Original Article

Comparisons of a chicken-based formula with soy-based formula in infants with cow milk allergy

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Objective: To determine whether chicken-based formula can replace soy-based formula in infants with cow milk allergy. **Subjects and Methods:** Thirty-eight infants with cow's milk allergy, aged between 2-24 months of age were randomized to receive either chicken-based formula or soy-based formula for 14 days. **Results:** In the group of soy-based formula, 12 out of 18 infants had evidence of intolerance and could not continue with the formula. However, only 4 out of 20 infants in the chicken-based formula group had evidence of clinical intolerance. All other 16 infants were fed the chicken-based formula with success. The number of infants who were intolerant to chicken formula was significantly lower than the number of those fed soy-based formula (p = 0.009). **Conclusion:** Chicken-based formula can be used more effectively than soy-based formula in infants with cow milk allergy.

Key Words: Chicken-formula, cow milk allergy, soy-formula., Thailand, infants

INTRODUCTION

Cow milk allergy (CMA) occurs in 2% to 3% of infants.[1,2,3] About half of the reactions to CMA are IgE-mediated hypersensitivity, the skin and gastrointestinal tract being the most common targets of these reactions. However, almost half of these infants begin to tolerate cow milk by the age of 2 years.[4,5] Dietary alternatives for infants with CMA are limited. For breast-fed infants, maternal elimination of dairy products may lead to a resolution of the symptoms.[6] Most infants with IgE-mediated CMA can tolerate soy-based formula (hereinafter: soy formula)[7], but among those with non-IgE-mediated CMA, almost 50% react to soy.[8] Klemola et al.[9] reported that 10% of infants with CMA had adverse reactions to soy formula compared with 2% of those who were assigned to an extensively hydrolyzed formula. Infants who can tolerate neither soy nor extensively hydrolyzed formula need an amino acid-based formula.

Although hen eggs are commonly reported to be highly immunogenic in infants, chicken meat is rarely reported as a contributing factor to an allergic reaction. Chicken meat is cheap and easily available in all countries. Some investigators have used both comminuted (blenderized) and minced chicken-based diets. There are several advantages of using these diets such as being lactose-free, better digested, of lower osmolality, and less expensive than other specialized formula.[10]

In order to determine the efficacy of chicken-based formula as an alternative formula for infants with CMA, we produced such a formula by homogenizing chicken meat (hereinafter: chicken formula) and adding vitamins and minerals as recommended by an European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) coordinated international expert group for infant formula.[11]

The aim of this study is to compare between soy formula and chicken formula in infants with CMA. We prospectively randomized the infants to receive either soy formula or chicken formula and studied the tolerance and intolerance of the given formula for 14 days.

MATERIALS AND METHODS

Subjects

The study involved 38 infants and children with cow milk allergy, whose ages were between 2-24 months. The study protocol was approved by the Ethics Committee for Clinical Research, Faculty of Medicine Siriraj Hospital, Mahidol University. All parents of subjects were informed and provided their written consent.

Study design

After CMA was diagnosed, infants were randomized by a computer program to receive either soy or chicken formula for 14 days. The nutritional contents of the soy and chicken formula are listed in Table 1. The chicken formula was freshly prepared in our laboratory: breasts of chicken bought from the same company were homogenized until the meat was homogenously fine, then other nutrients were added. The energy content of the chicken formula was measured by

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Manuscript received 12 December 2006. Initial review completed 21 March 2007. Revision accepted 24 May 2007.

Table 1. Compositions of soy formula and chicken formula used in the study

Per (100 mL)		Soy formula	Chicken formula
Energy	(kcal)	68	67
Protein	(g)	1.8	2
Fat	(g)	3.7	4
Carbohydrate	(g)	6.9	7
Sodium	(mg)	32	42
Potassium	(mg)	76	68
Chloride	(mg)	59	66
Calcium	(mg)	70	90
Phosphorus	(mg)	50	46
Magnesium	(mg)	5.4	7
Iron	(mg)	1	1.3
Zinc	(mg)	0.8	0.9
Iodine	(µg)	10	44
Copper	(µg)	47	60
Vitamin A	(µg)	79	80
Vitamin E	(mg)	1.7	1.7
Vitamin C	(mg)	7	12
Vitamin B1	(µg)	65	90
Vitamin B2	(µg)	60	90
Vitamin B6	(µg)	40	50
Niacin	(mg)	0.7	1.1
Folic acid	(µg)	13.2	14
Pantothenic acid	(µg)	0.5	0.4
Biotin	(µg)	3	1.8

bomb calorimetry. Fat was extracted by a standard methodand nitrogen content was measured by micro-Kjeldahl.

All vitamins and mineral contents were analyzed by the Department of Science Service, Ministry of Science and Technology, Bangkok, Thailand. Final compositions of the chicken formula are listed on Table 1.

This was a prospective randomized controlled study in infants with CMA. Infants aged 2-24 months who were diagnosed clinically with cow milk protein allergy were recruited into the study. The diagnosis of cow milk protein allergy was based on: 1) disappearance of the infant's symptoms upon elimination of cow milk or exclusive extensively hydrolyzed formula feeding or free amino acids formula, and 2) reappearance of clinical symptoms in the infant during provocation with lactase treated cow milk. Infants who had systemic diseases, moderate to severe malnutrition or organ defects were excluded from the study. After informed consent was signed by one of the parents, the infant was randomized to receive either soy formula or chicken formula for 14 days.

During the fourteen days on the test formula, the parents were contacted daily by the investigators. Infants' body weight and length were measured on the first and fifteenth day of the study. Daily formula intake was recorded for 14 days, as long as the infant did not show any allergic symptoms. On entering the study, 5 mL of blood was drawn from each infant for a complete blood count and a specific IgE test to cow milk protein. Any untoward symptoms after taking the assigned formula were immediately reported to the investigators. Whenever a parent reported that their infant had developed any symptoms compatible with allergy, the infant was brought to the clinic and examined by the investigators. If it was considered that the test formula was the cause of the symptoms, this was discontinued and the infant was

Table 2. Characteristics and clinical symptoms of infants diagnosed with cow milk protein allergy and tested with soy formula or chicken formula

Characteristics	Soy formula† n (%)	Chicken formula‡ n (%)	*p*-value
Age (month)	6.7 ± 4.4	7.6 ± 6.6	0.63
Sex (M/F)	10/8	11/9	0.77
Weight (g)	7500 ± 1800	7200 ± 1700	0.60
Length (cm)	67 ± 7	66 ± 7	0.66
Age at onset (months)	3 ± 2	2 ± 2	0.90
Allergy in parents	12/18	13/20	0.81
Symptoms			
Respiratory	3 (17)	1 (5)	0.32
Cutaneous	8 (44)	11 (55)	0.74
Gastrointestinal	7 (39)	8 (40)	0.79
Laboratory			
Anemia (Hct < 34%)	10 (56)	10 (50)	0.98
Eosinophilia (> 700/cu mm)	4 (22)	3 (15)	0.69
Positive specific IgE to cow milk (> 0.35 kU_A/L)	4 (22)	1 (5)	0.16

† number of subjects = 18; ‡ number of subjects = 20

Table 3. Comparisons between numbers of CMA infants who were tolerant and intolerant to soy formula with chicken formula

	Soy formula† (%) n=18	Chicken formula‡ (%) n=20
Number of Tolerant Infants	6 (33%)	16 (80%)
Number of Intolerant Infants	12 (67%)	4 (20%)*
Odds ratio (95% CI)	1.0	8.0 [1.5, 46.0]

† number of subjects = 18; ‡ number of subjects = 20; *p = 0.009

Table 4. Details of symptoms of intolerance and number of infants in each group (Pre-challenge) challenged with soy formula and chicken formula (Post-challenge)

Soy formula		Chicken formula	
Pre-challenge Symptoms (n)	Post-challenge Symptoms of intolerance (n)	Pre-challenge Symptoms (n)	Post-challenge Symptoms of intolerance (n)
Cutaneous (8)	Cutaneous (7)	Cutaneous (11)	Cutaneous (2) Gastrointestinal (1)
Respiratory (3)	Respiratory (1) Gastrointestinal (2)	Respiratory (1)	None
Gastrointestinal (7)	Cutaneous (2)	Gastrointestinal (8)	Gastrointestinal (1)

n = number of infants

placed on a free amino acid formula until all the symptoms had resolved.

Statistical analysis

Two independent Student's *t* tests were used to compare the data between each group. A Chi-square test was used to compare the sex difference and numbers of infants with each presenting symptom. The significant difference between the two groups was set at $p < 0.05$.

RESULTS

Characteristics and clinical symptoms of infants in both study groups are shown in Table 2. Eighteen infants were randomized to the soy formula group and 20 to the chicken formula, respectively. Groups were not different in their mean age, sex distribution, weight, length, age of onset and presenting symptoms. More than 50% of the infants in both groups were anemic defined as a hematocrit less than 34%. Almost 20% of infants in both groups had eosinophilia defined as eosinophil in blood more than 700 per mm^3. Approximately 20%, and 5% of infants in the soy and chicken formula group, respectively, had elevation of specific IgE to cow milk protein.

Table 3 shows the number of infants who were allergic to soy and chicken formula. Twelve infants in the soy group were intolerant to the formula, whereas 4 out of 20 infants in the chicken group were intolerant to the chicken formula. The chicken formula was tolerated by a significantly greater number of infants with cow milk allergy than the soy formula (p = 0.009). The odds ratio was 8.0 with 95% confidence interval between 1.5 - 46.0. In the soy group, 7 out of 8 cases with cutaneous symptoms still had the symptoms, 2 out of 3 cases with respiratory symptoms had severe constipation, 1 out of 3 had the same respiratory symptom, and 2 out of 7 cases with gastrointestinal symptoms also had cutaneous symptoms. While in the chicken group, 2 out of 11 cases with cutaneous symptoms had cutaneous symptoms and 1 out of 11 cases of cutaneous symptom also had severe constipation, while 1 out of 8 cases of gastrointestinal symptoms also had severe constipation (Table 4).

DISCUSSION

Since our study groups are positive of specific IgE to cow milk not more than 25%, they are probably non-IgE-mediated CMA. Non-IgE-mediated CMA is a benign infantile condition.[12] However, it was reported that nearly 50% of infants with non-IgE-mediated CMA reacted to soy.[8] Rozenfeld et al.[13] identified a soy protein component, the A5-B3 glycinin molecule which could cross react with caseins from cow milk. In terms of immunogenicity, Birmingham et al.[14] found that in mice, soy bean has the least immunogenicity compared to that of almonds, spinach, peanuts, cherries, lettuce, walnuts, chicken eggs, and carrots. Furthermore, Muraro et al.[15] reported that soy formula is nutritionally adequate and can be used in children with immunoglobulin E mediated non-gastrointestinal manifestations of cow milk allergy. Soy formula has a long history as an alternative formula for infants with CMA. The reasons may be due to the lower cost and the fact that it is more palatable than hydrolyzed cow milk protein formula. However the most recent recommendation from ESPGHAN is not to use soy formula in infants under 6 months of age.[16] Also in the developing countries, they have to import commercial soy-based formula to feed the CMA infants. It is better to prepare chicken-based formula of their own by using the chicken meat which is easily available in every part of these countries.

In our study, there are quite a large number of infants who are allergic to soy formula. The reasons behind this are that our center is one of the few centers in the country that pediatricians will refer the CMA infants to. The infants then have partly failed with the soy formula before being referred to our center. It is a common practice for pediatricians when they suspect CMA in their patients to switch the cow milk formula to extensively hydrolyzed cow milk protein formulae,[17,18] which triggers less

adverse reactions.[9] However, extensively hydrolyzed cow milk protein formulas are quite expensive. It may be difficult for the parents to afford the formula especially for those in developing countries. Chicken protein has rarely been reported as a causative agent for allergic reactions and it is easily available in all countries. Larcher et al.[19] reported a series of infants with protracted diarrhea who were fed a comminuted chicken diet and showed satisfactory tolerance. In a randomized controlled comparison of a comminuted chicken diet with an elemental formula based on hydrolyzed lactalbumin, Godard et al.[20] observed comparable recovery times in both groups, with a clinical success rate in excess of 20%. With the techniques that we used to produce the chicken formula, the components were homogenously mixed, and the result was a sustainable, palatable compound with complete and standardized levels of vitamins and minerals that could be easily sucked through a rubber nipple. In addition, our study showed that chicken formula caused significantly less allergic reactions than soy formula.

In our study almost 60% of the subjects in the soy group and only 20% in the chicken group demonstrated adverse reactions to the test formulas. This may be because most infants in the chicken group were non-IgE-mediated CMA. Finally, but importantly in developing countries, chicken formula is much cheaper than extensively hydrolyzed cow milk protein formula and also cheaper than soy (Per litre: USD 1.5 for chicken formula, USD 2 for soy formula, USD 3 for extensively hydrolyzed formula). Therefore, for infants who are allergic to cow milk and soy protein, we recommend chicken formula as a choice for their feeding.

In conclusion, homogenized chicken formula demonstrated satisfactory results in the infants with cow milk protein allergy. The study of benefits and adverse consequences from long-term consumption is further needed in infants with CMA.

ACKNOWLEDGEMENTS

This study was supported by a grant of the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University. We gratefully acknowledge Suthipol Udompunthurak for statistical assistance and also thank Professor Carlos H. Lifschitz for his thoughtful review of the manuscript.

AUTHOR DISCLOSURES

Pipop Jirapinyo, Narumon Densupsoontorn, Renu Wongarn and Nuchnoi Thamonsiri, no conflicts of interest.

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雞肉和黃豆蛋白配方奶對牛奶過敏症嬰兒之比較

目的：測定對牛奶過敏症的嬰兒，是否可以用雞肉蛋白配方奶取代黃豆蛋白配方奶。**對象和方法**：38 位 2-24 個月對牛奶過敏的嬰兒，隨機分派至接受雞肉蛋白配方奶或黃豆蛋白配方奶 14 天。**結果**：在黃豆蛋白配方奶組，18 個中有 12 個嬰兒證實不耐受而無法繼續使用此配方奶。然而，20 個使用雞肉蛋白配方奶的嬰兒中只有 4 個確認為臨床不耐。所有其他 16 位都成功餵食雞肉蛋白配方奶。雞肉蛋白配方奶不耐受的嬰兒數明顯比餵食黃豆蛋白配方奶少($p = 0.009$)。**結論**：對牛奶過敏症的嬰兒而言，雞肉蛋白配方奶比黃豆蛋白配方奶更有效。

關鍵字：雞肉配方奶、牛奶過敏症、黃豆配方奶、泰國、嬰兒。