6.36–8.75)	<0.001
30 min–1 hr	833 (36.4)	171 (9.0)		
>1 hr	196 (8.6)	18 (0.9)		
Sleeping problems				
0–3	559 (23.1)	1424 (60.3)	3.58 (3.27–3.91)	<0.001
4–6	1,065 (44.0)	482 (20.4)		
7–10	793 (33.0)	454 (19.2)		
Infant behavior: calm/agitated				
0–3	540 (23.1)	1,459 (63.8)	3.99 (3.63–4.39)	<0.001
4–6	1,172 (50.1)	394 (17.2)		
7–10	625 (26.7)	434 (18.9)		
Parental anxiety				
0–3	522 (21.6)	1,560 (66.3)	6.20 (5.66–6.80)	<0.001
4–6	1,028 (42.6)	518 (22.0)		
7–10	860 (35.7)	275 (11.7)		

Values are presented as number (%).

OR: odds ratio, CI: confidence interval.

significantly from 8.2% (n=199/2413) at inclusion to 5.4% (n=129/2,397, $p<0.001$). The number of infants with hard stools decreased from 14.4% (n=347/2,415) to 2.6% (n=63/2,387, $p<0.001$).

Parents of 34.4% (n=813/2,364) of the infants indicated that the thickened formula caused a more rapid bowel transit than the unthickened formula did. However, at the same time, 11.6% (n=274/2,368) of the infants were reported to have a slower transit time with the thickened formula than with the unthickened formula (**Table 8**). The number of gas episodes decreased significantly ($p<0.001$). Frequency and duration of crying decreased (**Table 9**, $p<0.001$). All other quality of life indicators of sleep quality, agitation, and parental anxiety levels improved significantly over the study period.

DISCUSSION

This large-scale investigation of 2,604 infants with moderate to severe regurgitation according to parental perception showed that the LBG-thickened anti-regurgitation formula was effective and well tolerated. The LBG-thickened formula increased stool frequency and softened the consistency, both of which remained within the normal physiological range. LBG consists of high-molecular-weight polysaccharides which are responsible for the

thickening property of the gum. These glycosidic polymers make LBG indigestible and when fermented, have a prebiotic effect on the gastrointestinal microbiota [13].

LBG chelates metal ions and impairs their intestinal absorption at higher concentrations than those in infant formulas. However, no effect on the mineral status has been reported in infants fed LBG-thickened formulas [14,15]. The anthropometric parameters remained within the expected normal expected range as no deviation from the expected weight and growth rate were reported by any of the pediatricians. The decrease in the number and volume of regurgitation episodes demonstrated that the thickened formula was effective. Specifically, 94% of the infants regurgitated three times or more at inclusion, whereas only 13% did so after being fed the thickened formula for 1 month.

According to the Rome IV criteria, two episodes or more per day are the criterion for infant regurgitation [16]. Moreover, nearly half of the infants no longer regurgitated. Because 96% of the infants were younger than 4 months old at inclusion, age was unlikely to have had a clinically relevant effect on the efficacy of the formula, as epidemiologic data show a natural decrease of episodes of regurgitation only after the age of 6 months [2]. Tolerance to the LBG-thickened formula was excellent and only 3.2% of the 2,604 infants included in the study were reported to have dropped out of the study.

Reasons for dropping out were digestive tolerance-related factors such as crying, or changes in consistency of defecation that were significantly severe enough to require stopping trial participation. The percentage of withdrawals was well below the lower range of dropout rates associated with tolerance reported in other clinical trials with infant formulas, which showed dropout rates of 15 to 20% [17,18]. LBG has not been reported to be associated with onset of true diarrhea leading to a risk of dehydration [8].

Only approximately one-third of parents estimated that intestinal transit had become more rapid with administration of the test formula. The increased frequency of defecation and decreased firmness of stool consistency remained within the normal range previously reported for this age group, bringing it closer to the rate and consistency of breastfed infants [19,20]. A review including 13 studies evaluating adverse events associated with infant formulas containing LBG reported an increase in stool frequency in only three of these studies [8]. A reduction in the number of episodes and duration of crying episodes was also reported by the parents, as well as a decrease in the number of episodes of gassiness. Life quality parameters, evaluated as periods of agitation and sleep quality, also improved. Parental anxiety decreased during the intervention.

Previous studies have shown no difference in tolerance between formulas thickened with LBG alone and those thickened with both LBG and starch [21]. The large size of the study population and the low number of drop-outs are strong aspects of our study. Major limitations of our trial are the open design and the lack of a control group. However, blinding would have been almost impossible since it is not possible to effectively blind an intervention with thickened versus unthickened formula. Furthermore, it would be unethical to feed non-regurgitating healthy infants a thickened formula. Blinding of the intervention and inclusion of a control group would also create conditions that would not reflect a “real-life study.”

The aim of the study was to collect information regarding the efficacy and adverse effects of this thickened formula based on parental observations in daily routine practice. Because

this was an observational study, we cannot exclude the possibility that some improvements occurred spontaneously because of natural development over the course of the study or that there was a parental bias in the reporting of symptoms. However, this aspect provides interesting information as it confirms that in the daily routine, prenatal reassurance and dietary guidance decrease symptoms, improve the quality of life, and provide parental reassurance based on the parental perception.

Crying decreases and the sleep quality improves during the first months of an infant's life, particularly after the age of 3 months [22,23]. Because regurgitation decreases spontaneously mainly from the age of 6 months [1,2], the impact of natural physiological changes on regurgitation seems less likely because the majority of infants were younger than 4 months old at inclusion. The relatively short period of observation of 1 month could have caused the underestimation of the occurrence of adverse events. Finally, we cannot exclude the possibility that the presence of probiotics in the test formula contributed to the outcome of this trial.

In conclusion, this large-scale, open, 1-month, observational study showed that the number of episodes and severity of regurgitation decreased significantly following administration of the LBG-thickened formula tested. Moreover, the number of adverse effects was limited, suggesting that the formula was well tolerated. The defecation frequency and stool consistency were closer to those of breastfed infants. The outcome of this trial suggests that there should be no concerns regarding the gastrointestinal tolerance of LBG in infants.

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