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Preterm Infants May Better Tolerate Feeds at Temperatures Closer to Freshly Expressed Breast Milk: A Randomized Controlled Trial

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Abstract

Purpose: Feeding intolerance is one of the most frequent problems among preterm infants. These infants are fed with expressed breast milk or preterm formulas of which the temperature is not routinely measured. In this study, we aimed to examine the effects of feeds with warm milk versus room temperature milk in preterm infants.
Materials and Methods: Infants with a birth weight ≤1,500 g or gestational age ≤34 weeks were included in the study and assigned to two different feeding temperature groups (22–24°C and 32–34°C). Some infants in both groups were exclusively breast milk-fed, and some received breast milk and artificial milk (mixed feeding). Feeding tolerance of infants in both groups and the consequences were evaluated.
Results: In total, 80 preterm infants (group 1 fed with milk at 22–24°C, $n=40$; group 2 fed with milk at 32–34°C, $n=40$) were prospectively included in the study. There was a slight decrease in gastric residual frequency in infants fed with breast milk in group 2. Apnea was significantly more frequent in group 1 ($p=0.006$), and these infants needed more anti-reflux treatment ($p=0.013$).
Conclusion: According to our results, warming enteral feeds close to body temperature are encouraging especially due to the decrease in gastric residual frequency, apnea of prematurity, and need for anti-reflux treatment. More studies may confirm the positive effect of warm enteral feeds on feeding tolerance in preterm infants.

Keywords: prematurity, enteral nutrition, feeding tolerance, temperature

Introduction

Feeding intolerance is frequent among preterm infants in neonatal intensive care units (NICUs).[1] Although there are many studies about enteral nutrition strategies and content in preterm infants, no evidence-based standards exist for the optimal milk temperature for preterm infants.[2]

Preterm infants are fed with expressed breast milk or standard preterm formulas in NICUs. Preterm infants who have feeding intolerance have difficulty with the digestion of formula or breast milk. Factors that contribute to feeding intolerance include poor sucking and swallowing, small gastric capacity, delayed gastric emptying time, and intestinal hypomotility. Symptoms of feeding intolerance include the presence of gastric residuals, vomiting, abdominal distention, visible bowel loops, diarrhea, or bloody stool. Apnea, bradycardia, and temperature instability are also included as symptoms of feeding intolerance. Abnormal intestinal colonization, poor balance between microbiota, immune response, and tolerance mechanisms may result in feeding intolerance in early postnatal life and in gastrointestinal disease in childhood.[3–6]

While standard formulas are kept at room temperature, expressed breast milk is either refrigerated or frozen. The powder formulas are prepared with boiled water, or ready-to-feed glass containers are used in NICUs. Previously expressed breast milk is defrosted and warmed before each feeding. There is not a standard temperature for this process, and no detailed literature for the possible morbidities is available.[7,8] Therefore, in this study we aimed to examine the effects of feeding temperature and the possible morbidities.

Materials and Methods

This prospective, randomized controlled trial was approved by Ege University's Ethics Committee (October 3,

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2012, 12-8/4) and was registered at ClinicalTrials.gov under identifier NCT03743207. A total number of 80 preterm infants with a birth weight ≤1,500 g or gestational age ≤34 weeks who were hospitalized in the Ege University Children's Hospital NICU between October 2012 and April 2014 were prospectively included in the study. Infants with a genetic syndrome, gastrointestinal system anomalies, and those born small for their gestational age were excluded, whereas infants matching the study criteria with written consent from the families were included in the study.

The infants were randomly assigned using the last digit of their hospital identification number to two different groups based on different feeding temperatures. The infants in group 1 were fed with milk at 22–24°C, close to room temperature. For group 2 infants, we performed a preliminary study to ascertain a more physiological temperature for feeding. Fifteen of our NICU mothers volunteered and expressed their milk for rapid measurement of freshly expressed breast milk. The mean (±SD) temperature of freshly expressed breast milk was found to be 33 ± 1.5°C in these preliminary measurements. Confirming this finding, we decided to feed the infants in group 2 with milk at 32–34°C to examine the effects of feeding temperature and the possible comorbidities with a hypothesis that warmer feeding at the temperature of freshly expressed breast milk may be better physiologically. At this point, we supposed that the freshly expressed breast milk's temperature was a little lower (1–2°C) than the body temperature due to the breasts' localization just outside of the main body. All infants were hospitalized in Dräger® incubators (Dräger Medical, Lübeck, Germany) and received standard nursery care aside from the temperatures of their feeding. The nurse was not blinded to the study, but this did not affect the primary care of the infant. All infants were bolus-fed every 2 hours in the supine position via an 8Fr orogastric tube with a 20 mL standard syringe based on the assigned temperature from the beginning till discharge. The orogastric tube was properly placed and was confirmed by aspiration of the stomach content or by auscultation of 2 mL air injected through the tube over the stomach region. The infants were fed with either human milk or liquid preterm formula (Milupa®, Prematil, Germany) when human milk could not be obtained. No human milk fortifier or other special formula was used during the study. The enteral feeds were warmed to prescribed temperatures using a bottle warmer (Sümer bottle warmer; SM-ASB, Ankara, Turkey). After this procedure, the temperature was checked using a laser food thermometer (TROTEC Pyrometer BP20, Germany). The enteral feeding procedure lasted <5 minutes. The temperature of the milk/formula was recorded with a laser food thermometer during the whole feeding period and did not show any change. During the study, the room temperature was maintained between 25°C and 26°C, and no difference in body temperature was detected between the two groups. The body temperature was measured at 36–36.5°C for all babies. All infants were in the supine position during and after feeding.

Apnea is defined as the cessation of respiratory airflow for >20 seconds or for a period of ≥2 breaths accompanied by significant desaturation (<85%), hypoxemia, or bradycardia at <85 beats per minute.[9,10] A gastric residual volume was recorded before each feeding. Residuals greater than half of the volumes were considered significant. Residuals more than the physiological gastric fluid and less than one half of the feed were given back, and the remaining volume was added. The orogastric tube was clamped after every feeding unless the infant was on continuous positive airway pressure.

Primary and secondary outcomes

The primary outcome of this study was to determine physiological enteral feeding for premature infants by measuring the number of residuals and the residual volumes. The feeding temperatures, feeding volumes, daily weight gain, transition time to total enteral feeding, need for anti-reflux medical treatment, and body weight at discharge were recorded as the secondary outcomes of the study.

Statistical analysis

Data were analyzed with SPSS for Windows 19.0 software (IBM Corporation, Armonk, NY) using chi-square test and Mann–Whitney *U* test. Values are reported as mean and SD. *P*-values <0.05 were considered statistically significant. The sample size was calculated with a 95% confidence interval due to population size. In our data, with repeated measurements, considering $\alpha = 0.05$, power analysis was calculated as 83.3%, which is considered to be significant.

Results

The demographic characteristics of the two groups were similar ($p > 0.05$). The demographic data and other prematurity-related complications are summarized in Table 1. According to birth weight (<1,000, 1,000–1,500, and >1,500 g), no significant difference was found in patient distribution between the two feeding temperature groups ($p > 0.05$).

In group 1, 28 infants were fed with only breast milk, and 12 infants were fed with mixed feeds (breast milk and formula). Of the infants fed with mixed feeds, the percentage of formula-fed was 55.3% in group 1 and 53.6% in group 2 ($p > 0.05$). In group 2, 27 infants were fed with only breast milk, and 13 infants were fed with mixed feeds. Gastric residuals were seen in 23 infants of group 1 (15/28 cases of only breast milk feeding, 8/12 cases of mixed feeding) and 15 infants of group 2 (10/27 cases of only breast milk feeding, 5/13 cases of mixed feeding). Residuals were detected more frequently in group 1 compared with group 2 for both exclusive breast milk and mixed feeding subgroups, but no significant difference was detected.

Time to achieve full enteral feeds was 20.50 ± 15.01 days in group 1 and 20.80 ± 13.43 days in group 2 ($p > 0.05$). No statistical significance was present between the groups for daily weight gain. Time needed to catch up to their birth weight was significantly lower in mixed feeding infants in group 2. Although no statistical significance was present between the groups, 95% of the infants in group 2 caught up to their birth weight at discharge (group 1: 82.5%) ($p = 0.064$).

Apnea was significantly more frequent in group 1 (27.5%) compared with group 2 (5%) ($p = 0.006$), and group 1 infants needed anti-reflux treatment more frequently (70%) than group 2 (42.5%) ($p = 0.013$). During the study, 12 infants (11 with stage 1a, 1 with stage 3) were followed up for necrotizing enterocolitis (NEC). Of these infants, five were in group 1 and seven in group 2. In group 1, four infants were

Table 1. Demographic Data of Patients

Variable	*Group 1* (n = *40*)	*Group 2* (n = *40*)	p
Gestational age (weeks), mean ± SD	31.05 ± 2.34	30.68 ± 2.10	0.45
Birth weight (g), mean ± SD	1525.50 ± 460.86	1539 ± 358.69	0.88
Study onset (weeks), mean ± SD	32.58 ± 2.30	32.35 ± 2.13	0.65
Study onset weight (g), mean ± SD	1516.58 ± 376.66	1537.25 ± 283.38	0.78
Apgar, 1st minute	6.45 ± 1.78	6.72 ± 1.58	0.48
Apgar, 5th minute	8.42 ± 1.08	8.29 ± 1.08	0.62
Gender (male)	23	18	0.26
Antenatal steroid, *n* (%)	24 (60)	25 (62.5)	0.82
Resuscitation in DR, *n* (%)	12 (30)	9 (22.5)	0.45
Respiratory distress syndrome, *n* (%)	18 (45)	13 (32.5)	0.25
Surfactant need, *n* (%)	13 (32.5)	11 (27.5)	0.63
Nasal mechanical ventilation, *n* (%)	23 (57.5)	29 (72.5)	0.16
Patent ductus arteriosus, *n* (%)	10 (25)	8 (20)	0.59
Treatment for PDA, *n* (%)	4 (10)	2 (5)	0.40
Inotrop need, *n* (%)	7 (17.5)	0 (0)	0.005
Intracranial hemorrhage, *n* (%)	8 (20)	4 (10)	0.21
Bronchopulmonary dysplasia, *n* (%)	8 (20)	3 (7.5)	0.10

DR, delivery room; PDA, patent ductus arteriosus.

fed with only breast milk, one was under mixed feeding, and the only infant with stage 3 NEC was fed with only breast milk. In group 2, four infants were fed with only breast milk, three were under mixed feeding. All primary and secondary outcomes are summarized in Table 2.

Discussion

Enteral feeding should start with human milk, which is the preferred nutrient source for all preterm infants. Special cow milk-based formulas for preterm infants are used when human milk is not available or its volume is extremely limited.[11] Hypothermia is a major cause of morbidity and mortality in infants; for that reason, maintaining normal body temperatures starting from the delivery room is crucial.[2] The effects of cold stress in neonates are observed in all systems of the body, resulting in cool skin, tachypnea, respiratory distress, desaturation, increasing episodes of apnea and bradycardia, increased gastric residuals, and emesis.[2,12] Therefore, in this study, we hypothesized that infants fed at room temperature (22–24°C) will have more feeding tolerance and therefore more co-existing morbidities.

Although the measurement of feeding temperature is not routinely done in NICUs, the common practice is to feed infants at room temperature. Lawlor-Klean et al.[13] found that milk temperature just before feeding may vary between 22°C and 46.4°C, and variability exists due to the lack of standardization for warming. A similar variation was also observed in warming procedure in water baths. Dumm et al.[2] stated that during warming procedure, the temperature of the refrigerated milk was between 3.8°C and 27.1°C and increased to 21.8–36.2°C at feeding time. The American Dietetics Association and the American Academy of Pediatrics guidelines call for hand hygiene and placement of milk containers in a warm bowl of water. National Association of Neonatal Nurses (NANN) recommends the placement of milk container in warm water bath. None of these guidelines offer a standard temperature for water bath and length of time for warming the milk.[14–16] Therefore, enteral feeding temperature was adjusted using a bottle warmer in our study to standardize the temperature.

We found that infants fed with expressed breast milk at 32–34°C had slightly less gastric residuals compared with infants fed with milk at 22–24°C. Also, in a study by Gonzales et al.,[7]

Table 2. Outcomes of Patients

Variable	*Group 1* (n = *40*)			*Group 2* (n = *40*)			
	Breast milk (n = *28*)	*Mixed feeding* (n = *12*)	p	*Breast milk* (n = *27*)	*Mixed feeding* (n = *13*)	p	p[a]
Time to achieve full enteral feeding (days), mean ± SD	19.57 ± 11.43	22.67 ± 21.70	0.62	22.07 ± 14.18	18.15 ± 11.81	0.25	0.92
Time to catch birth weight (days), mean ± SD	10.36 ± 4.39	12.50 ± 6.83	0.46	13.04 ± 5.58	8.64 ± 3.50	**0.008**	0.63
Catching birth weight at discharge, *n* (%)	23 (82.1)	10 (83.3)	0.93	25 (92.6)	13 (100)	0.32	0.06
Apnea, *n* (%)	8 (28.5)	3 (25.0)	0.82	2 (7.4)	0 (0)	0.32	**0.006**
Anti-reflux treatment, *n* (%)	20 (71.4)	8 (66.7)	0.77	10 (37.0)	7 (53.8)	0.32	0.01
Necrotizing enterocolitis, *n* (%)	4 (14.3)	1 (8.3)	0.61	4 (14.8)	3 (23.1)	0.52	0.53

Bold indicates $p < 0.05$ is statistically significant.
[a]*p* for group 1 versus group 2.

preterm infants fed with milk at body temperature had less gastric residuals compared with infants fed with milk at room temperature or 10°C.[7] Dumm et al.[2] recently investigated the effect of temperature on the physiological status and noted that different milk temperatures produce no negative physiological effects on preterm infants.

Postnatal growth restriction is associated with poor neurocognitive development, and efforts are made to increase nutrient intake.[17,18] When full feeding is achieved, providing nutrients to support the infant's growth is the goal; however, there is no literature about its relationship with enteral temperature.[19] Although no statistical significance was present between the groups, 95% of the infants in group 2 caught up to their birth weight at discharge (group 1: 82.5%). Time needed to catch up to their birth weight was significantly lower in mixed feeding infants in group 2, but this may be due to the small sample size. Therefore, a more detailed and enlarged study in the future may propose feeding at 32–34°C for postnatal catch-up.

Gastroesophageal reflux (GER) is a common physiologic phenomenon in preterm infants.[20] Many strategies may be helpful in the non-pharmacological treatment of GER.[21] Interestingly, in our study, infants in group 1 needed more anti-reflux treatment compared with group 2. To date there are no other data in the literature about feeding temperature and GER. This may be explained by more physiological feeding similar to the temperature of breast milk. In our NICU, conservative, pharmacologic, and surgical treatment is considered to treat infants with GER. Careful and noninvasive pretreatment differential diagnosis, a conservative approach, and preventive methods are effectively applied before starting multiple pharmacologic drugs and ceasing anti-reflux treatment, if not effective.

We monitored the infants for apnea 1 hour before and after feeding from the beginning of the study for 1 week. Apnea was more frequent in infants fed with milk at 22–24°C in our study. There was no correlation between residual milk and the occurrence of apnea. No difference was found between the groups regarding the incidence of chronic lung disease and intracranial hemorrhage grade 3–4 or periventricular leukomalacia.

NEC is the most severe gastrointestinal emergency of the preterm neonate.[22] No significant effect of feeding temperature was detected between the groups regarding NEC development in our study. Feeding with infant formula rather than human milk was found to result in a significantly higher risk of NEC.[23] Therefore, breast milk remains the preferred feed for all premature infants.[24]

Conclusion

Our data about warming enteral nutrition to 32–34°C are encouraging, especially considering the decrease in gastric residual frequency, apnea of prematurity, and need for anti-reflux treatment. More studies are needed to investigate the effect of enteral feeding temperature on feeding tolerance in preterm infants.

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Disclosure Statement

No competing financial interests exist.

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