Enhanced weight gain in preterm infants receiving lactase-treated feeds: A randomized, double-blind, controlled trial

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Objective: To evaluate whether lactase-treated preterm feeds enhance weight gain and feeding tolerance in premature infants.

Study design: Prospective, double-blind, randomized, controlled trial involving 130 infants (26-34 weeks postconceptual age). The primary outcome variable was weight gain (g per day). Other outcome measures included gains in length and head circumference, biochemical indexes of nutritional status, feeding intolerance, and incidence of necrotizing enterocolitis.

Results: On study day 10, weight gain (mean ± SEM) of the treatment group was significantly greater ($P < .05$) than that of the control group (20.4 ± 1.8 g/day vs 15.5 ± 1.6 g/day). By study end, no significant difference in weight gain between treatment and control groups was observed. The difference in serum albumin level was significant at study day 14, with a value of 29.3 ± 0.6 g/L in the treatment group compared with 27.1 ± 0.4 g/L in the control group ($P < .01$). There were no significant differences in caloric intakes, length gain, head circumference gain, feeding intolerance, and incidence of necrotizing enterocolitis.

Conclusions: Weight gain may be enhanced during the period of low functional lactase activity of prematurity by addition of lactase to preterm feeds. No adverse effects on feeding tolerance resulted from this treatment. (J Pediatr 2002;141:532-7)

Lactase is first detectable in the fetal intestine by 10 weeks' gestation.[1] At 28 to 34 weeks, lactase activity is only ~30% of that found at term.[1,2] By 35 to 38 weeks, it reaches 70% of term activity.[2] Because of insufficient functional development of lactase, premature infants may not digest and absorb their main source of carbohydrate energy—lactose—as well as their term counterparts.[3-5]

The high osmotic load associated with undigested lactose is one of many possible causes of diarrhea and feeding intolerance in premature infants.[3,6] As a result of temporary diarrheal brush border damage, low functional lactase activity will be further reduced and weight gain may be compromised significantly.[6] It takes up to 2 weeks for lactase activity to be restored.[6]

Lactose intolerance is often managed with soy protein, protein hydrolysate, low lactose, or lactose-free formulas.[7] However, these term formulas do not meet the nutritional requirements for growth and development of preterm infants, who require preterm human milk with commercial human milk fortifier or preterm formula.[8,9] Ideally, lactose-intolerant preterm infants should receive a lactose-hydrolyzed version of these feeds.

NEC	Necrotizing enterocolitis
SDAY	Study day
SSC	Similac Special Care
NICU	Neonatal intensive care unit

Carlson et al[6] demonstrated that the addition of lactase to preterm formula reduces the amount of lactose by 70% after a 2-hour incubation period at room temperature, with negligible effect on osmolality. It seems reasonable to suggest that the same mechanism of conversion of lactose would occur in human milk, as demonstrated in premature formula. In this study, we hypothesized that the use of lactase to hydrolyze lactose in preterm feeds would result in enhanced weight gain and improved feeding tolerance.

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METHODS

Study Population

A prospective, double-blind, randomized, controlled trial was conducted to evaluate growth and feeding tolerance in preterm infants who received either (1) fortified human milk or preterm formula treated with Lactaid drops (McNeil Consumer Products Company, Guelph, Ontario, Canada) (lactase group), or (2) untreated fortified human milk or preterm formula (control group). A total of 130 premature infants were enrolled in the Royal University Hospital Neonatal Intensive Care Unit (NICU) between April 1997 and July 2000. The following enrollment criteria were used: 26 to 34 weeks postconceptual age (determined by known date of last menstrual period or early ultrasonogram and subsequently confirmed by neonatal examination), ≥75% estimated energy requirement from enteral feeds, absence of major congenital malformations or gastrointestinal diseases, including necrotizing enterocolitis (NEC), and no postnatal steroids or diuretics. Small, appropriate and large for gestational age infants were eligible for the study. The study was approved by the Ethics Review Committee for Human Experimentation at the participating site. Written informed parental consent was obtained.

Study Design

Infants (n = 130) were enrolled in this study and stratified by gestational age (26-30 weeks vs 31-34 weeks) before being randomly assigned to the lactase or the control group. Study day (SDAY) 1 was the day on which enteral feedings provided ≥75% of daily intake. The study was terminated when the infant reached 36 weeks or was discharged from the unit, whichever came first.

Study infants were fed according to parental choice. Infants fed human milk received human milk alone on SDAY 1 and SDAY 2. Human milk was assigned an estimated caloric value of 68 kcal/100 mL (see reference 13). On SDAY 3, each infant received a 1:1 ratio of human milk and a liquid human milk fortifier, Natural Care [Ross Laboratories, Division of Abbott Laboratories Ltd, Saint-Laurent, Quebec, Canada] and continued with this feeding regimen for the duration of the study. Natural Care provides 81 kcal/100 mL. Infants fed formula received the preterm formula, Similac Special Care (SSC) (Ross Laboratories, Division of Abbott Laboratories Ltd, Saint-Laurent, Quebec, Canada). On SDAYs 1 and 2, these infants received SSC 20 (68 kcal/100 mL). They were advanced to SSC 24 (81 kcal/100 mL) on SDAY 3 and received this formula for the duration of the study. Some infants received both fortified human milk and preterm formula during the study (Table I).

Infants randomly assigned to the lactase group received feeds treated with Lactaid drops. The method for treating the study feeds with Lactaid drops was developed based on the publication by Carlson et al,[6] which indicated that the addition of 2 drops of Lactaid to 120 mL of 81 kcal/100 mL preterm formula resulted in a 70% decrease in lactose concentration (from 35.3-10.3 g/kg) when held at room temperature for 2 hours, and subsequent refrigeration for 24 hours resulted in a continued conversion of lactose at a decreased rate.

Preterm formula and liquid human milk fortifier for study infants was prepared in the central food production area, which was not accessible to the blinded care givers or researchers in this study. The formula preparation staff followed the study protocol for study feed preparation. Preterm formula and human milk fortifier for infants randomly assigned to the treatment group was treated with 2 Lactaid drops per 120 mL. Formula and human milk fortifier for control group infants was untreated.

For the infants receiving fortified human milk, expressed milk from the infant's mother was prepared in the NICU. A study placebo solution composed of the identical carrier agent in Lactaid was developed by McNeil Consumer Products Company. The enzyme and matched placebo solutions were packaged in identical bottles labeled "lactase study drops" and were identifiable only by the research nurse according to assigned code numbers. After random assignment of human milk-fed infants, the research nurse labeled the appropriate bottle of enzyme or placebo with the infant's name and delivered it to the infant's bedside in the NICU. The infant's neonatal nurse prepared the daily supply of the infant's mother's milk, adding 2 drops of lactase study drops to 120 mL human milk or 1 drop to 60 mL when small volumes were available or required. The bottle of treated feed was sealed, labeled "lactase study feed," with the infant's name, date, and time of treatment with study drops and held at room temperature for 2 hours before refrigeration. The feed was then kept refrigerated and used for up to 24 hours. The supplies of active enzyme and placebo solution, with identifiable code numbers for each lot, were shipped every 2 months from the McNeil Consumer Products Laboratory to the study site.

Researchers and care givers remained blinded for the duration of the study; only the research nurse and central food production staff had access to randomization information and did not participate in patient care.

Outcome Measures

Serial measurements were recorded for growth, caloric intakes, biochemical indexes, and tolerance of feeds. The primary outcome variable was weight gain (g/day). Additional outcome variables included gains in crown-heel length and occipitofrontal head circumference (cm/week); serum concentrations of protein, albumin, sodium, and potassium; and measurements of feeding tolerance (emesis, gastric residual volumes, number of stools, and reducing substances in stools). In addition, with-

Table I. Characteristics of study infants

	Control group	Lactase group
Gestational age (wk)	31.4 ± 0.2 (64)	31.4 ± 0.3 (66)
Birth weight (g)	1420.9 ± 56.3 (64)	1394.0 ± 49.1 (66)
Age at study entry (d)	10.8 ± 0.9 (64)	11.2 ± 0.9 (66)
Body weight at study entry (g)	1434.2 ± 48.7 (64)	1408.8 ± 41.6 (65)
Body length at study entry (cm)	41.0 ± 0.4 (61)	40.7 ± 0.5 (65)
Head circumference at study entry (cm)	27.9 ± 0.3 (62)	27.9 ± 0.3 (65)
Feed type		
Fortified human milk (1)	25.0% (16)	21.2% (14)
Premature formula (2)	32.8% (21)	39.4% (26)
Combination (1 + 2)	42.2% (27)	39.4% (26)
Study length (d)	25.7 ± 1.9	24.1 ± 1.7

Values are mean ± SEM (number of infants).
There were no statistically significant differences between the two groups by unpaired *t* test.

drawal from the study because of feeding intolerance or NEC was recorded.

Weights were recorded daily on the same electronic scale for all study infants. Contrasts in weight gain were analyzed on SDAYs 7, 10, and 14 and study exit. The crown-heel length measurements were obtained with a fixed headboard and movable footboard, and occipitofrontal head circumference was measured with a standard tape to the nearest 0.1 cm. Length and head circumference measurements were recorded on SDAY 1 and SDAY 14. If study exit was before SDAY 14, these measurements were taken at the time of study termination. Caloric intakes and feed type were recorded daily. Blood samples were collected and analyzed in the Department of Laboratory Medicine, Saskatoon District Health, to determine serum concentrations of total protein, albumin, sodium, and potassium on SDAY 1 and SDAY 14 or at study exit, if this occurred earlier.

Statistical Methods

The primary outcome measure for this study (weight gain, g/day) was used as the basis for calculating sample size. The sample size was chosen to allow detection of 33% increase in mean weight gain per day in the treatment group, with a power of 0.80. Differences between groups were considered statistically significant at a level of $P < .05$.

The characteristics of the infants assigned to the lactase and control groups at study entry were compared by unpaired *t* test. Differences between the lactase and control groups in caloric intake, weight gain, length gain, head circumference gain, gastric residual volume, daily number of episodes of emesis, daily stool number, and serum concentrations of albumin, total protein, sodium and potassium were examined by unpaired *t* test.

The proportion of infants in each group who reached SDAY 14, developed feeding intolerance, had at least one episode of emesis during the study, or had the study terminated because of medical condition or parental request was compared by means of the Pearson χ^2 test. The proportion of infants in each group who had NEC was compared by means of the Fisher exact test.

RESULTS

Sixty-six infants were randomly assigned to the lactase group; of these, 52 reached SDAY 14 (Table I). The average length of the study in this group was 24.1 ± 1.7 days. Sixty-four infants were randomly assigned to the control group, of which 50 reached SDAY 14. The average study length for this group was 25.7 ± 1.9 days. No significant differences were observed between the entry characteristic variables or study length for the treatment and control groups.

There were no significant differences between the two groups for caloric intakes at SDAYs 7, 10, or 14 or study exit (Table II). There were also no significant differences between the two groups for weekly length gain or weekly gain in head circumference.

Weight gain was analyzed on SDAYs 7, 10, and 14 and at study exit. Rate of weight gain was calculated as the average weight gain of all preceding days. The lactase group had a rate of weight gain that was 4.5 ± 2.7 grams per day greater than the control group on SDAY 7. The weight gain for the lactase group when measured on SDAY 10 was significantly greater ($P < .05$) than the control group (difference = 4.9 ± 2.4 g/d). On SDAY 14, the rate of weight gain was 2.7 ± 2.1 g/d greater in the lactase group. At study exit the lactase group rate of weight gain was 2.2 ± 1.6 g/d greater than the control group.

Table III demonstrates the laboratory results for each variable at SDAY 1 and SDAY 14 (or at study exit, if this occurred earlier). The difference in serum albumin level was statistically significant at SDAY 14, with the lactase group value of 29.3 ± 0.6 g/L greater than the control group value of 27.1 ± 0.4 g/L ($P < .01$).

The reasons for study termination were recorded, with the majority of infants in each group reaching SDAY 14 (52/66 in the lactase group and 50 of 64 in the control group). The difference was not statistically significant. The incidence of development of feeding intolerance was lower in the lactase group (4/66) than in the control group (6/64), although this difference was not statistically significant by Pearson χ^2 testing. There were no cases of NEC in the lactase group (0/66) compared with one case in the control group (1/64). The number of infants removed from the

study because of medical condition, requirements for clinical treatment, or parental request was 9 of 66 in the lactase group versus 6 of 64 in the control group. This did not reflect a statistically significant difference. No significant differences were observed between the groups with respect to number of episodes of emesis per day (0.4 ± 0.1 in the lactase group vs 0.6 ± 0.1 in the control group). The number of infants with at least one episode of emesis during the study also showed no significant difference (51 in the lactase group vs 52 in the control group). There were no significant differences in gastric residual volumes (2.9 ± 0.3 mL/day in the lactase group vs 2.6 ± 0.4 mL/day in the control group). The number of stools per day (3.7 ± 0.2 in the lactase group vs 3.4 ± 0.2 in the control group) did not show a significant difference.

Table II. Effect of lactase treatment on growth and caloric intake

	Control group	Lactase group
Weight gain (g/d)		
7 d	12.9 ± 1.9	17.4 ± 1.9
10 d	15.5 ± 1.6	20.4 ± 1.8*
14 d	18.6 ± 1.4	21.3 ± 1.6
Study exit	23.0 ± 1.2	25.2 ± 1.1
Caloric intake (kcal/kg/d)		
7 d	109.7 ± 1.9	111.9 ± 3.1
10 d	111.8 ± 2.0	113.4 ± 3.1
14 d	113.2 ± 2.2	112.5 ± 2.2
Study exit	113.7 ± 1.8	117.5 ± 2.7
Length gain† (cm/wk)	0.7 ± 0.1	1.0 ± 0.2
Head circumference gain† (cm/wk)	0.7 ± 0.1	0.8 ± 0.1

Values are mean ± SEM.
*Denotes statistically significant difference between the two groups by unpaired *t* test ($P < .05$).
†Measured on SDAY 1 and SDAY 14 or at study exit, if this occurred earlier.

Table III. Laboratory results at SDAY 1 and SDAY 14

	SDAY 1		SDAY 14*	
	Control group	Lactase group	Control group	Lactase group
Serum albumin (g/L)	27.9 ± 0.6	29.3 ± 0.6	27.1 ± 0.4	29.3 ± 0.6†
Serum total protein (g/L)	50.3 ± 0.9	51.5 ± 0.9	47.9 ± 0.6	49.8 ± 0.8
Serum sodium (mmol/L)	139.3 ± 0.5	139.2 ± 0.5	136.0 ± 0.4	136.2 ± 0.5
Serum potassium (mmol/L)	5.2 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1

Values are mean ± SEM.
*Or at study exit, if this occurred earlier.
†Denotes statistically significant difference between the two groups by use of unpaired *t* test ($P < .01$).

DISCUSSION

This study examined whether preterm infants show improved feeding tolerance and weight gain on lactase-treated feeds. Undigested lactose can contribute to feeding intolerance, which frequently results in withholding of feeds[10] and can negatively affect weight gain. The trend toward a greater rate of weight gain in the lactase group reached significance on SDAY 10. The difference in rate of weight gain was no longer significant at study exit. In this study, lactase treatment was only started once enteral feeds provided ≥75% daily intake, at several days or weeks of age. Since the safety of this treatment has now been established, lactase-treated priming feeds could be provided earlier to the very immature gut.

The difference in weight gain may be attributed to improved carbohydrate and overall nutrient absorption, as it is possible that avoidance of lactose malabsorption prevents the cycle of diarrhea and malabsorption. SDAY 10 occurred at an average gestational age of 33 weeks, when lactase activity can still be as low as 30% of that found in term infants.[1,2] The lactase group may have had expedited weight gain at this stage as a result of improved lactose absorption. The similarity in the rate of weight gain at study exit, which averaged 35 weeks' gestational age, probably reflects increased functional lactase activity in all infants. It is possible that intestinal exposure to lactose caused induction of lactase activity, thus diminishing differences in rate of weight gain over time.

Weight gain difference can result from variations in caloric intakes. Differences in nutrient and ingredient composition between feeds can also affect growth.[11] None of these variables were significantly different between the study groups. Although infants in both groups were fed fortified human milk or premature formula or a mixture of both, the numbers in each feed-type subgroup were similar (Table I). Meetze et al[12] identified a concern with a study design in which infants receive 3 types of feeds in 2 groups, creating 6 different feeding regimens, but feed types are combined for comparison between the groups. A large trial, analyzed by feed type, could address this concern.

In designing this study, we hypothesized that lactase treatment should have the greatest impact on the youngest

preterm infants; one study supports this hypothesis.[13] Others found that the infant's maturational state did not affect lactose absorption, even though lactase activity increases 5-fold during the third trimester.[14]

Infants in this study were stratified by gestational age (26-30 weeks and 31-34 weeks) before random assignment to treatment or control groups. The study size was not sufficiently large to allow for a weight gain analysis by gestational age subgroups, but there was a similar distribution of infants in each group. In the lactase and control groups, 17 and 20 were in the 26- to 30-week subgroup and 49 and 44 were in the 31- to 34-week subgroup. This similarity was important to avoid bias of results due to disproportionate representation of less mature infants in one group because they may have more feeding intolerance.[13]

Studies have found that preterm infants fed a reduced lactose formula had a better rate of weight gain than those receiving 100% lactose formula. In two of these studies, weight gain was improved despite consumption of fewer calories.[15,16] In the third study, however, the low lactose formula group had higher caloric intake.[13] Our study results show a greater rate of weight gain in the lactase-treated group, with no difference in caloric intakes. We believe this reflects improved absorption facilitated by the effect of added lactase.

On SDAY 1 and SDAY 14, the serum albumin concentrations of both groups remained within a reference range for well-fed premature infants.[17] Although the lactose group had a significantly higher serum albumin concentration on SDAY 14, this may not be clincially important. Since the distribution of the type and amount of feed was similar between the two groups, the serum albumin concentration difference cannot be attributed to a difference in protein intake. The lactase group's greater rate of weight gain and higher serum albumin concentration may be indicative of improved nutritional status.

Lactose has been shown to promote calcium absorption.[3,18,19] The beneficial role of lactose in calcium absorption may therefore be retained or even enhanced in the presence of lactase.

A limitation of this study design could be the decision to leave feeds at room temperature for 2 hours before refrigerating and using within 24 hours, based on the in vitro work of Carlson et al.[6] We also considered the guidelines of the American Academy of Pediatrics for storage of human milk[20] and those of the American Dietetic Association for open liquid formula.[21] We did not test the study feeds for bacterial colonization, which could have a negative impact on feeding tolerance and should be considered.

One case of NEC occurred in the control group. It has been hypothesized that low-lactose formula could decrease the incidence of NEC in preterm infants or play a preventative role in the development of NEC.[13,22] Colonic bacterial fermentation of undigested carbohydrates, including lactose, may be beneficial in older children and adults. However, this effect in preterm infants is controversial. Undigested carbohydrates in the lower intestinal tract of preterm infants can lead to gas and organic acid production by bacterial fermentation. Gaseous distention may predispose to localized ischemia. In addition, accumulation of organic acids lowers the intraluminal pH and is one of the main factors in the induction of late-onset, feeding-associated NEC.[23]

Our observations suggest that a multicenter trial with a large number of infants would provide adequate power to determine the effect of lactase-treated feeds on growth, feeding tolerance, and incidence of NEC. The large subject numbers would facilitate analysis by gestational age and by type of feed. The study should commence at initiation of enteral feeding, when functional lactase activity level is lowest.

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50 Years Ago in The Journal of Pediatrics

ACUTE GANGRENOUS APPENDICITIS IN A PREMATURE INFANT

Meyer JF. J Pediatr 1952;41:343-5

Lieutenant Meyer reports from the Naval Hospital in Key West, Florida the case of a prematurely born neonate who died at 9 days of age after a rapidly progressive course of illness, and who was found at autopsy to have gangrenous appendicitis. This was, and still is, a rare event in the neonate and young infant, probably because of the relatively wide mouth of the appendix at the cecum. Associated conditions, such as Hirschprung's disease, should be suspected and sought; the appendiceal problem could also be part of necrotizing enterocolitis or a more generalized infection. The concurrent finding of a constricted descending colon, sigmoid, and rectum in this infant, as well as the presence of a circumferential perianal ulceration with a black margin, suggest that one or more associated conditions were indeed present.

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