0021-7557/06/82-05/335
Jornal de Pediatria

doi:10.2223/JPED.1504

ORIGINAL ARTICLE

Fractional sodium excretion, urinary osmolality and specific gravity in preterm infants fed with fortified donor human milk

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Abstract

Objective: This research was performed with the objective of investigating the renal effects on premature newborn infants of fortifying banked donor human milk.

Methods: Clinical intervention trial, of the before-and-after type, involving 28 premature newborn infants split into two groups by postconceptional age at the start of the study: GI < 34 weeks (n = 14) and GII ≥ 34 weeks (n = 14), and assessed at three sample points: S1, on unfortified donor human milk, S2, after 3 days, and S3, after 10-13 days on fortified donor human milk. Nutrient intake, weight gain, fractional sodium excretion, urinary osmolality and specific density were compared with two-way ANOVA for repeated measures.

Results: Fluids, energy and sodium intakes were similar for both groups, and weight gain was satisfactory. Among the preterms with < 34 weeks postconceptional age, serum sodium was lower at the end of the study and the fractional sodium excretion was elevated at the start and at the end of the study (S1 = 2.11±1.05; S2 = 1.25±0.64; S3 = 1.62±0.88), with a significant difference in relation to GII (S1 = 1.34±0.94; S2 = 0.90±0.54; S3 = 0.91±0.82). Osmolality and urinary specific density were normal, with no differences between groups or collection dates.

Conclusions: No adverse effects on the renal function of these preterms were detected as a result of being fed fortified donor human milk.

J Pediatr (Rio J). 2006;82(5):335-40: Human milk, nutritional supplementation, renal function, preterm infants.

Introduction

The optimization of nutrition early in life is one of the greatest challenges for neonatologists, with respect to both short term and long term benefits, but the ideal nutritional management regime for small preterms remains a subject of debate.[1] While the use of breastmilk fortified with supplements is a well-established practice in the nutritional management of very low birth weight infants,[2-4] existing studies into the composition of supplements, the point at which fortification is begun and at which it is withdrawn, the method by which the milk is fortified and the potential adverse effects of fortifying human milk, in particular on the renal function of premature infants, are too scarce to confirm the ideal use of fortified breastmilk.[5,6]

Concerns with the potential adverse effects of diet on the renal function of preterms is justified, since the point of renal maturity is at around 34 weeks' gestational age, and it is premature infants younger than this who require fortified breastmilk. The renal function of premature infants is faced by a variety of limitations, the most significant of which are: glomerular tubular balance dysfunction, characterized by a low glomerular filtration rate and an even more accentuated reduction in tubular reabsorption capacity, elevated fractional sodium excretion (FENa) and limited urinary concentration capacity.[7,8]

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Manuscript received Nov 24 2005, accepted for publication Apr 26 2006.

Suggested citation: Tanaka A, Rugolo LM, Miranda AF, Trindade CE. Fractional sodium excretion, urinary osmolality and specific gravity in preterm infants fed with fortified donor human milk. J Pediatr (Rio J). 2006;82:335-40.

Considering that several aspects of the efficacy and safety of fortifying human milk for premature infants have not been entirely elucidated, in addition to the scarcity of studies into the effects of the diet on the renal function of these newborn infants, the objective of this study was to investigate the renal effects of fortifying donor human milk, comparing FENa, urinary osmolality and specific density in premature infants and in infants with 34 weeks or more postconceptional age (PCA).

Patients and methods

This was an intervention study, in the form of an uncontrolled clinical trial, in which patients are assessed before and after an intervention.

Sample size was calculated using Sigma Stat statistical software, and was projected to detect a 20% difference in FENa between the two study groups, based on reference FENa levels for premature infants with 30-34 weeks' gestational age.[8] Accepting an α error of 5% and ß of 10%, an estimation of 13 premature infants in each group was made.

The study was undertaken at the Intermediate Care Unit at the Hospital de Clínicas, Marília Medical Faculty during 2003, after approval from the Research Ethics Committee of that institution.

After obtaining maternal consent, newborn premature infants with gestational ages of less than 34 weeks, exclusively fed on banked donor human milk, were selected when they reached an intake of at least 100 mL/kg/day via orogastric tube. Inclusion criteria were: singleton, inborn infants, absence of malformations and congenital infections, with 5th minute Apgar scores over 5 and not requiring fluid and electrolyte infusions after the first week of life. Preterms were excluded if they exhibited sepsis, respiratory disturbances requiring mechanical ventilation, had been given vasoactive drugs, aminoglycosides, diuretics, indomethacin or xanthines, had surgical pathologies, if there was any barrier to performing all of the tests on the study protocol or if they had been regularly breastfed.

Gestational age was determined by maternal menstrual date or score by the New Ballard if the menstrual date was uncertain.[9] For the purpose of this study, the postconceptual age (PCA), i.e., gestational age plus postnatal age (in weeks) was considered.

Enteral feeding was started during the first days of life, as soon as preterms exhibited hemodynamic stability. Only preterms weighing 1,000 g or less were fed parenterally during the first week of life. Newborn infants were fed exclusively on banked donor human milk, via intermittent gavage every 2 hours, and the volume of milk was increased gradually, according to medical criteria, dependent on patient tolerance.

Routine procedure at the service is to add commercial supplement when the intake of human milk reached 100 mL/kg/day. Supplementation is with FM85® (Nestlé) at 5 g per 100 mL of breastmilk, providing an additional supply of 1 g of protein, 3.4 g of carbohydrates, 20 mg of sodium, 75 mg of calcium and 45 mg of phosphorous, according to the manufacturer. In order to calculate the level of sodium intake, an assumption was made of an average of 15 mg/dL of sodium in banked donor human milk[10] summed to that provided by FM 85®. Therefore, the estimated total sodium content of 100 mL of fortified breastmilk was 35 mg.

Blood samples and urine were collected on three different days: S1, immediately before starting fortification; S2, after 3 days on fortified human milk; S3, after 10-13 days on fortified breastmilk. The transition to oral route and initiation of breastfeeding was done after the third collection.

At each sample point, blood and urine samples were assayed for sodium by the ion-selective electrode method, and for creatinine by the alkaline picrate method. These test results were used to calculate FENa. Urinary specific gravity was measured by refractometer and urinary osmolality by the freezing point depression. Urinary sample volumes were those forthcoming from a single micturition.

In order to assess the influence of fortification on FENa, urinary specific gravity and osmolality, we defined 34 weeks PCA as a marker of renal maturity.[7,8,11] Therefore, the preterms were split into two groups: GI – preterms < 34 weeks PCA and GII – preterms ≥ 34 weeks PCA.

Descriptive statistics were calculated, with results expressed in means with standard deviation, medians with percentiles and minimum and maximum values.

Two-way ANOVA for repeated measures was used to compare the results for the two groups at the three assessment points, using Sigma Stat 3.01. Significance was set at 5%.

Results

Thirty premature newborn infants were enrolled, but two were excluded because they initiated breastfeeding before the third sample point.

Fourteen of the 28 preterms began the study (S1) with PCA greater than or equal to 34 weeks while 14 of them did not reach this marker of renal maturity (34 weeks) during the study.

Mean gestational age and birth weight were lower in GI than GII (31±0.7 vs. 33±0.4 weeks; $p < 0.001$ and 1354±241 g vs. 1610±202 g; $p = 0.005$). There was a predominance of weight appropriate for gestational age in GI (65%) when compared with GII (35%), but without statistical significance ($p = 0.053$). Antenatal steroids

were given frequently to both groups (GI = 64% and GII = 57%; p = 0.699).

The study began at the end of the first week and had a mean duration of 11 days for both groups.

Mean milk intake volumes and estimated amounts of sodium and energy in the diet fed the two groups are listed in Table 1. None of the newborns presented signs of feeding intolerance or any other intercurrent condition during the study.

Mean daily weight gain did not differ between groups or across sample points. The GI newborns gained an average of 15 g/day between S1 and S2 and those in GII increased 20.5 g/day (p = 0.193). Mean weight gain between S2 and S3 was 23 g/day in GI and 24 g/day in GII (p = 0.867). Both groups exhibited significant weight gain from S1 (1230±220 g in GI vs. 1514±203 g in GII) to S3 (1445±278 g in GI vs. 1763±240 g in GII). At all three sample points the GI preterms had lower mean weight than the GII infants.

Serum sodium levels (mEq/L) for the < 34 weeks PCA preterms (GI) were significantly lower at the end than at the start of the study (S3 < S1), whereas, in GII, there were no significant differences across the three sample points. When the two groups were compared, levels in GI were lower than those in GII at all sample points with statistical significance at S2 and S3 (Table 2).

Table 3 contains FENa results, showing that in the < 34 weeks PCA preterms (GI) the highest levels were at S1, whereas in GII, there was no significant difference between the three sample points. Comparing the two groups reveals significant differences at all three sample points: GI > GII.

Urinary specific density remained normal and stable throughout the study with no differences between groups (p = 0.311) or sample points (p = 0.901). For GI, mean gravity was 1,004 for all the three sample points; in GII it was 1,005 at S1 and 1,006 at the other two points. Urinary osmolality levels did not differ between the two groups (p = 0.946) nor across different sample points (p = 0.077), as can be observed in Figure 1.

Discussion

There is no question that it is preferable to give premature infants their own mother's milk than to feed them on banked human milk, since the latter, particularly if it is pooled milk from donors who have carried to term, is nutritionally inadequate for premature infants.[2,12-14] However, the longer that infants stay in hospital the greater the obstacles preventing mothers from participating in the daily care of their children. In these situations the nutritional option for preterms, in this study, was banked donor human milk. This results in a limitation to the quality of their diet, but provides the methodological advantage of relative stability in terms of the composition of the milk ingested, which would not be possible with infants' own mothers' milk which changes as lactation progresses.[2,13]

Table 1 - Mean milk intake volumes (mL/kg/day) and estimated quantities of sodium (mEq/kg/day) and energy (kcal/kg/day) for the two groups of preterms at the three assessment points

Sample point/Diet	GI, n = 14	GII, n = 14	ANOVA for repeated measures GI vs. GII p
S1 - DHM			
Volume (mL/kg/day) mean ± SD	138±11 *	140±15 *	0.665
Sodium (mEq/kg/day) mean ± SD	0.90±0.07 *	0.91±0.10 *	0.697
Energy (kcal/kg/day) mean ± SD	92±7 *	94±10 *	0.716
S2 - Fortified DHM			
Volume (mL/kg/day) mean ± SD	179±10 †	183±9	0.278
Sodium (mEq/kg/day) mean ± SD	2.72±0.15 †	2.78±0.13	0.255
Energy (kcal/kg/day) mean ± SD	152±8.5 †	156±7.7	0.541
S3 - Fortified DHM			
Volume (mL/kg/day) mean ± SD	186±5	188±5	0.653
Sodium (mEq/kg/day) mean ± SD	2.84±0.09	2.86±0.07	0.504
Energy (kcal/kg/day) mean ± SD	158±4	160±4	0.424

DHM = donated human milk; SD = standard deviation.
Comparison between sample points, ANOVA for repeated measures: * GI and GII, S1 < S2 < S3, p < 0.001; † GI, S2 < S3, p < 0.05; GII, S2 vs. S3, not significant.

Table 2 - Serum sodium (mEq/L) for both groups of preterms and all three sample points (mean ± SD, minimum and maximum)

Sample point/Diet	GI, n = 14	GII, n = 14	ANOVA for repeated measures GI vs. GII
S1 - DHM			p = 0.059
Mean ± SD	136±3.2 *	138±3.4	
Minimum-maximum	131-144	132-144	
S2 - Fortified DHM			p = 0.013
Mean ± SD	134±3.7	138±6.3	
Minimum-maximum	129-142	129-155	
S3 - Fortified DHM			p < 0.001
Mean ± SD	133±3.5	137±3.0	
Minimum-maximum	128-143	132-143	

DHM = donated human milk; SD = standard deviation.
Comparison between sample points, ANOVA for repeated measures: * GI, S1 > S3, p = 0.003; GII, S1 vs. S2 vs. S3, not significant.

Table 3 - Fractional sodium excretion (%)for both two groups of preterms and all three sample points (mean ± SD, minimum and maximum)

Sample point/Diet	GI, n = 14	GII, n = 14	ANOVA for repeated measures GI vs. GII
S1 - DHM			
Mean ± SD	2.11±1.05 *	1.34±0.94	p = 0.016
Minimum-maximum	0.81-4.72	0.42-4.30	
S2 - Fortified DHM			
Mean ± SD	1.25±0.64	0.90±0.54	p = 0.337
Minimum-maximum	0.42-2.47	0.26-1.91	
S3 - Fortified DHM			
Mean ± SD	1.62±0.88	0.91±0.82	p = 0.026
Minimum-maximum	0.67-3.29	0.07-2.77	

DHM = donated human milk; SD = standard deviation.
Comparison between sample points, ANOVA for repeated measures: * GI, S1 > S2, p = 0.009; GII, S1 vs. S2 vs. S3, not significant.

Current recommendations are for the aggressive nutritional support of preterms, with early initiation of enteral feeding and limited use of parenteral nutrition,[15] which was confirmed in this patient sample, who, at the end of the first week were receiving an average of 140 mL/kg/day enterally. Weight gain was satisfactory, but below what has been reported in other studies into nutritional strategies for preterms, primarily when fed with their own mothers' milk or preterm formula,[14] which may be a result of methodological differences, including age at start and duration of the studies and type of milk and supplements.[12,14,16-19]

Several different studies of the use of fortified human milk have evaluated biochemical parameters and shown them to be normal. Nevertheless, the parameters evaluated are basically restricted to calcium, phosphorous, alkaline phosphatase and urea. Rarely is serum sodium evaluated. In a study of the use of supplements obtained from human milk protein or bovine serum, starting fortification at the end of the third week of life and maintained for 20 to 40

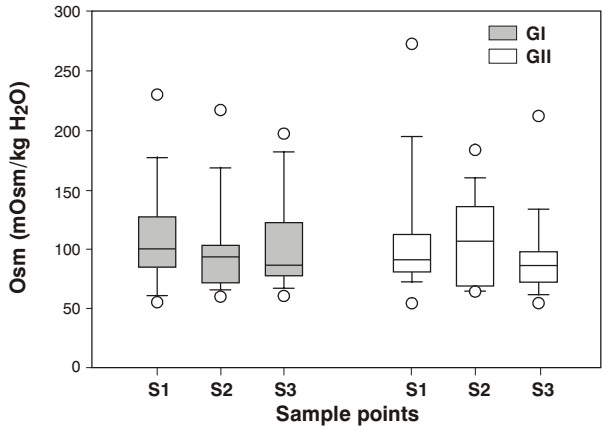

Figure 1 - Box plot of urinary osmolality levels (mOsm/kg H_2O) for both groups of preterms and all three sample points

days, normal serum sodium values were recorded at the end of the study: 138±2 and 136±3 mEq/L for human and bovine supplements, respectively.[12]

In the present study, serum sodium values in premature infants with less than 34 weeks' PCA were in decline and were relatively low, despite the estimated supply being adequate according to the recommendation of 2.5-4 mEq/kg/day for stable, growing preterm infants.[2,20] This suggests that there are elevated renal losses, which is a peculiarity of these preterms,[8,21,22] and leads us to question the adequacy of sodium supplementation of donor human milk, and also the biological significance of this biochemical finding. These aspects merit further investigation in future studies.

According to Al-Dahhan et al., glomerular-tubular immaturity results in a high sodium requirement, during the first 15 days of life of preterms at 30-35 weeks' gestational age, of at lease 4 mEq/kg/day.[23]

The FENa results for these preterms with less than 34 weeks' PCA corroborate the explanation ventured for lower serum sodium levels in this group, since their FENa levels were higher than those in the GII preterm group. Interestingly, in the under 34 weeks' PCA group, FENa reduced from S1 to S2, but remained unchanged between the second and third sample points, while it had been expected that it would continue to drop as a result of renal maturation as postnatal age increased, as documented by Delgado et al.,[24] who demonstrated a 1.2% reduction per week in FENa among premature infants under 30 weeks and a 0.4% reduction among those 30-31 weeks of gestational age. Nevertheless, in that study preterms were given parenteral nutrition and there was no reference to the type of diet, which could have contributed to the divergence from our results.

The ability of the preterm neonatal kidney to manipulate different levels of sodium supply has been little studied. Costarino et al. documented a positive sodium balance in very low birth weight preterms, with an intake of 3-4 mEq/kg/day.[25] In preterms under 30 weeks, they found that early sodium intake delayed physiological weight losses, but the sodium balance remained negative and FENa did not differ from that of preterms given supplementation later.[26]

There is great concern with sodium homeostasis in premature infants, since insufficient supply can compromise postnatal growth and excessive supply can affect body composition, promoting expansion of extracellular liquid volume.[26] Furthermore, the limited tubular capacity to retain sodium can facilitate renal calcium losses, making hypercalciuria more likely.[27]

Urine osmolality is the result of the renal solute load, which includes electrolytes and the final products of protein metabolism.[28] Fortification of breastmilk increases the osmolality of the milk by around 50%, consequently increasing the potential solute load on the kidneys. Supplementation discretely increase the supply of chloride and potassium, but the quantity of protein doubles and sodium and phosphorous are increased by around three times.[18] The hypothesis of this study, which was not confirmed, was therefore that urinary osmolality would increase with fortified human milk.

Urinary osmolality did not differ between the two groups of preterms and remained stable across all three sample points, which corroborates results published by Ziegler & Ryu,[28] who found that the actual renal solute load is lower than the potential load, since approximately half of what is provided by the diet is incorporated into new tissues. In the present study, the preterms were going through a weight gain phase, and so incorporation of protein into new tissues will have contributed to reducing the renal solute load and maintain urinary osmolality normal. Nevertheless, there are certain limitations to this study that need to be considered, since we did not perform any biochemical evaluation of the human milk used, nor of the preterms to document their growth, and urinary assays were made from isolated samples.

Urinary specific density is not referred to in studies that have evaluated the effects of diet on the renal function of preterms. It has a similar meaning to urinary osmolality, since it expresses the weight of solutes present in the urine. Thus, in this study it was not altered as a result of diet and remained within normal limits in both study groups.

Finally, this study may contribute to our daily practice, providing information on the use of fortified banked human milk. No undesirable effects of renal function were observed, which increases security when prescribing this

type of diet. Nevertheless, the decreasing levels of serum sodium in preterms below 34 weeks' PCA, despite supplements, are an alert to the need for monitoring of this biochemical parameter and for further studies to better investigate these observations.

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