Original Article

Effect of carob bean on gastric emptying time in Thai infants

Boosba Vivatvakin MD[1] and Vacharee Buachum MD[2]

[1]Department of Pediatrics, [2]Department of Radiology, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand.

Thickening agents, such as carob bean gum or galactomannan, have been successfully administered for the treatment of gastroesophageal reflux in infants. To study the effect of carob bean gum on gastric emptying and to symptoms of regurgitation, we recruited 20 full term Thai infants (mean age = 13.4 $\pm$ 7 week; mean body weight = 4943 $\pm$ 1272gm) without pathological gastroesophageal reflux. Initially, we determined half time gastric emptying (T 1/2 GET) by Tc99m radioscintigraphy method (mean T 1/2 GET = 116.1 $\pm$ 72 min) in infants consuming standard infant cow's milk formula for 2 weeks. Afterwards, carob bean infant formula was given for 2-4 weeks and weight gain, vomiting symptoms, night cough, colic, flatus, defaecation character and T 1/2 GET were assessed. There were statistically significant improvements in symptoms of vomiting (a smaller quantity $P<0.001$ and frequency of vomiting $P<0.0001$) and improvements in weight gain per week (W1 = 121.2 + 106.9gm, W2 = 221.3 + 136.1gm; $P= 0.005$) when infants consumed the carob bean formula. However, there was no significance difference in gastric emptying half time (GET1 = 116.1 + 72, GET2 = 148.5 + 130.9; $P= 0.154$). In conclusion, carob bean gum, as a thickening agent, improves the clinical symptoms of regurgitating infants, but does not significantly alter the gastric emptying physiology.

Key words: carob bean gum, gastroesophageal reflux, vomiting, regurgitation, gastric emptying time, infant, Thailand

Introduction

Various thickening agents have been successfully introduced as phase I treatment of gastroesophageal reflux in infants and children.[1,2,8] The thickening agents have been derived from cereals, polysaccharide from glass rice and carob bean gum, which are all sources of dietary fibre. Carob bean gum (Locust bean or St. John's bread) is obtained from the inner part of the carob bean kernel and is an off-white, odourless powder with no distinctive taste. It is composed of 80% polysaccharides (mostly galactomannan) and 20% protein. The carob bean is used as a chocolate substitute and as a sweetener. Cow's milk formulas with added thickening agents (like carob bean or galactomannan) for infants with problems of regurgitation or failure to gain proper weight, have been commercially available. Carob bean, which has been developed to mix with infant formula, has two specific characteristics: 1. it thickens the formula; 2. it has dietary fibre that will promote the bacterial flora in the large intestine which benefits constipation. Some fermentable dietary fibres, such as those found in carob bean gum, can act as food thickeners by increasing the viscosity of the food. In 1981 Tsai and Peng[3] demonstrated the reduction of gastric emptying rate in rats after feeding the locust (carob) bean gum enriched diet and a flattening of postprandrial serum glucose. Silk *et al.*, and others have demonstrated that gastrointestinal motility[4-6,30] can be positively affected by dietary fermentable fibres. These fibres are fermented by the intestinal microflora and are therefore predominantly of importance in stimulation of colonic motility. During this fermentation process, the short chain fatty acids produced can act as an energy source for the colonocyte and enterocyte and they also play a central role in osmoregulation. In adults, dietary fibres influence the prolongation of anal transit time and colonic transit time which suggested the potential use of dietary fibre in diabetic diarrhoea and some irritable bowel syndromes with diarrhoea. Vandeplas and Sacre in 1987[7] reported that milk thickening agents clinically improved symptoms of gastro-esophageal reflux in infants, but increased the duration of the longest reflux episodes significantly.

In this study we evaluated the effect of an infant formula enriched with a carob bean gum thickening agent on gastric emptying in Thai infants with symptoms of regurgitation and vomiting.

Correspondence address: Professor Boosba Vivatvakin, Paediatric Gastrointestinal Unit, King Chulalongkorn Memorial Hospital, 1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand.
Tel: 662 2564951 Fax: 662 2564911
Email: fmedbvv@md.md2.chula.ac.th, drboosba@hotmail.com
Accepted 23 August 2002

Materials and Methods

This study was approved by the Committee of Human Research, Faculty of Medicine, Chulalongkorn University on November 16, 1995. During 1 January 1996 to 31 January 1997 (13 month period) 20 Thai infants, 13 male and 7 female, aged 4 -24 weeks were studied. The study had a cross over trial design. All infants were all normally delivered, with full-term criteria by gestational age determined with ballard scores. All infants in the study were bottle-fed. Officially signed informed consents were obtained from either parent. All infants were born in Bangkok hospital or suburban hospital with uncomplicated pregnancy and routine antenatal care with normal blood checked to screen out the evidence of serious perinatal transmissible diseases such as HIV, hepatitis B virus HBV and syphilis. Infants were recruited using the following *inclusion criteria*: bottle fed with Cow's milk infant formula (protein = 18-20 gm/dl, whey:casein = 60:40, fat content = 3.5 gm/dl) without pathological gastro-oesophageal reflux, no family history of atopy or cow's milk allergy, severe heart, kidney, liver diseases, chronic diarrhoea or 2^o lactase deficiency and CNS anomalies. *Exclusion criteria* were as follows: infants who could not attend all follow up sessions or who developed other organic diseases during the 6 week study period.

Informed consents were addressed and signed by the legal parents. Baseline infant data were provided by the mothers completing the pre-test questionnaires.[19] These questionnaires described: gestational age; birth weight; age of recruitment; increment weight gain per day by casual feeding with formula milk [with comparable ratio of whey:casein (60:40); percentage of fat (3.5gm/dl)]; frequency and amount of meals; type of additional food; frequency, volume and character of vomiting; evidence of abdominal colic; night cough; flatus; duration of crying; character and frequency of each passed stool. Baseline data for the infants were collected for 1-2 weeks before the intervention period with the carob bean.

Gastric emptying time (GET) was assessed by using Radio-scintigraphy[9-14,26] technique using standard infant formula milk, 300ml/M^2 of body surface mixed with 5μCi (0.2 Mbq)/ml of ^{99m}Tc phytate. Within 5-10 minutes of consuming the standard formula milk the infant was placed under the collimeter to detect the radioactivity of the labelled milk in the stomach. The computer acquisition was accessed every 30 seconds for up to 30 minutes; time activity curves were generated and gastric emptying half time was calculated. If the infant vomited after ingesting the labelled milk, the procedure was repeated, at least 6 hours apart. After the assessment of first gastric emptying half time, all the infants were given carob bean gum milk formula for at least 2 weeks. The same symptom-questionnaires were completed by the mothers with weekly body weight measuring. A second gastric emptying half time was also performed. Infants who were satisfied with the carob bean milk formula consumed this special milk up to 6 months of age then changed to a cow's milk formula and supplementary foods. Infants who were not satisfied with the carob milk formula or who were diagnosed as having gastroparesis (by means of radionuclide study) were put on motility drugs, such as domperidone or cisapride.[15-17] Advice was not provided regarding infant position during and after feeding two kinds of milk formulae. Statistical analyses were performed using the paired t-test.

Results

Baseline data of the 20 full-term infants who entered into the study are shown in Table 1. Twenty infants aged 4-24 weeks (13.4 $\pm$ 7) were studied with gestation age ranging between 36 - 40 weeks (39.15 $\pm$ 1.42); birth weight ranged between 2080 – 3770g (3040 $\pm$ 420); actual body weight ranged between 2570g - 6800g (4943 $\pm$ 1272); cow's milk infant formula by the volume per feed was 45 - 120ml (84.5 $\pm$ 21.67) for 6-8 feedings (6.9 $\pm$ 0.9). The weight increment per day before entering into the study ranged between 1 to 31 grams (18.4 $\pm$ 6).

Table 2 compares clinical data obtained after feeding with cow's milk formula for 2 weeks followed by feeding with carob bean formula for another 2 weeks. The cow's milk formula had a similar whey:casein ratio and caloric density (20 Kcal per 30 ml) to the carob bean formula. The paired t test analysis showed that in the carob bean formula group, frequency of vomiting per week decreased significantly from 5.7 $\pm$ 2.13 to 2.25 $\pm$ 1.45 (P=0.001) and weight gain per week increased significantly from 121.5 $\pm$ 100.7g to 221.2 $\pm$ 136.2g (P=0.005) (Fig. 1). Fig.2 shows that the changes in gastric emptying times (mean GET1 = 116.16 $\pm$ 72 sec., mean GET2 =148.5 $\pm$ 131sec.) were not significant (P = 0.154). Non-numerical parameters of clinical symptoms from the mothers showed that there was significantly less vomiting (P <0.001), night coughing (P=0.002) and crying (P=0.02). Reported differences in symptoms of colic were not statistically significant (P=0.331). Flatus seemed to be observed more during the carob bean formula treatment (P=0.010). Stool frequency decreased during the carob bean feeding, but it was not statistically significant (P =0.679).

Discussion

There are various modalities of management for infants with recurrent regurgitation and vomiting, such as thickening agent added to milk formula, 30^o infant head raised up position,[4,18] motility drugs[20-25] (e.g. domperidone, erythromycin[31]), acid lowering agents (e.g. H_2 blockers, omeprazole,[32] cisapride) or surgical correction (e.g. fundoplication). Thickening agents such as cereal, gelatin and various polysaccharides were used in the trial therapy period of the study and many of the infants suffering from recurrent regurgitation responded to the phase I treatment quite well.

This study not only showed that the addition of carob bean gum into the milk formula was palatable to the infants, but that it resulted in a better clinical outcome (Fig. 1, Table 3). Several studies have shown that dietary fibre prolongs gastric emptying and may cause gastroparesis in adults[33-35] - this was also found in this study but it was not statistically significant (P value = 0.154). Table 3 shows that night coughing and

Table 1. Clinical data of Thai infant study group before intervention with carob bean infant formula (N=20)

Case No	Gestational[a] Age (week)	Birth Weight (gram)	Sex	Age (week)	Body Weight (gm)	Weight gain per day (gm)	No.of milk feeding per day (time)	Volume.of milk per feed (ml)
1	36	2450	F	16	2570	1	8	90
2	36	2080	F	12	4800	30	7	60
3	37	2600	F	24	4050	8	6	90
4	38	3300	M	12	4550	14	8	90
5	38	2800	M	24	6400	20	6	90
6	38	3400	M	4	4000	20	8	120
7	40	3200	M	4	3650	15	8	60
8	40	3000	M	24	5340	13	6	60
9	40	3700	M	20	6250	17	7	120
10	40	3115	M	4	3200	1	8	60
11	40	3770	M	20	6500	19	6	100
12	40	2500	F	16	6200	31	6	90
13	40	3250	M	16	5900	22	8	60
14	40	2790	M	4	3150	10	6	90
15	40	3000	M	4	4100	24	6	90
16	40	2950	F	16	6100	26	6	45
17	40	3200	F	8	4400	20	8	90
18	40	3400	F	16	6800	28	8	120
19	40	3300	F	12	5700	26	6	75
20	40	3000	M	12	5200	22	7	90
Mean	39.15	3040.25	M : F	13.4	4943	18.35	6.9	84.5
Std	1.42	420	12 : 8	7.02	1272	8.6	0.94	21.7

[a] Gestational age at birth

Table 2. Comparison of clinical data between cow's milk formula and carob bean formula feeding (cross over design)

			Weight gain per week (gm)		Frequency of vomiting		Amount of vomiting	
Case No.	GET1 (min)	GET2 (min)	Cow's milk	Carob bean	Cow's milk	Carob bean	Cow's milk	Carob bean
1	54	51.7	100	250	7	3	Half meal	Mouthful
2	208.2	288.2	150	150	7	5	Half-full meal	Mouthful
3	79	77.2	10	300	7	5	Mouthful	Mouthful
4	59.6	34.3	0	0	7	2	Full meal	Mouthful
5	302.7	449	0	100	7	2	Sporadic	None
6	109	133	185	165	5	5	Full meal	Mouthful
7	250	198	30	300	6	1	Half meal	Half meal
8	63.68	60.2	300	200	7	1	Half meal	Mouthful
9	48	46.5	100	300	4	1	Half meal	Mouthful
10	86.4	72.2	225	500	7	1	Half meal	Mouthful
11	92	16	150	200	7	3	Half meal	Mouthful
12	58.49	56.7	0	100	7	2	Full meal	Full meal
13	110	450	150	240	1	1	Half meal	Mouthful
14	102	94	200	450	4	1	Full meal	Half meal
15	42	94	75	25	7	3	Half meal	Mouthful
16	104	314	0	250	2	1	Mouthful	Mouthful
17	87.15	78	100	0	7	1	Half meal	Mouthful
18	156	169	400	250	1	1	Full meal	Mouthful
19	104	90	150	375	7	3	Mouthful	Mouthful
20	207	198	100	270	7	3	Full meal	Mouthful
Mean	116.16	148.5	121.5	221.2	5.7	2.2		
Std	72.03	130.9	100.7	136.2	2.3	1.45		

GET1 = Gastric emptying half time during cow's milk formula feeding; GET2 = Gastric emptying half time during carob bean formula feeding

crying improved significantly during the carob formula feeding phase, however, there may have been parent bias when recording these symptoms due to their positive attitude in being involved in the treatment phase of study. Even though the volume of vomiting was quite difficult to measure, parental feedback on this point was reliable because the parents also reported spending less time cleaning at night due to less vomiting and sleeping for longer periods during the night. The frequency of vomiting also decreased which correlated well with the weight gained per week during the carob bean formula feeding. This suggests that the infants were retaining more formula milk inside the stomach that later passed along the gastrointestinal tract and was absorbed for body utilization. Thickening agents, such as carob bean, appear to decrease stool frequency due to higher fibre content. The higher fibre intake did not result in significantly more flatus in the infants, possibly due to colonic bacterial fermentation of the dietary fibre (galactomannan) in the carob bean. Carob bean allergy has been reported in infants,[36] but we did not find any cases of allergy in our study. Only four infants were diagnosed with cow's milk allergy before the study and were excluded.

In this study we did not assess the role of feeding and sleeping position of the infant because recommendations about this are controversial. To reduce this variable as a possible confounder we decided to let all infants sleep in their usual position through the period of study.[37]

In conclusion, carob bean can be safely administered to young infants as a milk thickening agent to reduce clinical symptoms associated with regurgitation and to improve weight gain. The carob bean formula was palatable to the infants and was just as well tolerated and accepted as standard cow's milk formula. Infants with pylorospasm or severe gastroparesis may not respond to milk thickening agents because of the delayed gastric emptying time[6,38,39]. Furthermore, pathological gastroesophageal reflux or cow's milk allergy should be ruled out before prescribing special milk thickening formula.

Table 3. Clinical significance of carob bean formula feeding in Thai infants

Clinical symptom	Number of presenting cases out of total in the study N=20	*P* value (one-way sample test)
Decreased frequency of vomiting	15/20	*P*=0.001
Decreased amount of vomiting	14/20	*P*<0.001
Decreased night cough	14/20	*P*=0.002
Decreased colic	8/20	*P*=0.331
Increased flatus	1/20	*P*=0.010
Decreased crying	6/20	*P*=0.021
Decreased stool frequency	5/20	*P*=0.679
Increased weight gain per week	13/20	*P*=0.005

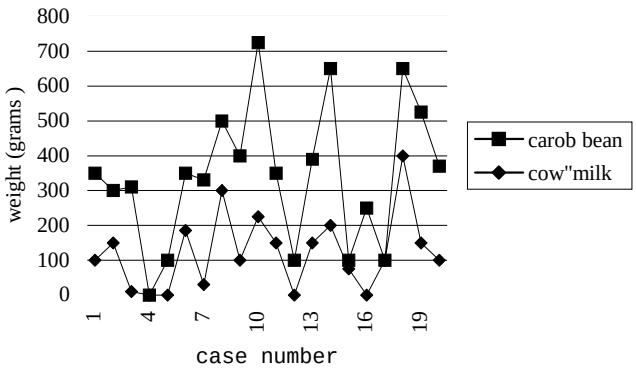

Fig.1 Comparison of weight gain per week (grams) between cow's milk and carob bean formula feeding in Thai infants.

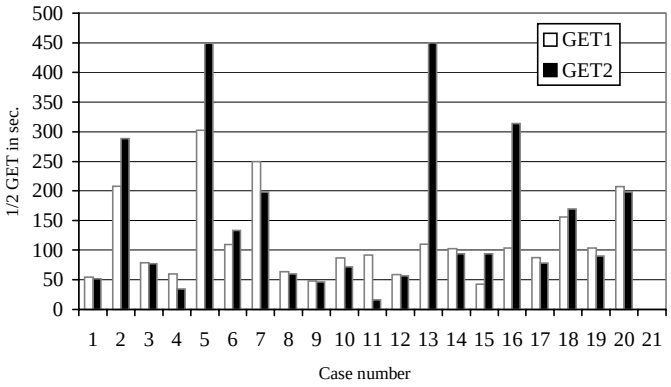

Fig.2 Cross over study of gastric emptying time of cow's milk feeding (GET1) and carob bean milk (GET2) in Thai infants

Acknowledgement
Thanks to Friesland Nutrition (The Netherlands) who provided the special formula for academic study.

References

1. Sheperd RW, Wren J, Evans S, Lander M, Ong TH. Gastroesophageal reflux in children. Clinical profile, course and outcome with active therapy in 126 cases. Clin Pediatr 1987; 26: 55-60.
2. Faubion WA Jr, Zein NN. Gastroesophageal reflux in infants and children. Mayo Clin Proc 1998; 73: 166-173.
3. Tsai AC, Peng B. Effects of locust bean gum on glucrose tolerance, sugar digestion and gastric motility in rats. J Nutr 1981; 11: 2152-2156.
4. Orenstein SR, Whitington PF. Positioning for prevention of infant gastroesophageal reflux. J Pediatr 1983; 103: 534 -537.
5. Zavoral JH, Hannan P, Fields DJ, Hanson MN, Frantz ID, Kuba K. The hypolipidenic effect of locust bean gum food products in familial hypercholesterolemic adults and children. Am J Clin Nutr 1983; 38: 285-294.

6. Kwiterovich PO Jr. The role of fibre in the treatment of hypercholesterolemia in children and adolescents. Pediatrics 1995; 96: 1005-1009.
7. Vandenplas Y, Sacre L. Milk thickening agents as a treatment for gastroesophageal reflux. Clin Pediatr 1987; 26: 66-68.
8. Herbst JJ. Gastroesophageal reflux. J Pediatr 1981; 98: 859-70.
9. Paton JY, Cosgriff PS, Nanayakkara CS. The analytical sensitivity of Tc 99m radionuclide "milk" scanning in the detection of gastro-oesophageal reflux. Pediatr Radiol 1985; 15: 381-383.
10. Siegel JA, Wu RK, Knight LC, Zelac RE, Stern HS, Malmud LS.Radiation dose estimates or oral agents used in upper gastrointestinal disease. J Nucl Med 1983; 24: 835-837.
11. Thomforde GM, Camilleri M, Phillips SF, Forstrom LA. Evaluation of an inexpensive screening scinitigraphic test of gastric emptying. J Nucl Med 1995; 36: 93-96.
12. Charles F, Camilleri M, Phillips SF, Thomforde GM, Frostrom LA. Scintigraphy of the whole gut: clinical evaluation of transit disorders. Mayo Clin Proc 1995; 70: 113.
13. Datz FL, Christian PE, Hutson WR, Moore JG, Morton KA. Physiological and pharmacological interventions in radionuclide imaging of tubular gastrointestinal tract. Semin Nucl Med 1991; 21: 140-152.
14. Carbonnel F, Lemann M, Rambaud JC, Mundler O, Jian R. Effect of the energy density of a solid-liquid meal on gastric emptying and satiety. Am J Clin Nutr 1994; 60: 307-311.
15. Reynolds JC, Putman PE. Prokinetic agents. Gastroenterol Clin N Am 1992; 21: 567-596.
16. Allan SG. Antiemetics. Gastroenterol Clin N Amer 1992; 21: 597-612.
17. Chaudhuri TK, Fink S. Update: pharmaceutical and gastric emptying. Am J Gastroenterol 1990; 85: 223-230.
18. Orenstein SR, Whitington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. N Engl J Med 1983; 309: 760-763.
19. Locke GR, Talley NJ, Weaver AL, Zinmcister AR. A New Questionnaire for gastroesophageal reflux disease. Mayo Clin Proc 1994; 69: 539-547.
20. Deerojanawong J, Vivatvakin B, Prapphal N, Saengchote S. Gastroesophageal reflux in infant with recurrent pneumonia. Chula Med J 1993; 37: 685-690.
21. Wager E, Tooley PJH, Pearee GL, Wilton LV, Mann RD. A comparison of two cohort studics evaluating the safety of cisapride. Prescription-Event Monitoring and a large phase IV study. Eur J Pharmaco 1997; 52: 87-94.
22. Van de Meer SB, Forget PP, Kuijten RH, Arends JW. Gastroesophageal reflux in children with recurrent abdominal pain. Acta Paediatr 1992; 81: 137-140.
23. Chen PH, Chang MH, Hsu SC. Gastroesophageal reflux in children with chronic recurrent bronchopulmonary infection. J Pediatr Gastroenterol Nutr 1991; 13:16-22.
24. Di Lorenzo C, Hyman PE. Gastrointestinal motility in neonatal and pediatric practice. Gastroenterol Clin N Am 1996; 25: 203-24.
25. Carre IJ. The natural history of the partial thoracic stomach (hiatal hernia) in children. Arch Dis Child 1959; 34: 344-52.
26. Camilleri M, Zinsmeister AR, Graydanus MP, Brown ML, Proano M.Towards a less costly but accurate test of gastric emptying and small bowel transit. Dig Dis Sci 1991;36: 609-15.
27. Cannon RA, Stadalnik RC. Postpandrial gastric motility in infants with gastroesophageal reflux and delayed gastric emptying. J Nucl Med 1993; 34: 2120-3.
28. Shinnick FL, Hess RL, Fischer MH, Marlett JA. Apparent nutrient absorption and upper gastrointestinal transit with fibre-containingenteral feedings. Am J Clin Nutr 1989; 49: 471-475.
29. Malfroot A, Vendenplas Y, Verlinden M, Piepsz A, Dab I. Gastroesophageal reflux and unexplained chronic respiratory disease in infants and children. Pediatr Pulmonol 1987; 3: 208-213.
30. Casteels-Van Daele M, Jaeken J, Van der Schueren P, Zimmerman A, Van den Bon P. Dystonic reactions in children caused by metoclopramide. Arch Dis Child 1970; 45: 130-133.
31. Keshavarzian A, Isaac RM, Erythromycin accelerates gastric emptying of indigestible solids and transpyloric migration of the tip of an enteral feeding tube in fasting and fed states. Am J Gastroenterol 1993; 88: 193-197.
32. Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. J Pediatr 1993; 123: 148-154.
33. Kao CH, Lai TL, Wang SJ, Chen GH, Yeh SH. Influence of age on gastric emptying in healthy chinese. Clin Nucl Med 1994; 19: 401-404.
34. Duan LP, Zheng ZT, Li YN. A study of gastric emptying in non ulcer dyspepsia using a new ultrasonographic method. Scand J Gastroenterol 1993; 28: 355-360.
35. Barnett JL, Owyang C. Serum glucose concentration as a moderlator of interdigestive gastric motility. Gastroenterology 1988; 94: 739-744.
36. Savino F, Muratore MC, Silvestro L, Oggero R, Mostert M. Allergy to carob bean gum in an infant. J Pediatr Gastroenterol Nutr 1999; Oct 29 (4): 475-476
37. Carroll AE, Garrison MM, Christakis DA. A systematic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. Arch Pediatr Adolesc Med 2002; 156 (2): 109-113.
38. Orenstein SR. Gastroesophageal reflux. Pediatr Rev 1992; 13: 174-182.
39. Bardhan PK, Salam MA, Molla AM. Gastric emptying of liquid in children suffering from acute rotaviral gastroenteritis. Gut 1992; 33: 26-29.