Prophylactic oral probiotic on prevention of feeding intolerance in Very Low Birth Weight (VLBW) neonates: Randomized Clinical Trial

Original Article

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Received: 7 Jan 2016
Revised: 3 Feb 2016
Accepted: 1 March 2016

Abstract:

Background: Feeding intolerance is prevalent in very low birth weight (VLBW) neonates and is a barrier for better and faster growth in these neonates. Some studies have supported the administration of oral probiotic to decrease feeding intolerance. The aim of this study was to evaluate the effect of probiotic on feeding intolerance in VLBW neonates.

Methods: This randomized clinical trial study was conducted on 60 VLBW neonates who were randomly divided into two equal groups. In the case group, the infants received probiotic in addition to routine therapy. Duration of hospitalization, time to reach to full enteral feeding and birth weight, the numbers of vomiting and defecation, c-reactive protein rising, daily weight gain were compared between two groups.

Results: No significant differences were observed between two groups in regard with gender, birth weight, method of delivery and gestational age. Mean of duration of hospitalization was 42.27 and 31.6 days in control and drug groups, respectively and there was significant difference (P-value=0.005). There was no significant difference between two groups in terms of reaching full enteral feeding, the numbers of vomiting and defecation, time to reach to birth weight, CRP rising and daily weight gain but these results were better in probiotic group.

Conclusions: This study showed that prophylactic administration of probiotic had significant role in reducing the duration of hospitalization of VLBW neonates and was effective in reaching full enteral feeding. It is suggested that the administration of probiotic can be helpful for feeding tolerance in VLBW neonates.

Keywords: Feeding Intolerance, Prevention, Oral Probiotic, , Very Low Birth Weight, Neonate

Citation:
Zahed Pasha Y, Akbarian rad Z, Yahyaee Shahandashti AR, et al. Prophylactic oral probiotic on prevention of feeding intolerance in VLBW neonates: Randomized Clinical Trial. Caspian J Pediatr March 2016; 2(1): 118-22.

Introduction:

Feeding intolerance is a well-known phenomenon in the neonatal intensive care unit (NICU) and is often associated with morbidity and mortality in preterm infants [1]. Feeding intolerance is the inability to digest enteral nutrition which is associated with gastric residual increase, abdominal distention with vomiting commonly seen in preterm infants and often leads to nutrition interruption [2]. Feeding intolerance occurs in76.4% of VLBW neonates (under 1500 grams) [3]. Poor digestion associated with a delay in transmission can damage bowel as a premature host [4]. Necrotizing enterocolitis (NEC) is the most common acquired gastrointestinal disease in preterm infants [5]. There is not a single theory to explain the pathogenesis of necrotizing enterocolitis and many mechanisms have been proposed for it including the immature intestinal

[DOI: 10.22088/acadpub.BUMS.2.1.118]

digestion and abnormal regulated blood circulation, and the innate immune system and bacterial colonization [6].

These factors not only can cause feeding intolerance, but also lead to life-threatening conditions such as NEC [7]. Although the specific etiology of necrotizing enterocolitis is still under discussion, epidemiologic analysis determines strategic risk factors of immaturity, enteral nutrition, ischemia/asphyxia and intestinal bacterial colonization [8]. Diagnosis is based on clinical symptoms and ruling out other diseases [9].

Modified Bell classification includes stage I: suspected necrotizing enterocolitis with abdominal distention, bloody stools and vomiting/gastroesophageal residual stage II: proven necrotizing enterocolitis with symptoms associated with abdominal tenderness±metabolic acidosis and thrombocytopenia, stage III: advanced necrotizing enterocolitis with symptoms associated with hypotension, metabolic acidosis, thrombocytopenia/DIC, neutropenia [8]. Reaching to full enteral feeding can cause removing catheters, less sepsis, and other catheter-related complications [10].

Antenatal use of glucocorticoids with preferential feeding with fresh breast milk, serious prevention and treatment of sepsis and a cautious enteral nutrition are required strategies to prevent necrotizing enterocolitis [11]. Premature infants in the NICU have different intestinal microbial environment than healthy infants fed with breast milk. Contact with the native microbial environment is reduced but the exposure to organisms that had been colonized in the NICU increases due to antibiotics advising and delay in enteral feeding [12].

Many researchers have tried to modify the microbial environment of the preterm infants' gut for being similar to full-term breastfed babies hoping that growth and development will be improved and the nosocomial episodes of infection and necrotizing enterocolitis will be decreased [13]. Recent studies have investigated the use of probiotic for the prevention of necrotizing enterocolitis in preterm infants and convinced neonatologists to apply them routinely in the near future [14]. Several proposed mechanisms include maintenance of mucosal barrier, preventing bacterial replacement, setting to bacterial colonization, enabling the general resistance of the body and regulating intestinal inflammation [15].

Probiotic, prebiotics and symbiotic are essential to prevent this disease [16]. Recent studies have shown that the administration of probiotic supplementation improves the feeding tolerance, time to reach full enteral nutrition, better weight gain, lower incidence of necrotizing enterocolitis and death due to necrotizing enterocolitis (NEC) stage is lower [17, 18, 19, 20, 21, 22 and 23]. Most of the studies had investigated the probiotics effect in preventing necrotizing enterocolitis on VLBW neonates (under 1500 grams), but in this study, feeding intolerance in neonates under 1500 grams, i.e. 1000 grams, was examined.

In the current study, the probiotic drops containing three strains of bacteria (made in Iran), 1-Lactobacillus Rhamnosus 2- Lactobacillus Ruteri 3- Bifidobactrium Infantis, were used while fewer strains had been used in most studies. Experimental studies on animals and humans advocated the idea that the administration of probiotic reduced feeding intolerance and NEC which led to death in preterm neonates, but the matter is still controversial. This study was designed to investigate the feeding intolerance in neonates under 1500 grams.

Methods:

This clinical trial was conducted on 60 VLBW neonates who were randomly divided into two equal sizes (control and intervention group). Neonates with gastrointestinal obstruction, congenital heart disease, major congenital abnormalities, death in the first 72 hours of life, the babies whose mothers used probiotic supplement and the formula-fed neonates were excluded from the current study.

All patients received standard treatment, were breastfed and their information were confidential and no additional tests were not imposed on the patients. In addition, the written consent was taken from all parents before the start of treatment.

In the intervention group with reaching feeding volume to 5 cc/kg/day, 3 drops as daily oral probiotic in neonates 1500- 1000 grams and two drops in a day in infants less than 1000 grams were added to mother's milk in every 12 hours until the enteral feeding was completed (160-120 cc per kilogram for body weight).

Consumed probiotic named Pedilact manufactured by Zist takhmir company (Iran), which contained 3 strains of microorganism products as follows:

Lactobacillus reuteri (4×108 - colony forming unite-cfu/gtt), Lactolacillus rhamnosus (2×109 cfu/gtt) and Bifidobactrium Infantis (3×108 cfu/gtt) and pharmaceutical storage was according to company protocol during the study.

In the control group, routine treatment of the underlying condition was done and there was no placebo intervention. CRP, CBC, blood cultures,

[DOI: 10.22088/acadpub.BUMS.2.1.118]

sodium, potassium, glucose, calcium, ABG (Arterial blood gas) and a chest x-ray were performed for all included patients at the initiation of the admission in NICU. Weight, time to starting of feeding, daily weight gain, numbers of vomiting and stool passing of patients were recorded. When respiratory rate was reached to 60 breaths per minute and also respiratory distress was diminished, oral feeding was started and the start time was recorded.

For all neonates, intravenous route was established and 80-100 cc per kilogram of body weight fluid were calculated and used. All patients were treated with antibiotics (ampicillin-aminoglycoside) and when the blood cultures were negative, the antibiotics were discontinued. For neonates whom their feeding reached 5 cc/kg/day, probiotic drops in the intervention group was administrated daily and until the patient's feeding reached to 120 cc/kg/day, simultaneously, with the start of high-calorie milk, probiotic drops were cut in the intervention group. The increasing amount of daily milk was similar in both groups.

This study was registered in the Iranian Registry of Clinical Trial (www.irct.ir) with registration number ID: IRCT2015111925125N1. The study was approved by the local Ethics Committee of Babol University of Medical Sciences, Iran. All patients gave informed written consent. Data collection was done via observing and recording the information in the questionnaire by a trained nurse in NICU. Data were analyzed using SPSS 21, T-test and X2 tests and Kaplan-Meier and Cox regression methods were also used in the present study and P<0.05 was considered significant.

Results:

VLBW neonates were examined in two groups. There was no significant difference between gender, birth weight, mode of delivery (vaginal delivery or C-section) and gestational age (Table 1).

. This study showed that probiotics had significant impact on reducing the duration of hospitalization (P Value=0.05). Also in the intervention group, time to oral feeding and reach to birth weight (Table 2), incidence of sepsis and numbers of vomiting and stool passing were less than the control group, but the difference was not statistically significant.

No significant difference was observed between the two groups for NEC≥Stage II Bell, but two deaths occurred in the intervention group, who were less than 1000gr and none of them had positive blood cultures. Moreover, one of these two dead infants had hyperkalemia and hyponatremia and the other one had NEC with CRP rising; however, mortality in both groups had not significant difference (0.492) (Table 3). One of them was intra uterine growth retarded (IUGR) infant, too.

Table 1. Basic demographic characteristics in newborns into drug and control group*

Variables		drug (n=30)	control (n=30)	P Value
Sex	Male	16 (53.3)	13 (43.3)	0.438
	Female	14 (46.7)	17 (56.7)	
Type of delivery	Caesarean section	25 (83.3)	21 (70)	0.222
	Normal	5 (16.7)	9 (30)	
Birth weight (mean±SD)		1245±176	1223±206	0.667
Gestational age (weeks) (mean±SD)		30.24±1.57	30.4±2.65	0.775

*There was no significant difference between gender, birth weight, mode of delivery and gestational age

Table 2. Outcomes of birth weight, time to full enteral feeding and duration of hospitalization in drug and control group* (n=60)

Variables	Group	Mean (CI=95%)	Median (CI=95%)	P Value Range Test (10)
Time to birth weight (days)	drug	18 (14.01-21.99)	16.43 (14.22-18.64)	0.058
	control	19 (16.70-21.30)	18.87 (15.81-21.2)	
Time to oral feeding (days)	drug	10 (9.11-10.90)	10.43 (9.43-11.44)	0.253
	control	10 (8.94-11.06)	11.23 (9.76-12.71)	
Duration of hospitalization (days)	drug	30 (26.17-33.83)	31.16 (35.49-26.82)	0.005
	control	40 (23.90-56.10)	42.77 (35.32-50.22)	

* - Done with survival analysis by Kaplan-Meier method
- No significant difference was observed between the two groups for Time to birth weight and Time to oral feeding
- Significant impact on reducing the duration of hospitalization (P Value=0.05)

[DOI: 10.22088/acadpub.BUMS.2.1.118]

Table 3. comparing vomiting, increasing CRP*, 2≤NEC, daily stool numbers, daily weight gain and death in the drug and control groups (60 = n)**

Variables	Probiotic (n=30)	Control (n=30)	P Value
Vomit(Number/day)	11 (36.7)	١٤ (46.7)	0.432
Increasing CRP(mg/dl)	4 (13.3)	3 (10.1)	0.500
NEC Bell stage≥2	1 (3.3)	1 (3.3)	1.000
Bowel movements per day (SD±mean)	2.67±0.39	2.68±0.47	0.484
Daily weight gain(gr) (SD ± mean)	15.92±5.32	13.8±5.53	0.135
Death	2 (6.7)	0 (0)	0.492

* CRP(C-Reactive protein)

** No significant difference was observed between the two groups for all data

Discussion:

This clinical trial evaluated the effect of probiotics in the prevention of feeding intolerance in VLBW neonates and showed that prophylactic probiotic was effective in reducing the duration of hospital stay and although it had better outcomes in other cases such as vomiting and increased CRP and daily stool numbers and daily weight gain and reaching to full enteral feeding and time to achieve weight birth in the probiotic group compared to control group, this difference was not significant. Though the death was not significant in both groups, the administration of probiotic would be done cautiously and carefully due to the mortality of two neonates under 1000 gr.

In a study performed by Cheng Huan et al., the incidence of feeding intolerance, time to full enteral feeding and serum bilirubin level was lower and weight gain was faster in the treatment group. Side effects were not observed in the intervention group so their results were nearly identical to the present study. [17].

Al-Hosni et al. showed that although the nutrition with probiotic improved growth of neonates less than 1000 grams, the improvement was not observed in some infants with developmental delay in 34 weeks. Moreover, no side effects of probiotic were reported [18]. The results of their study were in consistent with those of the current study because of different kinds of probiotic, probiotic prescription time and neonates less than 1000 grams. However, in their study, the incidence of NEC and death was similar to the present study.

Fernandez et al. evaluated the probiotic effect on the prevention of necrotizing enterocolitis in neonates under 1500 grams and they indicated that NEC reduced in the study group (8% compared with 16% in the control group) [20] so their study was consistent with the present study.

In a study performed by Yang et al, NEC≥ stage II and death were significantly lower in the probiotic group, but the risk of sepsis was not different between two groups and there was no difference between two groups in terms of weight gain and reach to enteral feeding [16].

Their study showed that at least the probiotic did not increase sepsis and mortality while in the current study, the mortality was observed because the neonates of this study were under 1000. The similarity of these two studies is that the probiotic can shorten the duration of the hospitalization.

The results of the present study indicated that the administration of prophylactic probiotic was effective in reducing the duration of hospitalization of VLBW neonates and was effective in other cases such as vomiting and increased CRP and daily stool numbers and daily weight gain and reaching to full enteral feeding and time to achieve weight birth, while the difference was not significant. Therefore, it cannot be concluded that the probiotic does not induce side effects in VLBW neonates and it must be cautiously prescribed for this group of neonates especially for ones under 1000 gr.

Finally, it is suggested that further studies should be done with larger sample size and changing the consumed dose and the duration of administration.

Acknowledgment:

We are grateful to the Clinical Research Development Committee of Amirkola Children's Hospital and Mrs Faeze Aghajanpour, the Research Council and Non communicable Pediatric Diseases Research Center, Health Research Center Babol University of Medical Sciences for their support and cooperation with study.

Funding: This study was supported by a research grant and neonatal Fellow thesis of Dr Alireza Yahyaee Shahandashti from the Non-Communicable Pediatric Diseases Research Center of Babol University of Medical Sciences (Grant Number: 9440942).

Conflict of interest: There was no conflict of interest.

[DOI: 10.22088/acadpub.BUMS.2.1.118]

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[DOI: 10.22088/acadpub.BUMS.2.1.118]