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Decretion of Late Onset Sepsis with Enteral Low Dose Lactulose in Very Premature Infants: A Double-Blind Randomized, Placebo-Controlled Pilot Study

*Amir-Mohammad Armanian[1], Nima Salehimehr[2], Hosein Saneian[3], Elahe Shirani[4], Mostafa HajiRezaei[5]

[1]Associate Professor of Isfahan Faculty of Medicine, Division of Neonatology, Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Science, Isfahan, Iran.[2]MD, General Physician, Department of Health, Academic Member of Almahdi-Mehr Isfahan Higher Education Institution, Isfahan, Iran. [3]MD, Associate Professor of Isfahan Faculty of Medicine, Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Science, Isfahan, Iran. [4]MD, Resident of Pediatrics, Medical Faculty, Isfahan University of Medical Sciences, Isfahan, Iran. [5]MD, Kashan University of Medical Sciences, Kashan, Iran.

Abstract

Background

Neonatal sepsis contributes substantially to neonatal morbidity and mortality, and is an ongoing major global public health challenge. We aimed to evaluate the effects of enteral feeding supplementation of low dose lactulose on the incidence of late onset sepsis in very premature infants.

Materials and Methods

In this randomized placebo-controlled trial preterm neonates with very low birth weight (VLBW) randomly received enteral supplementation of 1% lactulose (1 g per 100 mL feeds) (n=27) or distilled water (placebo, n=25) simultaneous with increasing volumes of milk. Incidence of late onset sepsis was considered as primary outcome. Feeding intolerance, time to reach full enteral feeding and duration of hospitalization in the course of the study were considered as secondary outcomes.

Results

Differences in baseline characteristics were not statistically important. The incidence of late onset sepsis was significantly lower in lactulose group compared to placebo (14.8% vs. 40%, p=0.04). The mean time to reach full enteral feeding was 12.85±3.33 and 15.20±5.24 in the lactulose vs. placebo group (p=0.03). Duration of hospitalization, occurrence of necrotizing enterocolitis and body weight on the 30th day of life were not significantly different between the two groups.

Conclusion

Enteral feeding supplementation with low dose lactulose in very premature infants for prebiotic purposes was deemed to be safe and reduced the incidence of late onset sepsis in our study.

Key Words: Lactulose, Neonatal sepsis, Prebiotic, Preterm infant.

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Corresponding Author:

Amir-Mohammad Armanian (M.D), Mail address: Child Growth and Development Research Center, Research Institute for Primary Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Hezarjerib Ave, Isfahan, Iran. Postal Code: 8184757851

Email: armanian@med.mui.ac.ir

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1- INTRODUCTION

Late onset neonatal sepsis (LOS) is defined as a clinical state characterized by signs and symptoms of systemic infection with or without accompanying bacteremia that occurs after the first 72 hours of age (1, 2). LOS is associated with nonspecific signs and symptoms such as reduction in activity, feeding difficulties (e.g. poor feeding, feeding intolerance, abdominal distension, etc.), hypotonicity, irritability or lethargy, respiratory distress (e.g. grunting, tachypnea, retraction, cyanosis and apnea), unexplained jaundice, hypothermia or hyperthermia, seizure or briefly "just not looking well" (3). Despite the general decline in neonatal sepsis incidence over the past decade, LOS is one of the most important global health challenges causing significant neonatal mortality and morbidity (4, 5).

The prevalence of LOS among hospitalised neonates is about 0.61 to 14.2% in different regions (6). It is inversely associated with gestational age and has the highest prevalence among the very premature infants. In addition to increased risk of LOS, prematurity increases the rate of neonatal sepsis complications (7, 8). Prevention of neonatal sepsis especially in the very premature neonates admitted to Neonatal Intensive Care Unit (NICU) remains an attractive challenge. Therefore different interventions such as intravenous immunoglobulin, anti-staphylococcal monoclonal antibodies, cytokines (e.g. granulocyte colony-stimulating factors) have been studied but no significant effects were observed (9-12). Prebiotics are typically non-digestible compounds that pass undigested through the upper part of the gastrointestinal (GI) tract; and have favorable effects on growth of intestinal flora (13, 14). They stimulate the growth and/or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them. Prebiotics could also reduce the amount of potentially pathogenic bacteria in the intestine, and also increase the amount of beneficial bacteria (15-17). Some studies reported the effects of prebiotics on the reduction of neonatal sepsis incidence, although they were not statistically significant (18-20). Previously, we conducted several studies, in order to find reduction strategies of neonatal infection, time to reach full enteral feeding and duration of hospitalization which, in some cases, yielded practical results (21-23). We found favorable effects of an oligosaccharides mixture (short chain galacto-oligosaccharides/long chain fructo-oligosaccharides [$_{SC}$GOS/$_{LC}$FOS]) on incidence of necrotizing enterocolitis (NEC), time to reach full enteral feeding and duration of hospitalization (23). It was, however, difficult to prepare and maintain these prebiotic mixtures. We were looking for a material that, in addition to having prebiotic effects, would be more easily accessible. Lactulose is a synthetic non-digestible disaccharide which is used in chronic constipation and hepatic encephalopathy, and has been shown to have prebiotic effects (24, 25). Therefore, due to the prebiotic effects of lactulose and ease of access, in this study, we evaluated the effects of enteral feeding supplementation of low dose lactulose on the incidence of late onset sepsis in very premature infants.

2- MATERIALS AND METHODS

2-1. Study design and participants

This double-blind, randomized, placebo-controlled trial, was conducted at the Isfahan University of Medical Sciences, Iran, in our tertiary neonatal intensive care units (NICUs) (Alzahra and Shahid Beheshti Hospital NICUs). Premature infants with the gestational age (GA) of ≤ 34 weeks, and the birth weight (BW) of ≤ 1500 gr who had initially been on parenteral nutrition were enrolled to the

study after the enteral feeding with their mothers' milk was started. The patients with major congenital anomalies, asphyxia, gastrointestinal anomalies, proven sepsis, fed with formula were excluded and replaced. After explaining the purpose and implementation of the study, written informed consent was obtained from parents of infants then all participants were visited by an expert neonatologist and baseline characteristics were recorded. Patients were randomly allocated to intervention (lactulose; two more infants), and control (placebo) groups using permuted block randomization method. Only one nurse who was responsible for preparing the drug and placebo was aware of group's allocation in both centers. The researcher responsible for reviewing the outcomes, other nursing staff and parents were blinded to the study group allocation. Based on the differences in incidences of late-onset sepsis (13% and 31%, respectively) in a previous similar study (26), a 2-tailed α=0.05, β=0.20, a sample size of 25 infants were calculated in each group.

2-2. Intervention

All infants were fed with an initial dose of 10-20 mL/kg/day of breast milk. Feeding volume was increased by 20 mL/kg/day until a volume of 150 mL/kg/day was achieved. Parenteral nutrition was gradually tapered as enteral feeding volume was increased. Infants in the lactulose group received a supplement of low dose sterilized lactulose (1 g per 100 mL feeds). Under sterile conditions, AlborzDarou lactulose syrup, (AlborzDarou-lactulose, Iran) containing 66% lactulose was added to each feeding based on feeding volume by an independent nurse. Administration of lactulose was continued with each feed until a few days after the maximum volume of milk (150 mL/kg/day) was achieved. Placebo was distilled water with the same color, appearance and volume as the lactulose solution that was prepared in similar syringes and numbered by a trained and independent nurse. The placebo was added to the control group's diet in a similar situation to the intervention group.

2-3. Primary and secondary outcomes

The primary outcome of the study was the incidence of neonatal sepsis following the initiation of intervention until discharge from hospital. Neonatal sepsis was defined as a clinical state characterized by signs and symptoms of systemic infection with or without accompanying bacteremia (1).

Secondary outcomes were the occurrence of feeding intolerance, time to reach full enteral feeding, duration of hospitalization and average body weight on the 30th day of life, oxygen dependence duration, mechanical ventilation duration, NEC, intraventricular hemorrhage (IVH), and patent ductus arteriosus (PDA). Feeding intolerance was defined as inability to digest milk and increasing gastric residuals (27) and full enteral feeding was defined as receiving 150 mL/Kg/day milk. Primary outcome was investigated by an experienced Neonatologist and secondary outcomes were evaluated by a trained nurse. The outcomes were checked and recorded in the questionnaire daily.

2-4. Ethical considerations

All ethical principles were observed according to the 196/96 resolution on research involving human subjects at all stages of the current study. All stages of the design and implementation of this study approved by the Ethics Committee of the Isfahan University of Medical Sciences and the approval number was 392273. Informed written consent was obtained from the parents before enrollment. This trial was registered at Iranian Registry of Clinical Trials (IRCT) as IRCT2015020110026N6.

2-5. Statistical analysis

Study data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of data was checked with the Kolmogorov–Smirnov test. The independent t-test (or Mann–Whitney U-test), and Fisher's exact test were applied for the comparison of quantitative and qualitative data, respectively, between the two groups. A p-value of <0.05 was considered statistically significant in all analyses.

3- RESULTS

3-1. Patients' characteristics

Overall, 90 infants with BW≤1500 and GA≤37 weeks were assessed for eligibility. Sixteen infants were excluded because of major congenital anomalies (n=4), gastrointestinal anomalies (n=3), receiving formula (n=4), and sepsis prior to the start of the study (n=5). Seventy four neonates met the eligibility criteria but parents of 14 infants refused to participate or were transmitted to another ward. Of the 60 neonates enrolled into the trial, 30 neonates were allocated to the lactulose group and 30 to the placebo group. Three and five neonates were transmitted to other wards after starting the intervention in lactulose and placebo groups respectively. Finally, 27 and 25 neonates completed the study in the lactulose and placebo groups, respectively (**Figure.1**). There was no significant difference in baseline characteristics between two groups, except for the time of first enteral feeding. Average time of first enteral feeding in lactulose and placebo groups was 4.96±2.76 and 3.16±1.30 days, respectively (p= 0.006). Baseline characteristics of the neonates are presented in **Table.1**.

3-2. Outcomes

As the primary outcome, the incidence of LOS was significantly less in the lactulose group compared to the placebo group. Only 4 neonates (14.8%) in the lactulose group suffered LOS/had incidence of LOS versus 10 infants (40%) in the placebo group (p=0.04). According to the results of the independent t-test, we observed that despite higher average time of first enteral feeding in the lactulose vs. placebo group (4.96±2.76 vs 3.16±1.30 days; p= 0.006), the average time to reach full enteral feeding was significantly lower in the lactulose group (12.85±3.33 vs. 15.20±5.24, p= 0.03). The frequency of feeding intolerance was not different between the two groups (4.96±3.95 and 3.25 ±3.99 infants in lactulose and placebo group, respectively; p= 0.13). Although the duration of hospitalization in the lactulose group was lower than the placebo group, there was no significant difference between the two groups (p=0.19). The average body weight on the 30th day of life, incidence of NEC, IVH and PDA and duration of oxygen dependency were not different between two groups. Primary and secondary outcomes were shown in **Table.2**.

Table-1: Baseline characteristics of study infants.

Variables	Groups, Mean ± SD		P-value	Mean Difference (95% CI)
	Lactulose, (n=27)	Placebo, (n=25)		
Gestational age (weeks)	30.57±2.84	29.86±2.09	0.312	071 (-0.69- 2.11)
Birth weight (grams)	1166.40±250.01	1190±192.24	0.701	-23.6 (-148.56- 101.36)
Time of first enteral feeding (days)	4.96±2.76	3.16±1.30	0.006	1.8 (0.6- 3.02)

95% CI: 95% confidence interval.

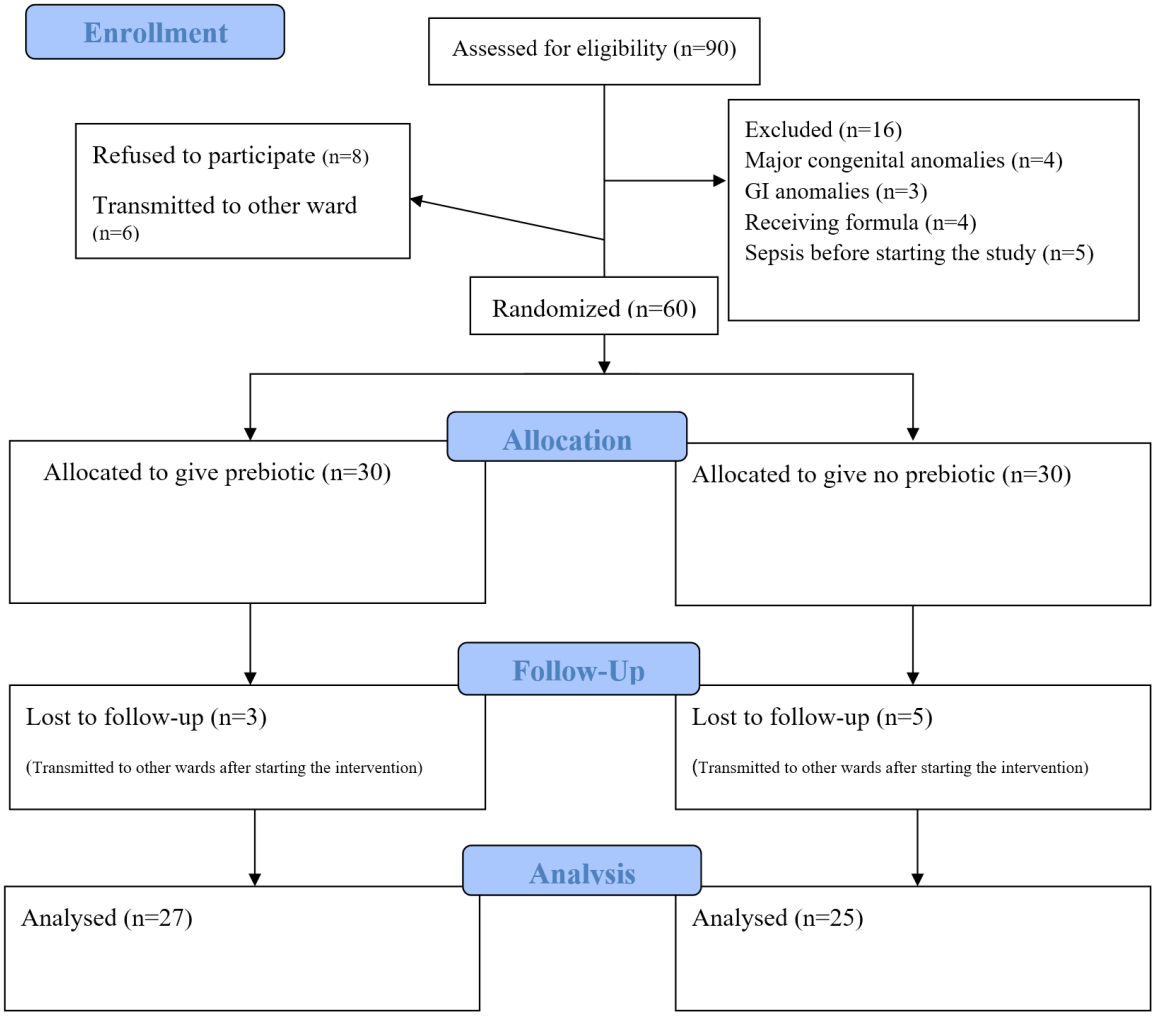

Fig.1: CONSORT diagram showing the flow of subjects through each stage of study.

4- DISCUSSION

This study was conducted to evaluate the effects of supplementation of low dose Lactulose on neonatal late onset sepsis. In the present study, we found that the incidence of LOS was significantly lower in infants who received enteral feeding supplementation of lactulose. This is in contrast with the results of previous similar studies. In a pilot clinical trial, Riskin et al. compared the effects of lactulose supplementation with placebo on infantile outcomes. Although the incidence LOS in lactulose group was lower than placebo group, there was not a statistically significant difference (26). The effects of other oligosaccharide prebiotics were studied in two separate studies. Westerbeek et al. studied the effects of a prebiotic mixture consisting of neutral oligosaccharides ((SC) GOS/(LC)FOS), and acidic oligosaccharides (AOS) on LOS in preterm infants. It was found that prebiotic supplementation cannot reduce LOS (18). In another similar study, Modi et al., evaluated the effects of short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides on enteral tolerance and blood stream infection. There were no significant effects of prebiotic supplementation on incidence of LOS and enteral tolerance (27). The cause of contradiction in the results of our study and previous studies can be found in the

difference in definition of neonatal sepsis. In the majority of similar studies, where the effects of prebiotics on the incidence of sepsis were evaluated, neonatal sepsis was defined as being blood culture positive regardless of clinical signs and symptoms (17, 18, 23, 26, 27). But considering the prescription of antibiotics from birth in premature infants and the resulting high probability of neonatal sepsis accompanied by negative blood cultures in symptomatic premature infants, neonatal sepsis was defined as "clinical sepsis" in our and some other studies (28).

Clinical sepsis is defined as the existence of signs/symptoms of neonatal infection with or without positive blood culture and ruling out other causes (1, 29). Dilli et al. (28) observed that when clinical sepsis was considered the same as neonatal infection, the incidence of neonatal sepsis was significantly lower in the prebiotic than the placebo group; while the incidence of neonatal infection was not different between the two groups when neonatal sepsis was defined as positive blood culture [(late-onset sepsis, clinical sepsis; 23 vs. 45 infants in the prebiotic vs the placebo group; $p < 0.001$), and (Late-onset sepsis, proven positive blood culture; 10 vs. 13 infants in the prebiotic vs the placebo group; $p=0.6$)].

In our study, average time of first enteral feeding in lactulose group was higher compared to the placebo group, but average time to reach full enteral feeding was significantly lower in the lactulose group. This suggests that enteral supplementation of lactulose in very premature infants may reduce the risk of feeding intolerance. This effect is in line with the capability of lactulose in stool relaxation and facilitating of defecation. However, we did not observe any cases of diarrhea in the evaluated neonates. This lower "time to reach full enteral feeding" is in line with the results of the study by Dilli et al. (28), who showed a reduction effect of inulin on time to reach full enteral feeding [17 (12-24) vs. 25 (15-37) days in prebiotic vs placebo group respectively; $p < 0.001$]. On the other hand, Westerbeek et al. (18), Riskin et al. (26), and Modi et al. (27) found no significant difference between the two groups. Westerbeek et al. defined full enteral feeding volume as 120 ml/kg/day, while Riskin et al. and Modi et al. defined full feeds as 150 ml/kg/day. Time to reach full enteral feeding in prebiotic versus control group was (10 (4-48) vs. 11 (7-50) days, $p = 0.47$), (12.4 ± 6.2 vs. 12.4 ± 4.2 days; $p > 0.05$), and (6 (5-8) vs. 7 (6-9) days, $P= 0.10$) in Westerbeek et al., Riskin et al. and Modi et al., respectively. Perhaps, complete exclusion of infants who were fed with formula (which could be a confounding factor) in our study, was the reason of lower time to reach full enteral feeding in the lactulose vs the placebo group (26, 27).

Although there was a significant difference, we observed favorable effect of lactulose on duration of hospitalization and body weight on the 30th day of life in our study. This is similar to the results of the previous studies which showed no significant statistical difference between the prebiotic and placebo groups (20, 27, 28). Probably, more extensive studies with larger sample sizes could show clearer results.

4-1. Study Limitations

Despite the efforts to accurately design and execute this study, there were some limitations. First, due to ethical limitations and patient safety issues, the sample size of the study was relatively small. As a consequence, the results might be confounded. Second, because of the difficulties and challenges associated with conducting an intestinal intervention study on very-low-birth-weight preterm infants, the intervention duration was also relatively short. As a consequence, we were unable to observe the effects of prolonged periods of intervention on very

premature neonatal outcomes. Therefore if the intervention period was increased, perhaps the results would be different.

5- CONCLUSION

Enteral feeding supplementation with low dose lactulose in very premature infants for prebiotic purposes was deemed to be safe and reduced the incidence of late onset sepsis in our study. This finding suggests a possible beneficial effect that should be evaluated in larger studies.

6- CONFLICT OF INTEREST: None.

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