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Original Article

Effect of Probiotics on Enteral Milk Tolerance and Prevention of Necrotizing Enterocolitis in Preterm Neonates

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ABSTRACT

Background: There is a dearth of studies in Iran on the efficacy of probiotics in reducing necrotizing enterocolitis (NEC), yielding contradictory results. Therefore, the present study aimed to assess the effect of probiotics on milk tolerance and the prevention of NEC in preterm neonates.

Methods: This randomized triple-blind clinical trial study was conducted on all preterm neonates between 30 and 36 weeks gestation and birth weight >1250 g hospitalized in the neonatal intensive care unit (NICU) at Bentolhoda Hospital in Bojnurd, Iran. Thereafter, 76 eligible neonates were randomly assigned to two groups of oral placebo (n=38) and BB care probiotic (n=38). Subsequently, the following information was extracted based on the hospital checklist: early or late NEC (after 7 days of birth), types of NEC (grade I, II, and III), length of hospitalization, time to reach complete oral nutrition, weight at discharge, and milk tolerance.

Results: In the current study, 52.6% and 47.4% of newborns in control and intervention groups were male, and no significant difference was observed between the two groups (P= 0.646). The incidence of NEC was significantly reduced among the intervention group. The feeding onset in the placebo group was significantly later, as compared to that in the intervention group. A significant difference was detected between the two groups in the length of hospital stay and weight gain during hospitalization.

Conclusion: As evidenced by the obtained results, the administration of probiotics in preterm neonates might prevent NEC. Moreover, it can shorten the onset time of feeding and hospitalization duration.

Keywords: Milk tolerance, Necrotizing enterocolitis, Premature neonate, Probiotics

Introduction

Necrotizing enterocolitis (NEC) is still a life-threatening disorder in preterm neonates (1) with a worldwide incidence of 7%-10% in neonates born at <1500 g. The mortality rate of NEC was reported up to 50% of newborns, depending on the infection severity and prematurity degree (2). The main risk factors of this devastating gastrointestinal (GI) complication include low gestational age, very low birth weight (VLBW), intestinal ischemia, red blood cell transfusion, formula feeding in infancy, intestinal colonization with pathogenic bacteria (3, 4), intestinal epithelial barrier dysfunction, impaired intestinal motility, and immature immune system (5, 6).

Although advanced intensive care has improved the survival rate of preterm neonates, NEC incidence has not been changed. Newborns with NEC usually experience longer hospitalization, life-long gastrointestinal deficits, and long-term neurological dysfunction due to surgical resection of the affected gut (7, 8). The clinical manifestation of NEC includes abdominal distention, diarrhea, vomiting, feeding intolerance, abundant gastric residuals, and occult or frank blood within stool (2). The severity of NEC is classified into three stages based on the Bell's staging criteria: stage I (NEC suspected), stage II (definite NEC), and stage III (advanced NEC) (2).

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Premature neonates have inadequate swallowing of vaginal flora due to early passage through the birth canal or premature cesarean section. Moreover, there is insufficient primary colonization with low diversity of natural intestinal bacteria. These newborns also have an immature immune response against intestinal bacterial colonization which results in increased inflammatory responses to inflammation within the intestinal lumen (9, 10). Moreover, preterm neonates have immature immune responses; moreover, due to incomplete skin/mucosal barrier, exposure to the hospital environment makes these neonates vulnerable to infections (7) and facilitate NEC development (11).

Different approaches have been applied for the prevention of NEC, including early enteral feeding, breast milk feeding, enteral antibiotics, probiotic products, IgA supplementation, anti-cytokine agents, growth factors, and antenatal steroids (12). Oral probiotics have recently been used to reduce the risk of NEC. Nonetheless, the incidence and mortality of this disease have not decreased significantly (13). A probiotic food supplement contains live microorganisms that balance the intestinal flora (11).

Probiotic agents can colonize the GI tract, followed by competitive inhibiting binding of pathogenic bacteria. In addition, they decrease the probability of translocation, colonization, and life-threatening infections (14). As suggested by available evidence, the various types of probiotics were used, and different results were reported regarding NEC prevention (15). Probiotics protect premature neonates from NEC, sepsis, or both by the inhibition of migration of bacteria and their products via intestinal mucosa (16). They also improve the production of anti-inflammatory cytokines, increase the antioxidants activity, regulate cell death (13), increase mucosal responses to IgA immunoglobulin, and improve the body's immune response (17).

In general, probiotics appear to be the most effective way to inhibit NEC and decrease the mortality rate in preterm neonates born at ≤34 weeks' gestation or those with VLBW ≤1500 g (18). Considering the contradictory results of studies on probiotics' effectiveness in the reduction of NEC and a dearth of related studies in Iran, the present study aimed to assess the effect of probiotics on milk tolerance and prevention of NEC in premature neonates.

Methods

This triple-blind randomized clinical trial was conducted on 76 preterm newborns admitted to the tertiary neonatal intensive care unit (NICU) in Bojnourd, Iran, from March 2018 to May 2019. Newborns who met the inclusion criteria (including the gestational age of 30-36 weeks, birth weight > 1250 g, receiving intestinal nutrition during the first 48 h of birth, and hospitalized in the NICU) were enrolled in the present study. Thereafter, they were assigned to two groups of probiotic administration (intervention group) and placebo (control group) using the random allocation software.

The exclusion criteria were as follows: 1) gastrointestinal obstruction, 2) congenital heart disease, 3) emphysema, 4) gastroesophageal reflux disease, 5) asphyxia (grade II and III), 6) immunodeficiency, 7) neonates born to mothers with abuse drug disorder, 8) congenital and chromosomal malformations in the digestive system, and 9) active gastrointestinal bleeding in the first week after birth. The study protocol was approved by the Ethics Committee of North Khorasan University of Medical Science (ir.nkums.rec.1398.028). Moreover, the protocol was registered at Iranian clinical trial websites (code: IRCT44457). It is noteworthy that in the current study, neonates' parents, physicians, and the statistical analyzer were blinded to the type of milk given to neonates.

Prior to participation, the effects of the probiotic were fully explained to neonates' parents, and written informed consent was obtained. In addition, demographic information, such as gender, gestational age, birth weight, 5-min Apgar score, growth restriction, steroid prescription at the time of birth, delivery method, maternal diagnosis of preeclampsia or chorioamnionitis, and cause of mother's hospitalization were recorded. Furthermore, early or late NEC information (7 days post-delivery), types of NEC (grades I, II, and III), length of hospital stay, duration of feeding, the time of full oral feeding attainment, weight at discharge, and milk tolerance based on hospital checklist were extracted. Regarding the objectivity of the narrative and reliability questions, the collection of complete information was considered.

After stabilizing the neonates in both groups, gavage feeding was initiated in the first 24 h after birth. For neonates born ≤28 weeks+6 days, feeding started with 0.5 cc/kg/2 h, followed by 15 cc/kg daily, and finally reached 150-180 cc/kg/day. For neonates born at 29-35 weeks+6 days, feeding started with 15 cc/kg/day, followed by 30cc/kg in the second 24 h, and finally reached

150-180 cc/kg/day. In the treatment group, oral probiotics were administrated after the neonate's feeding reached 5cc/kg/day. To prepare the probiotic, one drop of BB care probiotic was diluted with normal saline solution to reach the final volume of 0.5 cc. In the control group, only 0.5 cc of normal saline was administered every 12 h.

In the present study, the prescribed probiotic was BB Care Drop (Zist takhmir, Pardis, Tehran, Iran), which is composed of 15 ml of a mixture containing *Bifidobacterium Lactis*. One drop of this product holds a minimum of 1000,000,000 CFU *Bifidobacterium Lactis*. Probiotic treatment continued until the total milk intake reached 150-180 cc/kg per day, which was defined as full enteral feeding. In the present study, NEC was defined as the presence of feeding intolerance (bilious residual), abdominal distention, bloody stool, and specific radiologic intestinal findings. Data analysis was performed in SPSS (version 16) using the Chi-square test, independent T-test, Manne-Whitney test, Wilcoxon tests, and Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

Results

A total of 76 eligible preterm neonates admitted to the NICU were randomly assigned to two groups of oral placebo (n=38) and BB care probiotic (n=38). Moreover, 18 (47.4 %) and 20 (52.6%) neonates in the intervention and placebo groups were male, signifying no significant difference between the two groups (P=0.646). Data of patients' characteristics and clinical variables at birth are displayed in Table 1.

The findings revealed that the cesarean section was the most used delivery mode in both groups (78.9% and 76.3% in probiotic and placebo group, respectively) with no meaningful differences (P=0.78). Furthermore, the mean scores of birth weight in the intervention and placebo groups were obtained at 1958.68±484.31 and 1942.63±581.29 g, respectively, illustrating no significant statistical difference between the two groups (P=0.896). The mean scores of neonates' gestational age were reported as 32.81±1.81 and 32.84±1.83 weeks in the intervention and placebo groups, respectively with no significant difference (P=0.95). In terms of feeding onset, there was a meaningful difference (P=0.009) between the two groups (18±18.32 and 37.68±41.13 h after birth in the intervention and placebo group, respectively). Therefore, feeding tolerance was meaningfully improved in the intervention group.

In the present study, NEC was served in 1 (2.6%) and 9 (23.7%) neonates in the intervention and placebo group, respectively, and there was a significant difference between the two groups in this regard (P=0.007). In detail, out of 38 neonates in the placebo group, 5 (13.2%) cases shows NEC grade II, followed by NEC grade I (5.3%) and III (5.3%), while the only found NEC in the intervention group was grade I. In addition, 22 (57.9%) and 17 (44.7%) neonates in the intervention and placebo group were prescribed steroids; however, the difference was not statistically significant (P=0.25). The most common pregnancy problems reported in mothers were preeclampsia (11.8%), followed by premature rupture of the membranes (6.6%), fetal abnormalities (3.9%), and gestational diabetes (3.9%) (Figure 1).

Table 1. Neonates' characteristics data and clinical variables at birth time

Variables		Probiotic (n=38)	Placebo (n=38)	P-value
Type of delivery	Vaginal	8 (21.1%)	9 (23.7%)	0.78
	Cesarian section	30 (78.9%)	29 (76.3%)	
Body weight at birth (g)		1958.68±484.31	1942.63±581.29	0.896
Height at birth (cm)		44.59±3.99	45.46±4.38	0.369
size of the head circumference		30.89±2.48	31.06±2.07	0.741
5 min Apgar score (cm)		8.71±1.85	8.34±1.59	0.357
Gestational age (week)		32.81±1.81	32.84±1.83	0.95
Start time of milk feeding (hr)		18±18.32	37.68±41.13	0.009
Cause of hospitalization (NEC)	no	37 (97.4%)	29 (76.3%)	0.007
	yes	1(2.6%)	9 (23.7%)	
Steroids therapy in premature infant	No	16 (42.1%)	21 (55.3%)	0.25
	yes	22 (57.9%)	17 (44.7%)	
Pregnancy Complications	No	22 (57.9%)	19 (50%)	0.49
	yes	16 (42.1%)	19 (50%)	

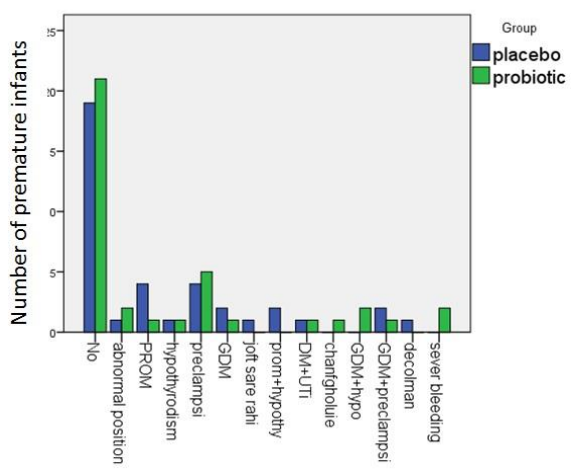

Figure 1. Distribution of maternal problems

Feeding tolerance was significantly improved among the intervention group, in comparison with the placebo group (94.7% vs. 71.1%, P). According to the findings, the mean scores of time to reach full enteral feeding were calculated at 27 and 36 days in the intervention and placebo groups, respectively, pointing to a significant difference between the two groups (P=0.007). At the end of the study, no meaningful differences were detected in the body weight, height, and head circumference (the patients' clinical variables at discharge are resented in Table 2). There was a significant difference between the two groups in terms of weight gain (weight difference from birth to discharge) (40.1 g in the placebo group vs. 45.65 g in the intervention; P= 0.034) and the length of hospitalization (10.3684 vs. 7.8684 days in placebo and intervention groups, respectively P=0.019). It is noteworthy that no mortality was reported in both groups.

Table 2. The infants' clinical variables at discharge.

Variables	Probiotic (n=38)	Placebo (n=38)	P-value
Body weight at discharge (gr)	1979.47±402.34	1890.03±514.59	0.401
Height at discharge (cm)	46.05±3.2	45.81±4.2	0.785
size of the head circumference	31.79±2.2	31.46±2.07	
Body weight at birth- Body weight at discharge	45.66±186.45	40.1±159.36	0.034
Hospital stay (day)	7.87±4.53	10.37±4.58	0.019

Discussion

Although the pathogenesis of NEC is still unclear, prematurity and microbial colonization play a major role in the development of NEC (3). Some evidence suggested that probiotics replace pathogenic bacteria with beneficial ones and inhibit abnormal intestinal colonization. Although the majority of studies have indicated that probiotic supplementation can significantly reduce the incidence of NEC in premature neonates, there are still concerns about the quality, safety, optimal dose, and duration of treatment with probiotics (19).

Furthermore, a meta-analysis study conducted by Chi et al. (19) demonstrated that the use of probiotics in premature neonates is a safe option and can reduce the incidence of sepsis, mortality, length of hospital stay, and full intestinal feeding time. Consequently, different probiotics treatments in premature neonates have resulted in various and contradictory findings. In this randomized clinical trial, the effect of oral probiotics was investigated on milk tolerance and prevention of necrotizing enterocolitis in premature neonates admitted to the NICU.

The findings also revealed that there was no significant statistical difference between the two study groups in terms of gender, type of delivery, steroid therapy, and pregnancy problems (P>0.05). Nevertheless, there was a statistically significant difference between the two groups in terms of NEC. The rate of NEC was higher and more severe in the placebo group. Moreover, feeding tolerance was better in the probiotic group (P= 0.040). In addition, oral feeding was started significantly earlier in the intervention group, compared to the placebo group.

The probiotic group showed more weight gain during hospitalization, in comparison with the placebo group (P=0.034). Moreover, the length of hospitalization in probiotic-exposed neonates was significantly shorter, compared to that in the placebo group (P=0.019). Therefore, probiotic administration could significantly decrease the incidence and severity of NEC and improve food tolerance. Furthermore, probiotic agents aid to establish early full enteral feeding and decrease the hospitalization period.

In a similar vein, Hunter et al. (20) pointed out that prophylactic initiation of Lactobacillus reuteri significantly decreased NEC rate in neonates with birth weight ≤ 1000 g. The results of the present study were comparable to those reported by

Bonsante et al (21). In the mentioned study, VLBW neonates were administered a probiotic (Lactobacillus rhamnosus Lcr35) on the first day of life up to 36 weeks gestation, and they displayed a significant reduction in the incidence of NEC. Along the same lines, Samanta et al. (11) obtained similar results and indicated that probiotic mixture (Bifidobacteria infantis, Bifidobacteria bifidum, Bifidobacteria longum, and Lactobacillus acidophilus, each 2.5 billion CFU) played a substantial role in reducing the incidence of NEC in newborns with a birth weight of <1500 g. In another study, Braga et al. (22) observed that the combined use of Lactobacillus casei and Bifidobacterium breve reduced the occurrence of NEC stage ≥ 2. Similar results were reported by Nouri Shadkam et al. (23), Benor et al. (24), and Lin et al. [23]. On the contrary, in a study carried out by Al-Hosni et al. [24], the incidence of NEC in the control and probiotics-supplementation group (received Lactobacillus rhamnosus GG and Bifidobacterium infantis) did not show any significant differences. Furthermore, the mortality rate and severity of NEC were almost the same in both groups.

Consistent with the findings reported by Hu et al (27) and Bonsanti et al. (21), in the present study, the mean duration to reach full eternal feeding in the probiotic group was shorter, compared to that on the control group. Nonetheless, the mean weight at discharge in the two groups did not differ significantly. As illustrated by the results of the present, the mean length of hospitalization in the probiotic-exposed group was decreased. Moreover, in their study, Samanta et al. (11) suggested that probiotic administration reduced the length of hospital stay in VLBW neonates. In accordance with the results of the current study, Nouri Shadkam et al. (23) reported that reaching full eternal feeding in the probiotic Lactobacillus Reuteri group was significantly shorter, as compared to that in the control group. In agreement with the present study, Braga et al. (22) observed that the time to reach full enteral feeding was significantly (P=0.02) shorter in the newborns exposed to the combined use of Lactobacillus casei and Bifidobacterium breve (28, 29).

All things considered, probiotic administration might be a useful way for the prevention of NEC and decreasing the rate of mortality in preterm neonates (30). The proposed mechanisms by which probiotics apply their beneficial effects are exerted through increasing gut barrier, immune response modulation, inhibition of pathogenic colonization, antimicrobial peptides production, secretion of short-chain fatty acid, reducing oxidative stress, modulating Paneth cell function, and regulation of apoptosis and restitution (31).

Conclusion

As suggested by the obtained findings, the oral administration of probiotics might decrease the incidence of NEC, enhance feeding tolerance, and reduce hospitalization in premature newborns. Therefore, BB care probiotics could be suggested as an adjuvant therapy to overcome feeding intolerance in preterm neonates. Consequently, this probiotic could be advised as a potential protective factor for NEC.

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Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the North Khorasan University of Medical Sciences (ir.nkums.rec.1398.028). Written informed consent was obtained from all parents, and the anonymity of the subjects was guaranteed.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of the current study.

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