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Bovine Colostrum in the Management of Nonorganic Failure to Thrive: A Randomized Clinical Trial

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ABSTRACT

Objective: The objective of the study was to evaluate the clinical efficacy of oral bovine colostrum in the management of nonorganic failure to thrive (FTT).

Materials and Methods: In a randomized clinical trial, 120 children (1–10 years of age) of either sex with mild or moderate nonorganic FTT were divided into 2 groups. Both groups were matched with regard to age, sex, weight, and height. One group (control) received routine treatments for FTT and the other group (case), besides routine treatments, received supplementary bovine colostrum at the dose of $40\,mg \cdot kg^{-1} \cdot day^{-1}$ for a 3-month period. Following the initial visit, subsequent visits were completed following 1, 2, and 3 months of supplementation. For quantitative measurements, Waterlow I (height for age) and Gomez (weight for age) indices were used.

Results: The mean value of Gomez index in the case group (81.72) was significantly higher than the control group (77.12) at the end of the third month of supplementation ($P = 0.003$). Such a difference was not reported based on Waterlow I index between the case and control groups (92.91 vs 91.71; $P = 0.094$). According to Gomez index 12 patients (20%) who received colostrum became healthy at the end of the third month, which was significantly higher than the control group (2 cases, 3.3%); $P = 0.006$.

Conclusions: Bovine colostrum supplementation for a 3-month period is a useful method without any side effects, in addition to known medical and psychological treatments, to increase the weight of children with nonorganic FTT.

Key Words: clinical trial, colostrum, failure to thrive

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One of the most common presentations in pediatric outpatient clinics is the complaint of parents regarding inadequate growth of their children. Growth failure or failure to thrive (FTT) is a broad term used to describe low or decreased growth rate over time in a child or infant because of undernutrition. FTT is diagnosed when height and weight measurements fall below the fifth percentile or a downward change in growth across 2 major growth percentiles using a standard growth chart (1–3). The most important factor in the diagnosis of FTT is the quantitative measurement of weight and height in routine clinical practice (4). Therefore, Raynor and Rudolf introduced different anthropometric indicators including Gomez (median weight for age), Waterlow (median weight for height), and McLaren (median weight/median height for age) indices (5).

FTT is classified as organic, nonorganic, or a combination of these 2 patterns. Appropriate management of FTT is based on a careful detailed history, clinical findings, and laboratory parameters. For organic FTT, the treatment should be directed to diagnose and cure the underlying cause. The other more common pattern, nonorganic FTT, is somewhat hard to manage. Usually, various environmental and psychosocial factors have a role in nonorganic FTT. A multidisciplinary approach, with inclusion of the family, is required. Providing adequate energy intake, instructing parents concerning correct nutritional habits, and limiting excessive fruit juice consumption all are factors that should be considered during the treatment of FTT (6).

Bovine colostrum is the early milk produced by cows during the first few days after parturition (7). The nutrient composition of colostrum is different from regular milk. Colostrum is rich in protein, immunoglobulins, antimicrobial peptides (lactoferrin), and growth factors (8,9). Therefore, researchers have tried to use bovine colostrum as a supplement in different conditions such as respiratory tract infection and diarrhea in children (10) or body composition and exercise performance in adults (11,12). It has been suggested that colostrum feeding improves nutrient absorption, and consequently energy status (13). Moreover, there are reports indicating the importance of increasing energy intake in the treatment of nonorganic FTT (14–17). Based on this evidence, we decided to evaluate whether bovine colostrum supplementation has a significant clinical efficacy in the management of children with nonorganic FTT.

MATERIALS AND METHODS

The present study was designed as a single-blind, randomized clinical trial, which lasted for a 2-year period (March 2006–February 2008) in the Children's Hospital Medical Center of our university hospital. Inclusion criteria consisted of children ages 1 to 10 years, of either sex, and were diagnosed as having nonorganic FTT. Diagnosis of nonorganic FTT was made for children whose growth failure was categorized as mild or moderate according to Waterlow I (18) and/or Gomez criteria (3,19). Based on Waterlow I criteria (height for age), a child's actual height was compared with

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the median (50th percentile) height at that age. Mild and moderate FTT were defined as heights 90% to 95% and 85% to 89% of the expected, respectively. In Gomez criteria (weight for age), the current weight of age was compared with the 50th percentile (expected weight) of that age. Mild and moderate FTT in accordance with Gomez criteria were determined as 75% to 90% and 60% to 74% of the expected weight, respectively. Both comparisons of weight and height measurements were done using reference standards on the World Health Organization Child Growth Standards (20,21).

Exclusion criteria consisted of children with severe nonorganic FTT (based on Waterlow I criteria [<85% of the expected], and Gomez criteria [<60% of the expected]), and those children with diagnosis of an underlying cause for their growth failure, that is, organic FTT. To rule out organic reasons for FTT, medical history was taken and a complete physical examination was performed by a board-certified pediatrician. Laboratory parameters including complete blood count, urine analysis and culture, stool examination, thyroid function tests, and liver function tests were ordered for all of them. Electrocardiogram, echocardiography, electroencephalography, and abdominal ultrasound were done, if indicated.

One hundred twenty consecutive eligible patients were randomized into 2 groups (case and control), based on a simple randomization protocol. The control group underwent routine medical management such as parents' instructions regarding correct dietary programs, daily multivitamins and minerals, and zinc sulfate syrup. The case group, in addition to the mentioned treatments, received bovine colostrum with a dosage of $40\,mg \cdot kg^{-1} \cdot day^{-1}$. Two groups were matched with regard to age, sex, weight, and height at the time of entry.

For production of colostrum, fresh milk from Waldenstrom cows was pasteurized and through the lyophilization process, capsule forms containing 500 mg of colostrum were produced. Each capsule contained 450 mg effective dose and 50 mg lactose.

All of the children were visited by a pediatrician 4 times during the study. The first visit was at the time of entrance to the study. Via a predefined checklist, the following variables were gathered: age, sex, weight (kilograms), height (centimeters), appetite for food, vaccination program, presence of breast-feeding and its duration, formula usage, time of beginning the supplemental nutrition, gestational age (preterm and term), and weight at the time of birth. The second, third, and fourth visits were done at the end of the first, second, and third month since starting the study. During these visits, according to Waterlow I and Gomez criteria, the process of child growth was monitored.

The parents of children were informed about the applied treatments, bovine colostrum, and possible hypersensitivity reactions to colostrum. Informed consent was obtained from all of the parents.

For statistical analyses, descriptive indices such as frequency, percentage, mean, and standard deviation were used to express data. For comparison of continuous variables, the independent sample t test or the Mann-Whitney U test and for categorical variables the χ^2 or Fisher exact tests were used. All of the analyses were done by SPSS software for Windows (version 13.0, SPSS Inc, Chicago, IL). The ethics committee of Tehran University of Medical Sciences approved the protocol of the study.

RESULTS

All 120 patients included in the study completed the trial. In Tables 1 and 2 variables evaluated at the initial visit before receiving treatments are presented. No statistically significant difference was observed with respect to baseline characteristics between the case and control groups (all of the P values were >0.05).

TABLE 1. Baseline continuous variables of 2 groups of children with the diagnosis of nonorganic failure to thrive before enrollment

Characteristic	Case (n = 60)	Control (n = 60)
Age, y	5.05 (2.33)	5.25 (2.62)
Breast-feeding duration, mo	10.48 (4.9)	10.29 (5.57)
Weight, kg	13.8 (3.95)	14.12 (4.26)
Height, cm	97.6 (15.65)	98.5 (16.29)
Gomez, %	72.36 (7.81)	73.53 (5.27)
Waterlow I, %	90.31 (4.06)	90.66 (3.35)

All of the data are expressed as mean (standard deviation). Comparison of all of the variables using the Mann-Whitney U test or independent sample t test did not show any statistically significant difference between the case and control groups.

Figures 1 and 2 present Gomez and Waterlow indices of growth insufficiency from baseline to the end of the third month after initiating the study. As shown, an increasing pattern is seen in both groups regarding Gomez index, and the difference between the mean values in the case (81.72) and control (77.12) groups becomes statistically significant ($P = 0.003$) at the end of the third month following treatment. However, such a difference was not reported at the end of the third month based on Waterlow index between the case (92.91) and control (91.71) groups ($P = 0.094$).

In Table 3, mild and moderate categories of FTT and normal state according to both Gomez and Waterlow indices are presented at the beginning of the study, first, second, and third month. According to Gomez index 12 patients (20%) who received colostrum became normal and did not have FTT at the end of the third month. However, in the control group only 2 cases (3.3%) showed normal growth and 22 patients (36.7%) still showed moderate FTT

TABLE 2. Baseline categorical variables of 2 groups of children with the diagnosis of nonorganic failure to thrive before enrollment

	Case (n = 60)	Control (n = 60)
Sex		
Boy	33 (55)	38 (63.3)
Girl	27 (45)	22 (36.7)
Gestational age		
Preterm	17 (28.3)	18 (30)
Term	43 (71.7)	42 (70)
Weight at birth, g		
<2500	26 (43.3)	26 (43.3)
≥2500	34 (56.7)	34 (56.7)
Breast-feeding	58 (96.7)	59 (98.3)
Formula feeding	31 (51.7)	35 (58.3)
Completed vaccination program	45 (75)	48 (80)
Beginning supplemental nutrition		
<6 mo old	18 (30)	19 (31.7)
≥6 mo old	42 (70)	41 (68.3)
Appetite for food	10 (16.7)	11 (18.3)

All of the data are presented as frequency (percentage). Comparison of all of the variables using the χ^2 test or the Fisher exact test did not show any statistically significant difference between the case and control groups.

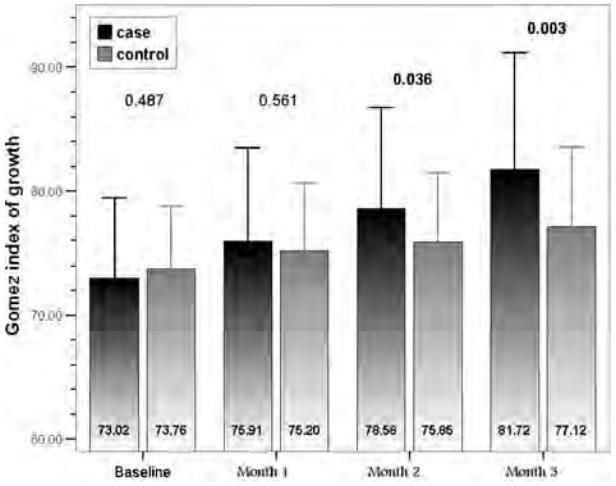

FIGURE 1. Gomez index of growth insufficiency from baseline to end of third month of study period.

($P = 0.006$). According to Waterlow index, 17 patients (28.3%) in the case group became normal. Although this number was higher than that of the control group (9 cases, 15%), the difference was not statistically significant ($P = 0.193$).

No adverse effects (diarrhea, abdominal distension, dyspepsia, and bloating) or hypersensitivity reaction was reported during the treatment course.

DISCUSSION

To our knowledge, this study is the first one to evaluate the clinical effect of bovine colostrum in the management of children with a diagnosis of nonorganic FTT. As a result, direct comparison between the present results and findings of former clinical trials for FTT treatment is somewhat difficult.

Although there is often an overlap, there is an attempt to define FTT in terms of causation such as organic versus nonorganic (2). The evaluation and management of patients with organic FTT, in which an identifiable medical problem exists, may be easier than

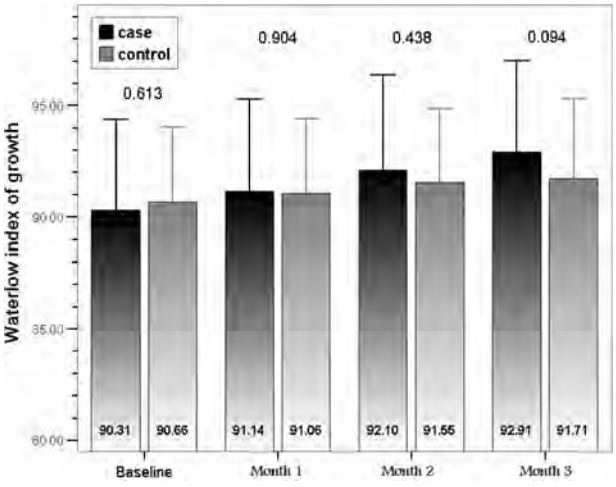

FIGURE 2. Waterlow index of growth insufficiency from baseline to end of third month of study period.

TABLE 3. Nonorganic failure to thrive categories according to Gomez and Waterlow I indices at the beginning, first, second, and third month

		Case (n = 60)	Control (n = 60)	*P*
Gomez index				
Beginning	Normal	0	0	0.356
	Mild	29 (48.3)	24 (40)	
	Moderate	31 (51.7)	36 (60)	
First month	Normal	2 (3.3)	0	0.276
	Mild	31 (51.7)	28 (46.7)	
	Moderate	27 (45.0)	32 (53.3)	
Second month	Normal	5 (8.3)	0	0.017
	Mild	38 (63.3)	32 (53.3)	
	Moderate	17 (28.3)	28 (46.7)	
Third month	Normal	12 (20.0)	2 (3.3)	0.006
	Mild	36 (60)	36 (60.0)	
	Moderate	12 (20.0)	22 (36.7)	
Waterlow I index				
Beginning	Normal	9 (15.0)	8 (13.3)	0.315
	Mild	19 (31.7)	27 (45.0)	
	Moderate	32 (53.3)	25 (41.7)	
First month	Normal	13 (21.7)	8 (13.3)	0.259
	Mild	20 (33.3)	28 (46.7)	
	Moderate	27 (45.0)	24 (40.0)	
Second month	Normal	16 (26.7)	9 (15.0)	0.137
	Mild	23 (38.3)	33 (55.0)	
	Moderate	21 (35.0)	18 (30.0)	
Third month	Normal	17 (28.3)	9 (15.0)	0.193
	Mild	27 (45.0)	34 (56.7)	
	Moderate	16 (26.7)	17 (28.3)	

All of the data are presented as frequency (range).

that of nonorganic FTT. Different factors such as difficult parent–child interactions, dysfunctional family, poor feeding skills, and others may contribute to nonorganic FTT. Furthermore, nonorganic FTT is more challenging and common than organic FTT to any pediatrician. Therefore, in this study we decided to include children with a diagnosis of nonorganic FTT. Almost all of the investigators agree that increasing energy intake (high-calorie diet) for children with nonorganic FTT is a useful intervention, which should be used with other treatments such as instructing parents to modify incorrect feeding behaviors (14–16). Therefore, there has been widespread use of energy-supplemented diets for infants with growth failure. Clarke et al (17), in a randomized study, compared the effectiveness of a nutrient-dense formula with an energy-supplemented formula for 49 infants with faltering growth. Infants fed by nutrient-dense formula received 42% more protein and 15% to 40% more vitamins and minerals, whereas blood urea concentration fell by 50%, suggesting a suboptimal protein:energy ratio among children fed by energy-supplemented formula. They concluded that increasing the energy content of normal-infant formula without also increasing protein and micronutrients should not be practiced in infants with faltering growth. In another study performed by Khoshoo et al (22), 15 infants with nonorganic FTT were fed with a regular-strength formula for 3 days and then switched to the same formula with a higher energy density. They observed that 9 infants (60%) during feeding with the higher-density formula had a significant increase in

their energy intake and weight gain. It is likely that the children in the colostrum group received more energy than the control group.

Bovine colostrum has been used previously in various illnesses among adults and children, for example, among children with recurrent episodes of upper respiratory tract infections (10), diarrhea among people with immune-deficiency syndromes (23,24), infectious diseases such as *Helicobacter pylori,* and some viral infections (7,25). Several researchers have evaluated the effect of bovine colostrum on body composition and exercise performance. Coombes et al (26) determined the dose effects of bovine colostrum on cycling performance among competitive male cyclists and concluded that supplementation with oral bovine colostrum at 20 or 60 g daily provided a significant improvement in the time trial performance in cyclists.

There are 90 known components in the colostrum. Specific antibodies, immunoglobulins (IgA, IgD, IgE, IgG, and IgM), and lactoferrin (iron-binding protein) are important immune factors. There are also growth factors such as epithelial growth factor, transforming growth factor, vitamins, and minerals. These growth factors may play an important role in the treatment of children with growth failure (27). Insulin-like growth factors are present in bovine colostrum, and similar to human growth hormone promote muscular growth (28,29). Although studies on neonatal animals have indicated the role of growth factors in feeding colostrum to increase intestinal nutrient absorption, similar effects in adult humans were not demonstrated (13).

Obtained results in this trial suggest that, in addition to routine management, supplementation with bovine colostrum at the dose of $40\,mg \cdot kg^{-1} \cdot day^{-1}$ for a 3-month period is a useful method for increasing the weight of children with nonorganic FTT. The significant difference in weight compared with the control group particularly was notable after the second month of starting the treatment and reached its highest level at the end of the third month. All of the children completed the trial without any adverse effects, and this matter shows an acceptable tolerability of colostrum at the administered dose. We propose additional clinical studies with higher doses of colostrum products in nonorganic FTT to evaluate its effect in increasing height of children.

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