ORIGINAL ARTICLE

Role of Probiotics in Prevention of Nectrotizing Enterocolitis in Preterm Low Birth Weight Neonates

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ABSTRACT

Aim: To compare the frequency of necrotizing Enterocolitis (NEC) in preterm low birth weight (LBW) neonates with and without prophylatically orally administered probiotics.

Methodology: This Randomized controlled trial was conducted at Nursery department, Jinnah Hospital Lahore for period of Six months after approval of synopsis. 300 preterm neonates with birth weight o Six months after approval of synopsis<2.5kg were included through Non-probability, purposive sampling technique. Neonates wererandomly divided in two groups by using random number tables. Group-1 was given probiotics named Bifidobacteria prophylactically (hiflora/gutcare one sachet daily) and Group-2 neonates were given any probiotics. Effectiveness of probiotics was considered if neonate did not show above signs and symptoms of NEC. If any 4 out of 5 clinical features of ENC observed during study period, the neonate was labeled as suffering from NEC.

Results: The mean gestational age of neonates was 33.27±1.48 weeks. Mean gestational age of neonates in probiotic group was 33.38±1.46weeks while mean gestational age of neonates in control group was 33.15±1.49weeks. There were 165 (55%) male and 135(45%) females. There were 44 (14.7%) neonates who develop NEC while 256(85.3%) neonates were normal. There were 44 neonates who had NEC, out of which 7(4.7%) belonged to probiotic group while 37(24.7%) belonged to control group.

Conclusion: Thus it was concluded from results of this study that probiotics given to pre-term neonates with low birth weight is effective and beneficial. Now we are able to recommend probiotics in such delicate cases and can prevent neonates from mortality or severe morbidity.

Key words: *Necrotizing enterocolitis, Preterm infants, low birth weight, neonates, Probiotics.*

INTRODUCTION

One of the commonest emergencies regarding gastrointenstinal health of the neonates is the Necrotizing Enterocolitis(NEC). This disease not only impacts approximately 5-10 infants constituting 3-5% rate of mortality that depends largely on the severity of disease, but also has crucial clinical implication for newborns health[1]. Clinicians suggest use of probiotics for prevention of NEC which are established in literature, to provide significant advantage regarding child health as well as prevention or atleast reduced risk of development of NEC particularly in low birth weight and preterm neonates[2]. Probiotics are actually live organisms that produce lactic acid and reside in the intestine which is their natural habitat. The most frequently mentioned of these lactic acid producing bacteria include Bifidobacteria and Lactobacilli. These have major responsibilities in body by revolting intensive effects of acid in stomach as well as low surface tension of the bile[3].

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A number of studies have reported the role of probiotics on the prevention and other health benefits in infants. One study was conducted by Hoyos in which the incidence of NEC was observed in infants administered with B. infantis and L. acidiphilius in Neonatal Intensive Care Unit (NICU). They reported thatin the historic control group, there were 85 NEC cases compared to 34 cases in the group that received probiotic prophylaxis (P <0.0002). In the historic control group, there were 35 NEC-associated fatalities compared to 14 fatalities in the group that received probiotic prophylaxis (P <0.005)[4]. One study by Bin Nundid a randomization on very low birth weight (VLBW) infants who either received B. infanitis, S. thermophilis and B. bifidus or did not receive any probiotics. They found that the incidence of NEC went down from 16.4% to only 4% in the 72 neonates who were fed by the supplementation and overall reported 20-30% less incidence[5]. The present study was conducted to determine the benefits of use of the probiotics in pre term and low birth weight neonates with NEC. No research has been conducted previously in regards of the role of probiotics in NEC in Pakistan. Therefore, it is extensive need of research in this regards. Moreover, if the efficacy of Bifidobacteria is proven, we can use

it in treating NEC in preterm low birth weight neonates more efficiently than before.

MATERIALS AND METHODS

This randomized controlled trial was conducted in Nursery Department, Jinnah Hospital Lahore during six months after approval of synopsis. Sample size of 300 cases; 150 cases in each group was calculated with 80% power of test, 1% level of significance and taking expected percentage of NEC in both groups i.e., 16.4% in without probiotics versus 4% in with probiotics. Sampling technique was non-probability, purposive sampling.

Inclusion criteria:

1. Pre-term neonates less than 36 weeks gestation
2. Low birth weight neonates less than 2.5 Kg
3. Both genders
4. Both NG feed and bottle feed neonates
5. All neonates that were admitted at day 1 of life

Exclusion criteria:

1. Neonates less than 30 weeks low birth weight neonates, less than 1.5 Kg
2. Neonate on mechanical ventilatory support
3. IUGR (gestational age>36 weeks and weight<2.5kg)
4. Patients with congenital cyanotic heart diseases or has birth asphyxia and persistent cyanosis and need of oxygen inhalation.

Data collection procedure: After recommendation from ethical committee of Jinnah Hospital Lahore, and informed written consent from parents of the patients, neonates were divided in two groups by using random number tables. Group 1 was given probiotics named Bifidobacteria prophylactically (hiflora/gutcare one sachet daily) and group 2 neonates were given any probiotics. Patients were included in study from day 1 of admission till day 5 of life because incidence is maximum during that period of life. Followings were observed in all neonates

1. Feeding intolerance
2. Abdominal distension
3. Grossly bloody stools (naked eye blood in stool)
4. Change in colour of skin of abdomen (erythema)
5. X-ray abdomen

Effectiveness of probiotics was considered if neonate did not show above signs and symptoms of necrotizing enteocolitis. If any 4 out of these 5 clinical features observed during study period, the neonate was labeled as suffering from NEC. Data was analyzed in SPSS version 20. Quantitative variables such as gestational age, weight were presented as mean and standard deviation and qualitative variables were in the form of symptoms and signs of necrotizing enterocolitis and they were presented in the form of frequency and percentages. Relevance tests of significance such as Chi square test was used to compare the frequency of necrotizing enterocolitis in both groups. P value <0.05 was considered as significant.

RESULTS

We included total 300 neonates who had mean gestational age 33.27±1.48 weeks with minimum gestational age of 31weeks while maximum gestational age of neonates was 35 weeks. Neonates were randomly divided in two groups. Mean gestational age of neonates randomized to probiotic group was 33.38±1.46 weeks while mean gestational age of neonates randomized to control group was 33.15±1.49 weeks. There were 51(17%) neonates who had gestational age of 31 weeks, 62(20.7%) neonates had gestational age of 32 weeks, 24 (8%) neonates had gestational age of 33 weeks, 82(27.3%) neonates had gestational age of 34 weeks while 81(27%) neonates had gestational age of 35weeks. In this study, there were 165(55%) male and 135(45%) females. Male-to-female ratio was 1.2:1. The mean birth weight of neonates was 1.99±0.26kg with minimum and maximum birth weight of neonates was 1.6kg and 2.4kg respectively. Mean birth weight of neonates in probiotic group was 2.0±0.26kg while mean birth weight of neonates in control group was 1.99±0.26kg. There were 96(32%) neonates had feeding intolerance, 78(26%) had abdominal distension, 83(27.7%) had grossly bloody stool, 103(34.3%) had change in colour of skin of abdomen while 81(27%) had abnormal abdominal X-ray. There were 96(32%) neonates who had feeding intolerance, out of which 34(22.7%) belonged to probiotic group while 62(41.3%) belonged to control group. There were 78(26%) neonates who had abdominal distension, out of which 28(18.7%) belonged to probiotic group while 50(33.3%) belonged to control group. There were 83(27.7%) neonates who had grossly bloody stool, out of which 19(12.7%) belonged to probiotic group while 64(42.7%) belonged to control group. There were 103(34.3%) neonates who had change in colour of skin of abdomen, out of which 38(25.3%) belonged to probiotic group while 65(43.3%) belonged to control group. There were 81(27%) neonates who had abnormal abdominal X-ray, out of which 27(18%) belonged to probiotic group while 54(35%) belonged to control group. There were 44(14.7%) neonates who develop NEC while 256(85.3%) neonates were normal. There were 44 neonates who had NEC, out of which 7(4.7%) belonged to probiotic group while 37(24.7%) belonged to control group. There was significant difference between both study groups (p-value =0.000).

Table 1: Comparison of Gestational age, birth weight and NEC in both study groups

		Study groups	
		Probiotics (n=150)	Control (n=150)
	Mean	33.38	33.15
	SD	1.46	1.49
Birth weight (kg)	Mean	2.0	1.99
	SD	0.26	0.26
NEC	Present	7 (4.7%)	37 (24.7%)
	Absent	143 (95.3%)	113 (75.3%)
	p-value	< 0.001 (highly significant)	

Table 2: Distribution of sign & symptoms of NEC with respect to study groups

Sign and symptoms of NEC	Study groups		p-value	Significance
	Probiotics	Control		
Feeding intolerance	34 (22.7%)	62 (41.3%)	0.001	Significant
Abdominal distension	28 (18.7%)	50 (33.3%)	0.004	Significant
Grossly bloody stools	19 (12.7%)	64 (42.7%)	0.000	Significant
Change in colour of skin of abdomen	38 (25.3%)	65 (43.3%)	0.001	Significant
X-ray abdomen	27 (18.0%)	54 (35%)	0.000	Significant

DISCUSSION

There has been reported a consensual conclusion through multicentre trial which shows that the use of probiotics may reduce the incidence of NEC but it may not be able to reduce the fatality caused by NEC. On the other end, there persists an increased risk of sepsis in in patients receiving probiotics. Although there has been a huge argument in favour of routine use of probiotics through current literature, it is suggested to be additionally careful while administering it to patients. It is particularly important to consider caution in prescribing frequent use of probiotice because of the fact that the Food and Drug authority has yet not approved the use of microorganisms in infants who are preterm or low birth weight[1,7,8].

We included total 300 neonates who had mean gestational age at time of delivery of neonate 33.27±1.48 weeks. The neonates born between gestational age of 31-35weeks. The mean birth weight of neonates was 1.99±0.26kg. Literature has reported that the incidence of NEC and NEC case fatality rates are inversely related to birth weight and gestational age[9,10,11,12].

In this study, there were 165 (55%) male and 135 (45%) females. Male-to-female ratio was 1.2:1.No difference with respect to gender for development of NEC has been indicated through literature.A number of conditions having similar presentations to NEC exist. However, in order to distinguish these from NEC it is important to identify key signs and symptoms that include bloody stools after 8-10 days of birth, intolerance in feeding and abdominal distension. The pathognomonic findings on abdominal radiography are pneumatosis intestinalis, portal venous gas, or both.[13] In our study, we observed that 96 (32%) neonates had feeding intolerance, 78 (26%) had abdominal distension, 83 (27.7%) had grossly bloody stool, 103 (34.3%) had change in colour of skin of abdomen while 81 (27%) had abnormal abdominal X-ray.

In our study, there were 44 (14.7%) neonates who develop NEC while 256 (85.3%) neonates were normal. Other studies have comparatively lesser frequency than reported in our study. One NICHD study conducted on LBW infants showed that 7% newborns developed NEC. Another study also reported similar percentage ranging between 6.0-7.1% in 10 years. Yet one more population based study reported a percentage of 7% in very low birth weight infants in one year[9,14]. One study however, showed little difference in percentage range reporting an incidence of 4-13% of NEC in very low birth weight (VLBW) newborns[15].

There were 44 neonates who had NEC, out of which 7 (4.7%) belonged to probiotic group while 37(24.7%) belonged to control group. There were 256(85.3%) neonates who were normal, out of which 143(95.3%) belonged to probiotic group while 113(75.3%) belonged to control group. There was significant difference between both study groups (p-value=0.000). This showed that risk of developing NEC in preterm neonates given probiotics was 20% less than that of preterm neonates not given probiotics. A study conducted by Lin et al., showed that when newborns with VLBW were administered with prophylactic of probiotics, they showed a dramatic decrease in incidence of NEC from 5.3% to 1.1% with a relative risk reduction of 79%.16Similarly, Dani et al., reported that those newborns who are administered with probiotics have lesser risk of developing NEC (1.4%) compared to control group

(2.8%) with relative risk reduction of 50%, noting that this was not statistically significant[17].

Samanta et al., conducted a Randomized Control Trial (RCT) in which they argued that provision ofprophylacticprobioticshas the potential to significantly decrease the risk of development and morbidity associated with NEC in VLBW neonates in the Neonatal Intensive Care Unit (NICU). In their study the incidence of NEC in neonates with provision of probiotics supplementation was 5.5% compared to control group (Without probiotics supplementation) 15.8% which was highly significant statistically. (p-value<0.05) Moreover they reported that its use may enhance the maternal feeding and reduce the hospital stay as well.[18]There was one study with contrary results too. In this study, no significant difference in the frequency of NEC was reported with the use of probiotics and without the use of probiotics. Infact, the frequency of NEC was lower in control group (2%) compared to infants with probiotics (4.4%) having p-value greater than 0.05[19.]

A large scale systematic review included 11 Randomized Control Trials (RCTs) in 2176 preterm birth infants with gestational age of less than 34 weeks showed that administration of oral probiotics may not only decrease risk of development of NEC but also let down overall all cause mortality by more than 50% (p-value=0.00001). This actually indicates that how many neonatal deaths could be eliminated from our community by use of probiotics[20]. Yet one more large scale review including 11 trials on 2176 infants showed that the patients with probiotics had lesser frequency of NEC (2.4%) compared to control group (6.6%) with relative risk of 0.35[20]. However, there exists some controversy, as many of the randomized control trials used a combination of bifidobacterium, because otherwise less or no benefit of probiotics was reported. Where at one end researchers continue to explore further, in order to choose the optimum ways and safest combinations to use, at the other end it is being suggested to consider it unethical and unnecessary to go on with trials, but it is being enforced to start practicing and providing the probiotics in communities[8,20]. The significant potential of probiotics in our dietary supplementation can be easily seen by the two major mata-analysis discussed here that have reported crucial role of probiotics in prevention from NEC. However, the quantity and administration criteria of probiotics needs to be considered carefully considering the results of these, and other studies being confined to specific geographical and demographical areas. Therefore, it is important to reconsider the dose, and for what period of time the use of probiotics are needed to be administered before making it a routine for newborns[21].

CONCLUSION

The frequency of NEC was reported in 14% cases, out of which 4.7% belonged to probiotic group while 24.7% belonged to control group. Thus it was concluded from results of this study that probiotics given to pre-term neonates with low birth weight is effective and beneficial. Now, the efficacy of Bifidobacteria is proven, we can use it in treating NEC in preterm low birth weight neonates more efficiently than before and we are able to recommend probiotics in such delicate cases and can prevent neonates from mortality or severe morbidity.

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