Effect of Fortification on the Osmolality of Human Milk

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Background: *Human milk is nutritionally better than formula milk for preterm infants. However, unfortified human milk may fail to meet the theoretical requirements of very low birth weight (VLBW). Human milk fortifier (HMF) increases the nutritional content of human milk. However, the important factor of concern in feeding VLBW is the osmolality, the higher the osmolality, the greater the risk of necrotizing entero colitis (NEC). Therefore, high osmolality in fortified human milk should be considered for this condition.*
Objective: *To evaluate the effect of fortification on the osmolality of human milk*
Material and Method: *Twenty samples of human milk were collected from mothers of gestational age less than 32 weeks, at about 1 week postpartum in Songklanagarind Hospital. The osmolality of each sample was determined at baseline and after supplementation with HMF at 10 minutes, 1, 2, 4, and 6 hours at room temperature and 24 hours at 4°C in a refrigerator.*
Results: *The mean osmolalities (SD) of human milk and HMF dissolved in sterile water were 285.3 (3.3) mOsm/kg H_2O and 64.6 (0.7) mOsm/kg H_2O, respectively. Thus, the expected osmolality of human milk after supplementation with HMF was 349 mOsm/kg H_2O. Mean measured osmolalities (SD) of human milk after supplementation with HMF at 10 minutes, and 1, 2, 4, 6 and 24 hours was 394.7(2.9), 399.5(2.8), 402.1(2.2), 401.0(2.7), 401.3(2.3) and 401.2(3.1) mOsm/kg H_2O, respectively. The mean osmolality at 10 minutes, 1, 2, 4, 6 and 24 hours were significantly higher than human milk ($p < 0.001$) and the mean osmolality at 10 minutes was significantly higher than expected osmolality ($p < 0.001$). There were no significant differences among groups of osmolality after supplementation with HMF at 10 minutes, 1, 2, 4, 6, and 24 hours ($p > 0.05$)*
Conclusion: *The supplementation of human milk with HMF induced an increase in osmolality after mixing. The osmolality, after mixing with HMF which was about 400 mOsm/kg H_2O, creates a greater risk of NEC. Therefore, HMF milk should be considered for feeding in only high risk preterm neonates.*

Keywords: *Human milk fortifier, Osmolality, Breast milk*

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Human milk is nutritionally better than formula milk and more suitable for the preterm infant. It affords increased benefits in nutrition, neurodevelopment, host defense, gastrointestinal function, and psycho-social well-being, compared with formula. However, in the absence of fortification, human milk alone does not match intrauterine rates of growth in preterm infants due primarily to poorer nutrient retention, particularly among infants weighing less than 1,500 g[1].

Specifically, unsupplemented human milk alone provides an insufficient quantity of protein to support the growth and lean body mass accretion of smaller preterm infants. Fortification or supplementation of human milk with energy and protein improves both rate of weight gain and indices of protein status[2]. Moreover, preterm infants are born with low skeletal stores of calcium and phosphate, and require large amounts of these minerals in order to attain adequate postnatal skeletal growth. Poor radiological bone mineralization, rickets and fractures have been described in premature infants receiving inadequate dietary intakes of calcium and phosphate as supplied by human milk alone. Human milk fortifiers (HMF) are available for the supplementation of human milk, which provide additional nutrients in the form of protein, calcium,

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phosphate and carbohydrate, as well as vitamins and trace minerals. Supplementation of HMF is associated with increased weight gain, linear and head growth[3]. Until recently there was only one powdered HMF available in the market in Thailand, S-26/SMA HMF. One specific area of concern with this commercial powdered HMF has been its osmolality when mixed with human milk. However, the energy in HMF is primarily provided by dextrins, which, acted on by human milk amylase, could be transformed into glucose with a consequent increase in osmolality[5]. An association between hyperosmolar preparations (higher than 400 mOsm/kg H_2O) and necrotizing enterocolitis has been reported[6]. Jocson et al[4] supplemented human milk with a HMF for 72 hours, which increased osmolation by about 4%. Curtis et al[5] found that human milk and HMF interacted to induce a rapid increase in osmolality after 10 minutes and after 24 hours at 4°C. Some very low birth weight (VLBW) infants need tube feeding by continuous gavage, hence the human milk- HMF mixture is left in room air for 4 hours. There was no data to show the osmolality of milk at this time. The authors performed a prospective experiment to evaluate the change in the osmolality of human milk after supplementation with S-26/SMA HMF at 10 minutes, and 1, 2, 4, and 6 hours at room air and 24 hours at 4°C in a refrigerator.

Material and Method

The present study was performed in the postpartum ward at Songklanagarind Hospital, Thailand between June and October 2001. A single sample of manually-expressed fresh breast milk from mothers of VLBW infants who had given their consent was sterilely collected. Osmolality was determined in triplicate using a Gonotech Osmometer® (Intertrade Ltd. USA) based on freezing point depression, before mixing the expressed breast milk with S-26/SMA HMF with a ratio of breast milk 50 ml to HMF 2 g (1 pack). The fortified human milk was divided into 2 parts. One was refrigerated at 4°C for 24 hours to measure osmolality. The other was kept in room air to measure the osmolality at 10 minutes, and 1, 2, 4 and 6 hours after fortification. The osmolality of HMF dissolved in water at the same concentrations as above was also determined.

Statistical analysis

Sample size was calculated by the equation

$N = (Z^2a/_2 . SD)d^2$

$Za/_2$ is a standard score at a 0.05

SD^2 is a variance of a previous study, calculated from a pilot study, where $SD^2 = 4$, and d was defined as acceptable error equal to 2. From the equation above the total minimum sample size required was 15.

Data were analyzed as mean (SD). ANOVA with repeated measurement was analyzed by STATA software version 7 was used to compare osmolality of human milk alone and the osmolality of fortified human milk at 10 minutes, 1, 2, 4, 6 and 24 hours. Student's paired-t-test was used to compare the osmolality of fortified human milk at 10 minutes and the theoretical values of osmolality of fortified human milk. A p value of < 0.05 was taken as the level of significance. The present study was approved by the Ethics Committee Board of Prince of Songkla University, and written informed consent was obtained from the mothers before the study began.

Results

Twenty samples of milk from mothers of VLBW infants were obtained. The mean age of the mothers was 31.7 years. The mean gestational age of the infants was 30 weeks (range 28-32 weeks). The mean birth weight was 1,078 g (range 720-1,390 g.). The mean postpartum age of the infants was 6 days (range 5-7 days). The mean $\pm$ SD osmolality of the human milk was 285.3 $\pm$ 3.3 mOsm/kg H_2O. The osmo-lality of the HMF dissolved in water was 64.6 mOsm/kg H_2O. By adding the values obtained before mixing, the authors were able to calculate the theoretical values of the osmolality of human milk and HMF to be 285.3 + 64.6 = 349.9 mOsm/kg H_2O. The means, maximums, and minimal osmolalities of human milk after fortification at 10 minutes, and 1, 2, 4, and 6 hours at room temperature and after 24 hours at 4°C are shown in Table 1.

The mean osmolality of the fortified human milk at 10 minutes, 1, 2, 4, 6 and 24 hours was statistically significantly higher than the mean osmolality of

Table 1. Changes of osmolality (mOsm/ kgH_2O.) of human milk after supplementation with HMF at various times (n = 20)

Time	Maximum	Minimum	Mean (SD)
Breast milk	291	280	285.3 (3.3)
10 minutes	399	390	394.7 (2.9)
1 hour	405	394	399.5 (2.8)
2 hours	405	399	402.1 (2.2)
4 hours	405	395	401.0 (2.7)
6 hours	405	395	401.3 (2.3)
24 hours	405	395	401.2 (3.1)

human milk alone ($p < 0.001$) and the mean osmolality of fortified human milk at 10 minutes was significantly higher than the expected osmolality of fortified human milk ($p < 0.001$). Compared to the mean osmolality of fortified human milk at 10 minutes, 1, 2, 4, and 6 hours with 24 hours, no statistical significance was found ($p > 0.05$).

Discussion

The use of HMF for human milk-fed premature infants has increased in neonatal centers. Previous studies of human milk fortification in preterm babies have demonstrated beneficial increases in weight gain, and calcium and phosphorus retention. The present study has added to the knowledge by showing that after fortification, the human milk-HMF mixture induces a rapid and clinically significant increase in osmolality within 10 minutes. After 1 to 6 hours at room temperature and 24 hours at 4°C, the osmolality of human milk after fortification did not change significantly. The amylase activity of human milk is an alpha amylase that hydrolyses starch and dextrins and is resistant to heat. About 95-100% of the initial activity was present after 24 hours of storage at 15-25°C[7]. Therefore, the fortification of human milk may lead to oligosaccharide production, depending on the carbohydrate composition of the HMF. Thus, the rise of osmolality observed in human milk supplemented with HMF can be explained by the fact that polysaccharides, present in the HMF, are broken down into their constituent mono and disaccharides.

To concern about osmolality of human milk after mixing with HMF, the new product of HMF would reduce the osmolality of the fortifier and further reduce an increase in osmolality produced by hydrolysis of the carbohydrate fraction of the powdered HMF by human milk amylase[2].A reduction in osmolality may improve the feeding tolerance of enteral products[8].

Conclusion

The use of human milk fortifiers increases osmolality more than would be expected from composition alone. The osmolality of fortified human milk after 1 to 6 hours at room temperature and 24 hours at 4°C did not change significantly, suggesting it is safe to feed infants with fortified human milk up to 24 hours after mixing. However, the relatively high osmolality of fortified human milk should be noted for side effects.

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ค่าออสโมลาลิตี้ของนมแม่หลังการผสมด้วย human milk fortifier

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ที่มา: *นมแม่เป็นอาหารที่ดีที่สุดสำหรับทารกแรกเกิด ในทารกเกิดก่อนกำหนดน้ำหนักน้อยมากนมแม่อย่างเดียว อาจไม่เพียงพอสำหรับการเจริญเติบโต human milk fortifier (HMF) จึงมีบทบาทในการเติมเต็มสารอาหารที่ไม่ครบส่วน แต่ปัจจัยเสี่ยงที่ต้องพิจารณาคือ ค่าออสโมลาลิตี้ของนมเนื่องจากค่าที่สูงเป็นปัจจัยเสี่ยงประการหนึ่งของการติดเชื้อในลำไส้ของทารก*

วัตถุประสงค์: *เพื่อศึกษาผลการเปลี่ยนแปลงของค่าออสโมลาลิตี้ของนมแม่หลังการผสมด้วย HMF ในน้ำนมแม่ ณ เวลาต่าง ๆ*

วัสดุและวิธีการ: *เก็บน้ำนมแม่ที่อายุครรภ์น้อยกว่า 32 สัปดาห์หรือน้ำหนักแรกเกิดน้อยกว่า 1,500 กรัมในโรงพยาบาลสงขลานครินทร์ หลังคลอดบุตร 1 สัปดาห์ และทำการวัดค่าออสโมลาลิตี้ของนมแม่เป็นพื้นฐาน และวัดหลังจากผสม HMF ที่ 10 นาที, 1, 2, 4 และ 6 ชั่วโมง ณ อุณหภูมิห้องตามลำดับและ 24 ชั่วโมง ณ อุณหภูมิ 4 องศาเซลเซียสในตู้เย็น*

ผลการศึกษา: *ค่าเฉลี่ยของออสโมลาลิตี้ (SD) ของนมแม่มีค่าเท่ากับ 285.3 (3.3) มิลลิออสโมลต่อกิโลกรัมน้ำ ค่าเฉลี่ยของออสโมลาลิตี้ของ HMF กับน้ำบริสุทธิ์มีค่าเท่ากับ 64.6 (0.7) มิลลิออสโมลต่อกิโลกรัมน้ำ โดยค่าออสโมลาลิตี้ที่คาดหวัง (expected osmolality) มีค่าเท่ากับ 349.0 มิลลิออสโมลต่อกิโลกรัมน้ำ*

ค่าเฉลี่ยของออสโมลาลิตี้ (SD) ของนมแม่หลังจากผสม HMF ที่ 10 นาที, 1, 2, 4, 6 และ 24 ชั่วโมง มีค่า 394.7 (2.9), 399.5 (2.8), 402.1 (2.2), 401.0 (2.7), 401.3 (2.3), 401.2 (3.1) มิลลิออสโมลต่อกิโลกรัมน้ำตามลำดับ ซึ่งสูงกว่านมแม่อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) และค่าเฉลี่ยของออสโมลาลิตี้ของนมแม่ที่ 10 นาที มีค่าสูงกว่า ค่าออสโมลาลิตี้ที่คาดหวัง (expected osmolality) อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) เมื่อเปรียบเทียบค่าออสโมลาลิตี้ที่ตั้งไว้หลังผสม ณ เวลา 10 นาที, 1, 2, 4, 6 ชั่วโมงกับระยะเวลาที่ 24 ชั่วโมง พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p > 0.05$)

สรุป: *การผสม HMF ในนมแม่ของทารกเกิดก่อนกำหนดจะเพิ่มค่าออสโมลาลิตี้ได้สูงกว่าค่าออสโมลาลิตี้ที่คาดหวังอย่างมีนัยสำคัญทางสถิติ และค่าออสโมลาลิตี้มีค่าประมาณ 400 มิลลิออสโมลต่อกิโลกรัมน้ำ ควรตะหนักถึงปัจจัยเสี่ยงของการเกิดภาวะติดเชื้อในลำไส้ก่อนที่จะใช้เลี้ยงทารก*