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Therapeutic effect of Novalac-IT in infants with constipation

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Abstract

Objective: Infant constipation is a frequent condition in formula-fed infants.

Methods: A prospective randomized clinical trial was performed in infants who had constipation with Novalac-IT (IT group) versus a 20% strengthened formula (S group). Enrolled subjects had difficulties in defecating, hard stools, or low frequency of defecation (≤3 times/wk).

Results: Ninety-three infants (47 boys, mean age 3.8 ± 1.7 mo) were included because of hard consistency of (50.5%), low frequency in (44.1%), or painful (33.3%) defecation. A statistically significant improvement was observed after 4 and 8 wk of intervention in the IT group ($P = 0.014$ and $P < 0.001$, respectively). In the IT group, significantly more infants were symptom free at 4 wk (82.9% versus 50%, $P = 0.029$) and at 8 wk (89.1% versus 54.1%, $P < 0.001$). Increased stool weight was significant in the IT group after 4 and 8 wk ($P = 0.048$ and 0.029).

Conclusion: Novalac-IT decreases constipation in formula-fed infants.

Keywords: Constipation; Defecation; Formula; Infants; Magnesium; Stool

Introduction

Infant constipation is a common problem in formula-fed infants in the developed and developing world. Constipation is usually diagnosed when an infant or child has hard stools or has difficulties in defecating. Weaver et al. [1] studied 240 infants 2 to 20 wk of age, 50% of whom were fed with breast milk and 50% with formula, and found that 93% of these infants passed one to seven bowel movements per day. Loening-Baucke [2] evaluated the prevalence rate of constipation according to criteria of the North American Society of Pediatric Gastroenterology and Nutrition [3] or Rome II [4] in 4157 children <2 y of age and found a prevalence of constipation of 2.9% in the first year of life. An Italian observational study in 2879 infants found a prevalence of constipation of 17.6% [5].

In this study, a commercialized formula, Novalac-IT (Intestinal Transit, Paris, France), was evaluated against a "strengthened regular formula." The latter is a traditional approach in infants with digestive problems in Taiwan.

Materials and methods

We prospectively evaluated the therapeutic and nutritional effects of a magnesium-enriched infant formula (IT group) and a 20% strengthened infant formula (S group) in 93 healthy infants 2 to 6 mo of age with constipation. All infants were included in one center (Chang Gung Memorial Hospital, Taoyuan, Taiwan). Because of this approach, it was not possible to blind the study. The composition of the formulas is listed in Table 1. All subjects were fed exclusively with formula and presented at a pediatric gastroenterology clinic in a medical center because of constipation for ≥2 wk. Participation in the trial was proposed before a more complete diagnostic workup for cow's milk protein allergy, Hirschprung's disease, and others. To prepare the strengthened formula, an assigned nurse educated the family to prepare correctly the 20% strengthened formula (20% extra formula), resulting in a concentration of about 15.6% (the

Intestinal Transit provided free samples of the Novalac-IT formula. There was no other grant from the company. The company was not involved in the design of the study.

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Table 1
Composition of Novalac-IT and 20% strengthened formula (per 100 mL)

Average composition	Novalac-IT formula	Novalac regular formula	Strengthened Novalac regular formula
Energy (cal/100 mL)	70.7	65	78
Protein (g)	1.70	1.60	1.89
Protein source (%)	Whey/casein 60/40	Whey/casein 50/50	Whey/casein 50/50
Fat (g)	3.54	3.30	3.96
Carbohydrate (g)	8.06	7.20	8.69
Carbohydrate source (%)	Lactose 100	Lactose 70, maltodextrin 30	Lactose 70, maltodextrin 30
Major minerals (mg)			
Sodium	17.46	18.20	21.84
Potassium	61.58	58.50	70.20
Chloride	43.40	39.00	46.80
Calcium	60.87	58.50	70.20
Phosphate	31.46	35.10	42.12
Magnesium	9.12	5.09	7.02
Osmolality	300	245	300

regular concentration of the formula is 13%; the strengthened formula had a concentration of 20% more, or 15.6%).

A severity scoring system was developed and evaluated in a pilot study. The severity score is based on stool consistence, frequency and volume, and difficulties in defecation and has a maximal score of 8 (Table 2). Stool weight was measured with a small balance (limited measurement of range 0–500 g) that was given to each participating family; the weight of diaper plus stool was measured after each bowel movement. The data are presented as mean weight (grams per kilogram) per week. Parents were instructed to record abdominal distention and irritability in the diary during the entire intervention period. Symptom assessment was based on the data in the diary during the last week before each visit.

Randomization was performed applying an envelope-drawing system. The intake of formula and clinical parameters regarding constipation and weight gain were recorded by the family. Infants were presented for evaluation and follow-up every 2 wk. Remission was considered if the infants were asymptomatic; a decrease in severity of ≥4 was considered a "good response" and a decrease of 1 to 3 was considered a "fair response." If the score did not change or increased, the intervention was considered a failure. Parents recorded all relevant information daily in a diary during the entire intervention period.

Continuous data were expressed as average ± SD. The data were analyzed using SAS (SAS Institutes, Cary, NC, USA). We used Student's t test for continuous variables and Mantel-Haenszel chi-square test for categorical data. $P < 0.05$ was considered statistically significant. The local ethical committee approved the protocol.

Table 2
Definition of severity score for constipation based on clinical symptoms

Symptoms	Score*		
	0	1	2
Hard stool		Hard and long form	Cobblestone form
Difficulties with defecation		Irritability	Crying
Frequency of defecation	>3 times/wk	1–3 times/wk	<1 time/wk
Stool weight (g · kg^{-1} · wk^{-1})	>35	20–35	<20

* Scoring: 1–3, mild constipation; 4–6, moderate constipation; 7–8, severe constipation.

Results

The study population consisted of 93 patients (47 boys and 46 girls) with a mean age of 3.8 ± 1.7 mo. Demographic and clinical features are listed in Table 3 (47 infants in the IT group and 46 in the S group). The main reasons for consulting were stool consistency (50.5%), frequency (44.1%), and defecation difficulties (33.3%). In the period

Table 3
Baseline demographic and clinical characteristics in two formula groups*

Characteristics	Novalac-IT	Strengthened formula†	P‡
Age (mo)	3.9 ± 1.6	3.8 ± 1.5	0.754
Boys/girls	24/23	23/23	
Symptoms			
Hard stools	24 (51.1%)	23 (50%)	0.917
Difficulty defecation	16 (34%)	15 (32.6%)	0.942
Low frequency	20 (42.6%)	21 (45.7%)	0.927
Weight (g · kg^{-1} · wk^{-1})	28.6 ± 14.9	28.2 ± 15.5	
Severity score			
Mild (1–3)	17 (36.2%)	17 (37%)	0.891
Moderate (4–6)	19 (40.2%)	19 (41.3%)	0.901
Severe (7–8)	11 (23.4%)	10 (21.7%)	0.955

* Categorical data were analyzed by chi-square and Mantel-Haenszel chi-square tests. Data for continuous variables are expressed as mean ± SD and were analyzed by Student's t test.

† Twenty-five percent strengthened regular formula.

‡ $P < 0.05$ considered statistically significant.

Table 4
Efficacy of two interventions*

Effect	Novalac-IT (n = 47)	Strengthened formula (n = 46)†	P
Improved			
2 wk	31 (66%)	23 (50%)	0.177
1 mo	39 (83%)	23 (50%)	0.002‡
2 mo	42 (89%)	25 (54%)	<0.001‡
"Good response"§			
2 wk	17 (36%)	13 (28%)	
1 mo	22 (47%)	11(24%)	
"Fair response"‖			
2 wk	14 (30%)	10 (22%)	
1 mo	17 (36%)	12 (26%)	
Not improved¶			
2 wk	16 (34%)	23 (50%)	
1 mo	8 (17%)	23 (50%)	
Symptom free			
2 wk	18 (38%)	12 (26%)	0.299
1 mo	28 (60%)	16 (35%)	0.029‡
2 mo	35 (75%)	18 (39%)	<0.001‡

* Categorical data were analyzed by Mantel-Haenszel chi-square test.
† Twenty-five percent strengthened regular formula.
‡ $P < 0.05$ considered statistically significant.
§ Decreases severity score ≥4.
‖ Decreased severity score 1–3.
¶ No change in severity score.

before inclusion, the mean stool weight was 28.4 ± 13.5 g/kg per week.

The effects of the interventions are listed in Table 4; improvement was noticed in 66% of the infants in the IT group compared with 50% in the S group. Two weeks after the start of the intervention, there was no significant difference between groups, although more infants in the IT group (38.3%) than in the S group (26.1%) were symptom free. However, after 4 wk of intervention, differences became statistically significant (Table 4). The results after 2 mo of intervention confirmed the data after 1 mo; in the IT group, 42 of 47 (89.4%) infants had improved compared with 25 of 46 (54.3%) in the S group ($P < 0.001$). Similar differences were observed for the number of infants who were symptom free (35 of 47, 74.5%, versus 18 of 46, 39.1%; $P < 0.001$). Stool weight was greater in the IT group than in the S group after 1 and 2 mo of intervention (P = 0.048 and 0.029; Table 5). Weight gain in the IT group was greater than that in the S group because the infants ingested a larger volume of Novalac-IT (Table 6). Symptoms (abdominal distention and irritability) decreased significantly more after 2 mo of intervention, but not after 1 mo, in the Novalac-IT group (Table 7).

Table 5
Stool weight in infants fed Novalac-IT and strengthened formula*

Stool weight ($g \cdot kg^{-1} \cdot wk^{-1}$)	Novalac-IT (n = 47)	Strengthened formula† (n = 46)	P
After 2-wk trial	42.2 ± 17.7	37.3 ± 16.7	0.169
After 1-mo trial	40.9 ± 17.1	34.1 ± 15.9	0.048‡
After 2-mo trial	41.2 ± 17.3	33.7 ± 15.5	0.029‡

* Data were analyzed by Student's t test.
† Twenty-five percent strengthened regular formula.
‡ $P < 0.05$ considered statistically significant.

Table 6
Weight gain and ingested volume in infants fed Novalac-IT and strengthened formula*

Weight gain (g)	Novalac-IT (n = 47)	Strengthened formula† (n = 46)	P
After 2-wk trial	242.3 ± 87.3	240.7 ± 81.5	0.927
After 1-mo trial	721.6 ± 193.2	679.2 ± 184.7	0.277
After 2-mo trial	1461.2 ± 315.1	1302.4 ± 293.3	0.013‡
Ingested volume/d			
Baseline	706.2 ± 136.3	703.8 ± 135.8	0.935
After 1 mo	804.1 ± 146.4	772.4 ± 143.9	0.290
After 2 mo	916.3 ± 158.2	822.6 ± 147.3	0.004‡

* Data were analyzed by Student's t test.
† Twenty-five percent strengthened regular formula.
‡ $P < 0.05$ considered statistically significant.

Discussion

Diagnosis and treatment of constipation in otherwise healthy infants and children is based on history and clinical evaluation. The Rome II and III criteria have been developed but are not fully adapted to this age group. Constipation is usually defined in terms of changes in frequency, size, and consistency of the stools or defecation difficulties. Defecation frequency in infants depends on age and feeding. The infants evaluated in this trial all had three or fewer

Table 7
Abdominal symptoms (after 1 and 2 mo of intervention)*

Symptoms	Novalac-IT (n = 47)	Strengthened group (n = 46)	P†
Abdominal distention			
After 1 mo			
Improved	28 (60%)	20 (43%)	0.178
Stationary/worse	19 (40%)	26 (57%)	
After 2 mo			
Improved	38 (81%)	27 (59%)	0.035
Stationary/worse	9 (19%)	19 (41%)	
Irritability			
After 1 mo			
Improved	30 (64%)	21 (46%)	0.120
Stationary/worse	17 (36%)	25 (54%)	
After 2 mo			
Improved	41 (87%)	29 (63%)	0.006
Stationary/worse	6 (13%)	19 (37%)	

* Symptoms assessment based on period of last week before each visit.
† Mantel-Haenszel chi-square test for categorical data analysis; $P < 0.05$ considered statistically significant.

defecations per week and stools were considered hard. According to the parents' subjective interpretation, after 2 mo of intervention, abdominal distention and irritability were significantly more reduced in the Novalac-IT group.

An increase in fluid intake may help many infants with simple constipation [6]. However, the efficacy of increasing liquid or the introduction of fibers is recommended but not thoroughly validated [7–9]. The vast majority of ingested liquid is absorbed in the proximal intestine and excreted through the urinary tract. Young et al. [10] reported that increasing the water intake or administration of hyperosmolar liquid had no effect in a series of 108 constipated children who were 2 to 12 y old. High osmolarity liquids such as apple juice and Karo syrup have been proposed because their limited absorptive capacity results in a relative carbohydrate malabsorption and an osmotic effect in the colon [11]. In Taiwan, a strengthened formula is traditionally used for infant constipation because of the possible osmotic effect. The results of this trial showed some efficacy of the strengthened formula in infant constipation: 34.8% of the infants were symptom free after 4 wk (however, the effect of Novalac-IT was greater). It is known that casein predominant formula causes more frequent constipation than whey predominant formula [12]. However, the difference in the whey/casein ratio between formulas is relatively small: the whey/casein ratio in Novalac-IT is 60/40% compared with a ratio of 50/50% in the regular formula. Moreover, although the group receiving the strengthened formula ingested more casein, the strengthening of the formula resulted in some efficacy with respect to constipation. As a consequence, the difference in the protein ratio is unlikely to have had a major effect on the stool pattern in this trial. In addition, differences in carbohydrate composition may have influenced bowel habits. Novalac-IT contains 100% lactose versus 70% in the regular formula. Lactose has been shown to have very limited laxative effects in lactose-tolerant adults [13]. However, lactose is known to be not completely absorbed in young infants and to stimulate the development of bifidogenic flora, which in turn bring the stools of formula-fed infants closer to the stools of breast-fed infants.

Because infants in the Novalac-IT group ingested larger volumes, the infants in this group ingested more calories (after 2 mo of intervention, a mean daily intake of 647.82 cal in the Novalac-IT group versus 641.27 cal in the strengthened-formula group).

Laxatives intervene in one or more mechanisms that cause constipation such as active electrolyte secretion, decreased water and electrolyte absorption, increased intraluminal osmolarity, and hydrostatic pressure [14]. Laxatives convert the intestine from a primarily absorptive organ (for water and electrolytes) to a secreting organ [15]. Magnesium is hypothesized to induce release of cholecystokinin, resulting in increased intestinal motor activity. Magnesium also has an osmotic effect [16,17]. Carbohydrate supplement (corn syrup) resolved constipation in 25% of children, whereas milk of magnesium and polyethylene glycol resolved constipation in 92% [4]. The milk of magnesium and polyethylene glycol were evaluated as safe [4]. Recently, Loening-Bauke and Pashankar [18] reported compliance rates of 95% for polyethylene glycol and 65% for milk of magnesia (milk of magnesia contains magnesium hydroxide formulated at about 8% weight per volume [8 g in 100 mL]; the strengthened formula contains 7.02 g and Novalac-IT 9.12 g of magnesium/100 mL). After 12 mo, 62% of children treated with polyethylene glycol and 43% of those treated with milk of magnesia exhibited improvement, and 33% of children treated with polyethylene glycol and 23% of those treated with milk of magnesia had recovered. Polyethylene glycol and milk of magnesia did not cause clinically significant side effects or blood abnormalities, except that one child was allergic to polyethylene glycol [18]. Magnesium-rich mineral water has been shown to be effective in formula-fed infants with constipation (Morali, 2003; personal communication).

The costs of magnesium-enriched and regular formulas are identical. In other words, magnesium-enriched formula is the cheapest intervention possible and is cheaper than the regular formula at increased concentration. Long-term constipation may negatively influence growth [19,20]. Constipation may be a contributing factor to poor growth in children with nocturnal enuresis [21]. In the present study, infants fed Novalac-IT had larger defecation volumes but a better weight gain than did those fed the strengthened formula. The better weight gain in contrast to the larger stool output is a measurement of safety of Novalac-IT and should not be regarded in view of normal ranges. In conclusion, Novalac-IT improves the clinical symptoms of constipation in formula-fed infants.

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