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COmparisoN of TastES of Available NutriTional integrated or non-integrated formulas for infants older than 1 year of age with cow's milk allergy: A multicenter, prospective, single blind, cross-sectional observational clinical study (CONTEST Study)

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Abstract
Palatability of the infant formulas lacking cow milk protein formulas is reported by parents to be an important drawback. The purpose of this study is to examine decisions made by mothers of infants having cow milk protein allergy, and physicians concerning the palatability of unflavored extensively hydrolyzed formulas and amino acid-based formulas. We conducted a multi-center, randomized, single-blinded, observational taste study involving 149 pediatricians from gastroenterology and allergy subspecialties at 14 tertiary healthcare units from different regions of Turkey and involving 94 mothers of infants with cow milk protein allergy. Blinding was performed for seven formulas available in the market, which were the most commonly prescribed for feeding: four AAFs (Neocate-Numil®, Aptamil Pregomin AS-Numil®, Alfamino-Nestle®, Comidagen-Mamma®), one AAF specifically designed to address the growing nutritional and lifestyle needs of children >1 year (Neocate Junior-Numil®), 2 eHFs (Bebelac Pepti Junior-Numil®, Similac Alimentum-Abott®). Considering all three formula characteristics, Neocate junior-Numil® ranked as the number 1 product among seven products by mothers (63.8%) and physicians (69.8%). The ratings of mothers were significantly higher than the physicians (8.1 points and 6.1 points, respectively; $p < 0.001$). No difference was found in terms of taste, smell, and appearance for Neocate junior-Numil® between the mothers' and physicians' ratings. Since caregivers have responsibility for careful selection of replacement products for infants with cow milk protein allergy, it is noteworthy that increased awareness and confidence in the palatability characteristics of these products should motivate mothers and physicians to comply with replacement treatment in the long term.

KEYWORDS
Cow's milk protein allergy;
taste perception;
protein hydrolysates;
infant formula;
compliance

Introduction

Cow's milk protein allergy (CMPA) is defined as a hypersensitivity reaction that occurs against proteins in cow milk through immunologic mechanisms. It is encountered in the early months of life when an infant is exposed to cow's milk and is generally resolved before adult life.[1] The incidence of CMPA has a wide variability geographically: 1.3–2.9% in the United Kingdom,[2] 1.9% in Spain,[3] and up to 7.5% in some locations, according to the literature.[4,5] According to the results of a multicenter study conducted in Turkey, the most common cause of food allergy and food anaphylaxis among children was cow's milk. It has been shown that the rate of CMPA in children with food allergies is 70.6% in the 0–2 age group and decreased to 25% in the 13–18 age group.[6]

The management of CMPA relies on the elimination of cow's milk protein from the diet and the introduction of a substitute formula for non-exclusively breastfed infants. Infants that are exclusively breastfed do not need formulas and elimination of CMP occurs in the mother's diet. Exclusively breastfed infants do not need formulas and elimination of CMP occurs in the mother's diet. Available formulas come as partially hydrolyzed formulas (pHFs), extensively hydrolyzed formulas (eHFs), and amino acid formulas (AAFs). AAFs are the only formulas that meet this criterion of 90% clinical tolerance. Differences in taste are related to protein constituent and source (i.e. casein, whey, bovine), degree of hydrolysis, and the presence of lactose[1,7,8]

During formula substitution, one of the major challenges reported by parents is the rejection of formula due to bitter taste, which depends on products of proteolysis, the chemical constitution of formula, and conformational factors.[3,9] Although AAFs and eHFs are first-line formulas based on the clinical features of cow's milk allergy and are considered to be all nutritionally equivalent, AAF formulas are usually used for those infants with multiple food allergies, severe cow's milk allergy, allergic symptoms, or severe atopic eczema when exclusively breastfed, severe forms of non-IgE mediated cow's milk allergy such as eosinophilic esophagitis, enteropathies, and food protein-induced enterocolitis syndrome (FPIES), faltering growth and reacting to or refusing to take eHF at nutritional risk.[1,7,8]

The aim of this study is to collect opinions of mothers of infants (who were ≥1 year of age) with CMPA and of physicians experienced in CMPA management about the taste, smell, and appearances of seven unflavored forms of dietary supplements available in the Turkish commercial market. An additional aim was to determine preferences and to understand the palatability of those infant formulas through responses to short questionnaires.

Methods

The present multicenter, prospective, single-blinded, cross-sectional, randomized study was conducted at 14 sites from different regions of Turkey. The study included 149 pediatricians from gastroenterology, allergy, and immunology subspecialties, who have been involved in the nutritional management of CMPA patients ranging from 2 to 35 years, and 94 mothers, who had infants with CMPA receiving substitution formulas. The study sites were tertiary centers: nine specialized in pediatric allergy and five in pediatric gastroenterology.

Participant eligibility for the study included informed consent to the single-blinded study procedure, having no food or drug allergy and intact taste sensation. In order to provide this condition, participants with current acute upper respiratory tract infections, history of previous nasal

surgery, history of anosmia/hyposmia as well as those taking drugs that might significantly affect the taste sensitivity were excluded from the study.

The palatability testing and questionnaires were done at study sites. Testing was conducted for seven substitution formulas available in the market: four AAFs (Neocate-Numil®, Aptamil Pregomin AS-Numil®, Alfamino-Nestle®, Comidagen-Mamma®), one AAF specifically designed to address the growing nutritional and lifestyle needs of children >1 year (Neocate Junior-Numil®), 2 eHFs (Bebelac Pepti Junior-Numil®, Similac Alimentum-Abott®). A white sheet of paper was used for the blinded test and three-digit codes were assigned to products. Taste ranking lists were prepared before the appointment and were presented to subjects in closed envelopes. Formulas were prepared behind a curtain according to preparation instructions.

Participants refrained from eating or drinking 1 h before sample testing to ensure a neutral state for their taste buds. 30 mL of each sample was offered serially with the ranking list. Participants tested each sample with at least a 15-min interval between them. Before tasting the next sample, water and table water crackers were given as palate cleansers.[10]

After completion of tasting of the samples, participants were required to complete the questionnaire to rank preferences in taste, smell, and appearance of blinded samples, and also to comment about decisions with respect to the convenience of children with CMPA. For each product, both mothers and physicians were asked to describe which characteristic, namely taste, smell, and appearance, they liked and disliked most. Personal evaluations were noted on an integer quantitative scale from 0 (the least liked) to 10 (the most liked).[11] Among the final questions, all participants were asked whether they had ever tasted an integrated formula previously.

The necessary approval for the study was given by the Clinical Research Ethics Committee of Istanbul University Faculty of Medicine (2011-KAEK-57-1231).

Statistical analysis

Continuous, normally distributed variables were described by standard parametric statistics (mean, standard deviation, median, minimum, and maximum). Categorical variables were described by using frequency and percentage. The normal distribution of variables was analyzed by using the Shapiro-Wilks test. Comparisons between two continuous normally distributed variables were determined by using the Student test. Comparisons of categorical variables were analyzed using the chi square test. The level of statistical significance was set for the threshold $p < 0.05$. Analysis was performed by using MedCalc statistics application version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

The highest-ranked product was Neocate Junior-Numil® (6.6±2.6), followed by Bebelac Pepti Junior-Numil® (5.6±2.7), and Neocate-Numil® (4.2±2.5) based on a subjective integer-based quantitative scoring from 0 to 10. Results of ranking, in decreasing order, according to taste are shown in Table 1; the table shows the top three products. Nearly two-thirds of mothers (63.8%) and physicians (69.8%) chose the Neocate Junior-Numil ® formula.

As for product appearance, both mothers and physicians also ranked Neocate Junior-Numil® the highest among products (Table 2). The same was true with respect to the sensation of smell, with Neocate Junior-Numil® having scored higher than other products (Table 3).

According to mothers and physicians, Neocate Junior-Numil® has become statistically significant higher scores on smell tests than all products except Bebelac Pepti Junior-Numil® ($p < 0.001$ for all comparisons except for Bebelac Pepti Junior-Numil®). These three characteristics of taste, appearance, and smell were also statistically analyzed as a group, and the ranking results of these formulations are presented in Table 4.

Physicians were asked which of these products was the most convenient for an infant diagnosed with CMPA. Table 5 shows these results, with the highest-ranked product being Neocate Junior-Numil® (6.6±2.6), followed by Bebelac Pepti Junior-Numil® (5.6±2.7), and Neocate-Numil® (4.2±2.5).

This study also examined the most liked and disliked characteristics of each product in Tables 6 and 7.

Among mothers, 79.8% ($n = 75$) tasted one of either the eHF or AAF formulations previously, or 14.8% of physicians ($n = 22$) had tasted these previously.

Table 1 Ranking in decreasing order according to taste.

Name of formula	Mothers ranking			Physicians ranking		
	First line *n* (%)	Second line *n* (%)	Third line *n* (%)	First line *n* (%)	Second line *n* (%)	Third line *n* (%)
Neocate®	3 (3.2)	22 (23.4)	36 (38.3)	6 (4)	22 (14.8)	60 (40.3)
Neocate Junior®	60 (63.8)	24 (25.5)	7 (7.4)	104 (69.8)	37 (24.8)	6 (4.0)
Aptamil Pregomin AS®	4 (4.3)	3 (3.2)	13 (13.8)	1 (0.7)	4 (2.7)	27 (18.1)
Bebelac Pepti Junior®	25 (26.6)	41 (43.6)	17 (18.0)	35 (23.5)	73 (49.0)	18 (12.1)
Similac Alimentum®	0	1 (1.1)	4 (4.3)	2 (1.3)	2 (1.39	5 (12.1)
Alfamino®	2 (2.1)	3 (3.2)	14 (4.9)	1 (0.7)	11 (74)	31 (20.8)
Comidagen®	0	0	3 (3.2)	0		2 (1.3)
Total	94	94	94	149	149	149

Table 2 Assessment of appearance of the products.

	Physicians ranking		Mothers ranking	
	Mean±SD	Med (min-max)	Mean±SD	Med (min-max)
Neocate®	7.3±2.1	8 (1-10)	7.0±2.2	7 (1-10)
Neocate Junior®	7.7±1.7	8 (3-10)	7.5±2.1	8 (1-10)
Aptamil Pregomin AS®	7.2±2.0	7 (1-10)	6.3±2.3	7 (1-10)
Bebelac Pepti JR®	7.2±1.9	7 (1-10)	7.1±2.1	8 (1-10)
Similac Alimentum®	5.0±2.6	5 (1-10)	4.1±2.6	4 (1-10)
Alfamino®	4.1±2.6	4 (1-10)	3.7±2.5	3 (1-10)
Comidagen®	5.9±2.7	6 (1-10)	4.7±2.8	5 (1-10)

1: I definitely dislike it at all, 10: I definitely like it very much.

Table 3 Assessment of smell of the products.

	Physicians		Mothers	
	Mean±SD	Med (min-max)	Mean±SD	Med (min-max)
Neocate®	4.1±2.2	4 (1-9)	4.9±2.7	5 (1-10)
Neocate JR®	6.4±2.3	7 (1-10)	7.7±2.2	8 (1-10)
Aptamil Pregomin AS®	3.6±2.1	3 (1-9)	4.1±2.4	4 (1-10)
Bebelac Pepti JR®	5.9±2.5	6 (1-10)	7.4±2.5	8 (1-10)
Similac Alimentum®	2.3±1.7	2 (1-7)	2±1.8	1 (1-10)
Alfamino®	3.4±2.0	3 (1-10)	3.6±2.4	3 (1-10)
Comidagen®	2.8±2.1	2 (1-8)	3.4±2.5	3 (1-10)

Table 4 Sample ranking list for taste, smell, and appearance of formulations of participants.

	Mothers		Physicians	
	Mean±SD	Median (min-max)	mean±SD	Median (min-max)
Neocate®	5.8±2.3	6 (1-10)	4.6±2.2	5 (1-10)
Neocate Jr®	8.1±1.9	8 (3-10)	6.8±2.2	7 (1-10)
Aptamil Pregomin AS®	4.4±2.2	4 (1-10)	3.9±2.0	4 (1-9)
Bebelac Pepti Jr®	7.2±2.1	8 (1-10)	5.9±2.4	6 (1-10)
Similac Alimentum®	2.3±1.8	1.5 (1-8)	2.4±1.6	2 (1-8)
Alfamino®	3.6±2.4	3 (1-10)	3.5±2.1	3 (1-8)
Comidagen®	2.9±2.0	2.5 (1-8)	2.4±1.7	2 (1-10)

SD: Standard deviation.
1: I definitely dislike at all; 10: I definitely like very much.

Table 5 The most convenient product for infants with CMPA according to physicians.

	Physicians	
	Mean±SD	Med (min-max)
Neocate®	4.2±2.5	4 (1-10)
Neocate JR®	6.6±2.6	7 (1-10)
Aptamil Pregomin AS®	3.5±2.2	3 (1-9)
Bebelac Pepti JR®	5.6±2.7	6 (1-10)
Similac Alimentum®	2.3±1.7	2 (1-8)
Alfamino®	3.3±2.3	3 (1-10)
Comidagen®	2.3±1.7	1 (1-10)

1: Definitely not convenient at all; 10: Definitely convenient very much.

Discussion

This study evaluated the palatability of the unflavored substitution formulas in primary caregivers of children with CMPA and experienced health care professionals (HCP) in the same setting, based on a literature review. The study design provided minimization of order and carry-over biases for all participants. Among the characteristics of taste, smell, and appearance, the taste was defined as the most prominent feature for the nutritional management of CMPA by caregivers and physicians. Using a simple ranking method, and taking taste, smell, and appearance together, mothers and physicians stated that they mostly preferred the AAF specifically designed to address the growing nutritional and lifestyle needs of children >1 year among seven commonly prescribed substitution formulas in the Turkish

Table 6 The most liked characteristics of each product by mothers and physicians.

Product and characteristics	Mothers *N* (%)	Physicians *N* (%)
Neocate®		
Appearance	49 (53.8)	91 (68.9)
Smell	13 (14.3)	13 (9.8)
Taste	29 (31.9)	28 (21.2)
Neocate JR®		
Appearance	9 (9.6)	20 (13.4)
Smell	21 (22.6)	22 (14.8)
Taste	64 (67)	107 (71.8)
Aptamil Pregomin AS®		
Appearance	54 (63.5)	113 (85)
Consistency	1 (1.2)	0
Smell	17 (20)	12 (9)
Taste	13 (15.3)	8 (6)
Bebelac Pepti JR®		
Appearance	11 (12)	37 (25.3)
Smell	31 (33.7)	36 (24.7)
Taste	50 (54.3)	73 (50)
Similac Alimentum®		
Appearance	38 (79.2)	65 (79.3)
Consistency	4 (8.3)	4 (4.9)
Smell	3 (6.3)	7 (8.5)
Taste	3 (6.3)	6 (7.3)
Alfamino®		
Appearance	20 (32.3)	27 (30.7)
Consistency	0	2 (1.1)
Smell	21 (33.9)	27 (30.7)
Taste	21 (33.9)	33 (37.5)
Comidagen®		
Appearance	47 (79.7)	74 (79.6)
Smell	9 (15.3)	16 (17.2)
Taste	3 (5.1)	3 (3.2)

Table 7 The most disliked characteristics of each product by mothers and physicians.

Product and characteristics	Mothers *N* (%)	Physicians *N* (%)
Neocate®		
Appearance	0	1 (0.7)
Smell	36 (42.4)	51 (36.7)
Taste	49 (57.6)	87 (62.6)
Neocate JR®		
Appearance	1 (1.5)	3 (5.1)
Consistency	0	1 (1.7)
Smell	13 (50)	36 (61)
Taste	12 (48.5)	19 (32.2)
Aptamil Pregomin AS®		
Appearance	0	1 (0.7)
Smell	37 (42)	56 (38.4)
Taste	51 (58)	89 (60.9)
Bebelac Pepti JR®		
Appearance	2 (4.4)	4 (4.8)
Smell	8 (17.8)	29 (34.9)
Taste	35 (77.8)	50 (60.3)
Similac Alimentum®		
Appearance	2 (2.1)	7 (4.8)
Smell	38 (40.4)	65 (44.2)
Taste	54 (57.4)	75 (49)
Alfamino®		
Appearance	19 (22.1)	51 (34.5)
Smell	25 (29.1)	37 (25)
Taste	42 (48.8)	60 (40.5)
Comidagen®		
Appearance	8 (8.7)	13 (8.8)
Smell	23 (25)	48 (32.7)
Taste	61 (66.3)	86 (58.5)

commercial market. Smell and appearance were ranked second and third in importance with respect to quality characteristics, respectively.

It is important to consider that acceptance of the formulas interferes with compliance in clinical practice. The flavor of food determines its acceptability and modulates its intake. Thus, it is critical to understand the factors that influence flavor preferences in humans.[12]

In this study, physicians were asked which of these products was the most convenient for an infant diagnosed with CMPA. Whether the perception of HCPs of a better taste improves acceptance of the hypoallergenic formula by the infant has not been studied. However, it is known from other healthcare domains that the belief and perceptions of HCPs are strongly associated with the beliefs and perceptions of the patient. Working alliance is important in medical treatment as it is associated with patient compliance and satisfaction.[13] This becomes more important, especially, in situations such as dietary interventions that will cause a change in living conditions.[14]

It may therefore be hypothesized that, although there is not a direct impact on the flavor acceptance of infants, the parental attitude and acceptance of the new feed may be impacted through the perception and belief of the HCP, which may help with the introduction of a hypoallergenic formula.[2]

The primary taste qualities which are sweet, salty, bitter, sour, and savoriness are developed during infancy in contribution to taste buds and nervous system.[12] Prenatal experiences with food flavors transmitted from the mother's diet to amniotic fluid lead to greater acceptance and enjoyment of these foods in children.[15] The newborn starts to develop the repertoire for flavor and thus selects which tastes to avoid or reject.[9] Research on basic flavor biology in youngsters revealed that they prefer a sweet taste and reject bitter taste innately.[16] While substitution formulas were accepted as the only therapeutic options for children with CMPA diagnosed with strict criteria, some studies indicated difficulty in implementing them in nutrition management due to bitter taste.[2,3,17,18] Experimental studies demonstrated that infants fed with hydrolyzed formulas before 4 months of age, readily accept them, whereas older infants strongly reject them within the first few minutes of feeding.[19-23] The effects of the flavor of the hydrolyzed formula fed in early life are long-lived. Children aged 4–5 years who were fed with hydrolysates during their first

several months, exhibited more positive responses after several years than children without such experience.[24-26]

In infant nutrition, enzymatic hydrolysis and microbial fermentation are technologies with a long history in the preparation of hydrolyzed formulas. Protein hydrolysates with different degrees of hydrolysis result in a broad range of flavors among these hydrolyzed formulas.[27] It is very difficult to carry out studies that will reveal the differences in taste characteristics of hydrolyzed formulas, especially in young children. In a randomized double-blind study, 150 trained panelists performed tests with different formulas and the smell, texture, taste, and aftertaste of each formula were evaluated, formulas showed a significant difference, as compared to cow's milk.[28] A randomized blind study of 90 mothers of children with CMPA evaluated five different hydrolyzed formulas used for the treatment of CMPA and showed whey hydrolysates were more palatable than others.[29] Poor palatability of substitution formulas, namely bitter taste, is due to the formation of bitter peptides during proteolysis and the palatability of formulas is determined by the number of bitter peptides obtained by hydrolysis.[30] Another study performed on healthy volunteers showed a significant correlation between the peptide weight, and the scores obtained for taste, texture, and palatability.[31] Small peptides, free amino acids, and possibly other substances, may be detected by receptors that mature after the infant is 3–4 months old.[32] Constitutional and conformational factors of peptides from beta-casein may also affect the bitterness of the hydrolyzed formulas.[33,34]

In the present study, the smell and appearance of the formula were also ranked. Volatiles in the hydrolyzed formulas may affect the perceptions of the child.[35] Odor of the hydrolyzed formula in the can may be nauseating due to the presence of peptides and amino acids.[36] Assessment of the odor preferences of the infants is much more difficult.

Children have innate responses to basic tastes such as sweet and salty, and some of them may be more sensitive to bitter tastes genetically.[37-39] The addition of flavors or sweeteners might improve gustatory sensation so that it would be easier for infants to stay on nutritional treatment.[3]

In the present study, results implied that some formulas without flavor might still be appealing for patients, even though they are older and have already built a matured flavor repertoire. Although AAF which is specifically designed to address the growing nutritional and lifestyle needs of children >1 year is without flavor, it was the most preferred product among the others. The technology used to modify and nutritionally fortify AAF for children >1 year may decrease the potency of hydrolyzed amino acids contributing to harsh tasting influences. Different processing methods may have led to a decrease in bitter amino acids, an increase in sweet or neutral-tasting ones and higher levels of antioxidants, which could change fat oxidation and play a role in the better tolerability of this formula.[40]

A treatment plan for infants with CMPA that will achieve better compliance will take into consideration many factors such as recommendations and guidelines, particularly related to the pathophysiology of the condition, and should include an understanding of the basic flavor biology of children.

There are some limitations of the present study. The children who would be consuming the formula and deriving its benefits were not involved in the study, and this study made use of proxies who could report in a way to provide a scientific understanding. Measuring or otherwise quantitating and thus understanding gustatory sensation in infants, mainly older than 1 year of age, is a challenge in nutritional treatment with substitution formula. Hypoallergenic formula as experienced in sensory perception by HCPs and the parents of infants may have an impact on formula choice and acceptance of the formula in a child with CMPA.

Since caregivers should have credit with replacement products for CMPA, it is noteworthy that increased awareness and confidence in the primary quality characteristics of the products will motivate mothers and physicians to comply with replacement treatment in the long term. Because we believe HCPs should be experienced not only in treatment planning but also should be acquainted with details of products in order to provide close collaboration of primary caregivers, this establishes a value for studies of this kind.

Conclusions

Mothers and physicians reported that the unflavored form of Neocate Junior-Numil® was significantly better than seven other widely prescribed and available formulations, especially with respect to taste, but also with respect to smell and appearance. Physicians reported that the AAF specifically designed for the lifestyle needs of children >1-year product was also the most convenient formula for an infant diagnosed with CMPA. As caregivers can replace products for CMPA, increased awareness and confidence in the main palatability characteristics of the products will motivate mothers and physicians to comply with replacement treatment in the long term. In the future, it may be a good idea to plan a study directly with children who will be consuming CMPA-compliant formulas.

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