

## Research Article

# Role of Enteral Probiotics for Prevention of Neonatal Necrotizing Enterocolitis (NEC) in Preterm Infants: A Randomized Placebo Controlled Trial

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### Abstract

**Background:** Necrotizing enterocolitis (NEC) is neonatal disease mostly occur in premature neonates, in which the parts of intestine get necrosis. Healthy probiotic agent may be given that can help to resist the condition. These are thought to be non-pathogenic & non-invasive, modify immune responses, do not develop resistance to antibiotics and develop from human microflora.

**Objective:** To compare the frequency of Neonatal necrotizing enterocolitis (NEC) with enteral probiotics versus placebo in preterm infants.

**Methods:** This randomized controlled trial was conducted at Department of Pediatrics, Mayo Hospital, Lahore for 6months. Total 220 cases were recruited via Non-probability consecutive sampling. Neonates were divided in two groups. One group (control) received milk (Breast or Formula) and second group (intervention) received probiotics Lactobacillus GG 3 billion units once daily with the milk for a week. Neonates were observed for NEC signs within 7days.

**Results:** The mean gestational age of neonates was 32.19±2.90 weeks. There were 133 (60.2%) males and 88 (39.8%) females. The mean weight of neonates was 1581.97±472.60grams. NEC was developed in 10 (9.1%) neonates with placebo while in 7 (6.4%) neonates received probiotics (p-value>0.05).

**Conclusion:** Our study did not support benefit of probiotics for prevention of NEC.

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**Keywords** | Necrotizing enterocolitis, probiotics, placebo, premature birth, neonates.

### Introduction

Improving survival rate of extremely low birth weight preterm neonates has motivated more attention. The medical technology has improved in last 2 decades, increasing the survival of such neonates, even neonates born during 22-23weeks.<sup>1</sup> NEC is an inflammation of intestines which mainly develops in premature neonates. The incidence

diverges from 0.3 to 2.4 per 1,000 live births and around 7-11% in very low birth weight neonates. It affect both genders equally. NEC is observed more common in very low birth weight and very premature neonates. But that is inversely proportion to increasing gestational age and birth weight among normally grown preterm infants,<sup>2,3</sup> i.e. around 5-10% neonates delivered at term.<sup>4,5</sup> In many cases of NEC, usually

enteral feeding is given; it develops after 7 days of life after beginning of enteral feeding.<sup>6</sup> The mortality rate for neonates diagnosed with NEC is around 20-50%.<sup>7</sup>

Prevention can help to decrease the development of NEC. Probiotics and breast-milk are two main preventive methods.<sup>8</sup> The detection of appropriate probiotics bacterial species, involved in gut homeostasis and potential therapeutic benefits have led to attentiveness in probiotics use to prevent NEC.<sup>9,10</sup> Probiotic supplementation was proposed as new promising interference to prevent NEC.<sup>12</sup> Researchers also did not find sepsis and other side effects.<sup>12-15</sup>

So this study was aimed is to compare the frequency of necrotizing enterocolitis with and without probiotics in preterm neonates. This study would help us to evaluate the role of probiotics in preventing the development of NEC in pre-mature neonates as previous studies done on this topic have not yet fully established the role of probiotics in preventing NEC. Moreover probiotic therapy is cheap and safe and thus will be a promising intervention for preventing NEC. But it is not clearly shown that whether the use of probiotics prophylactically is beneficial for premature neonates.

## Objective

To compare the frequency of Neonatal necrotizing enterocolitis (NEC) with enteral probiotics versus placebo in preterm infants.

## Methods

This Randomized controlled trial was conducted at Department of Pediatric Medicine, Mayo Hospital, Lahore for 6 months i.e. June 2014 to Dec 2014. Total number of 220 cases; 110 in both groups is estimated with 80% power of study, 5% significance level with estimated frequency of NEC i.e. 8% with probiotics and 16% without probiotics. Preterm infants (<37 weeks on antenatal record) of either gender with Birth weight < 2500g admitted to NICU were recruited via non-probability consecutive sampling. Neonate having major congenital malformations like visceral, skeletal, dysmorphism, preterm neonates having associated morbidity like asphyxia, sepsis, congenital heart disease, on ventilator, intubation or very preterm neonates (<30 weeks of gestation) were excluded. A written consent form was taken from

their parents or guardians. Demographic of neonates were also be obtained. Patients were divided randomly in two groups through lottery method. Controls were given milk (Breast or Formula) and patients in interventional group were given probiotics Lactobacillus GG 3 billion units once daily along with milk for one week (7 days) and both groups was receive same standard antibiotics and neonatal care in the form of temperature and glycemic control and electrolyte balance. Both groups were observed for development of any signs of NEC within 7 days. It was measured as Bell's NEC classification as presence of following sign and symptoms of NEC after 7 days of life:

- i. Feeding intolerance
- ii. Abdominal distension
- iii. Blood in stool
- iv. Change in skin color of abdomen
- v. Distended gut loops on abdominal X-ray

All this information was recorded on study Performa. Data was analyzed by using SPSS v-21. Both groups were compared by using chi-square test. P-value  $\leq$  0.05 was taken as significant.

## Results

The mean gestational age of neonates at birth was  $32.19 \pm 2.91$  weeks. Out of 220 patients, 132 (60%) were males and 88 (40%) were females. The male to female ratio was 1.5:1. The mean weight of neonates was  $1581.97 \pm 472.60$  grams ( $1.582 \pm 0.473$  kg). Table 1

Among patients randomized to placebo group, feeding intolerance was observed in 15 (13.6%) neonates, abdominal distension in 10 (9.1%) neonates, grossly bloody stools in 21 (19.1%) neonates, erythema, discoloration, abdominal wall edema was observed in 15 (13.6%) neonates and x-ray abdomen was observed in 23 (20.9%) neonates. Among patients randomized to probiotics group, feeding intolerance was observed in 16 (14.5%) neonates, abdominal distension in 7 (6.4%) neonates, grossly bloody stools in 20 (18.2%) neonates, erythema, discoloration, abdominal wall edema was observed in 16 (14.5%) neonates and x-ray abdomen was observed in 20 (18.2%) neonates. Table 2

NEC was developed in 10 (9.1%) neonates with placebo while in 7 (6.4%) neonates with probiotics.

The difference between both groups was found to be insignificant ( $p$ -value $>0.05$ ). Table 3

**Table 1:** Demographics of Neonates

N	220
Gestational Age (Weeks)	32.19±2.90
Gender	
Male	132 (60%)
Female	88 (40%)
Weight (grams)	1581.97±472.60

**Table 2:** Comparison of Clinical Symptoms on 7th Day in both Groups

Clinical Symptoms on 7 <sup>th</sup> day	Study group	
	Placebo	Probiotics
Feeding tolerance	15 (13.6%)	16 (14.5%)
Abdominal distention with or without tenderness	10 (9.1%)	7 (6.4%)
Grossly bloody stools	21 (19.1%)	20 (18.2%)
Erythema, discoloration, abdominal wall edema	15 (13.6%)	16 (14.5%)
X-ray abdomen	23 (20.9%)	20 (18.2%)

**Table 3:** Comparison of NEC in both groups

		Study group		Total
		Placebo	Probiotics	
NEC	Yes	10 (9.1%)	7 (6.4%)	17 (7.7%)
	No	100 (90.9%)	103 (93.6%)	203 (92.3%)
Total		110 (100%)	110 (100%)	220 (100%)

Chi-square = 0.574,  $p$ -value = 0.449 (Insignificant)

## Discussion

Though NEC is still one of the major challenge in field of neonatology, much information has already been attained to reveal its pathogenesis, permitting the better way of NEC prevention and management. Special attention is attained by probiotics supplementation for preterm neonates, particularly neonates who also have very low birth weight, in an effort to decrease the incidence of NEC. Intestinal flora is thought to have the substantial role in development of NEC. The advantageous effect of pro-biotics as “good microbes” to prevent NEC in premature and low birth weight neonates have already been evaluated by some trials, but according to the results of our study, there was no difference detected whether neonates were given probiotics or not in preventing NEC.<sup>12</sup>

Probiotics combat with other microorganisms in intestines for binding sites and substrates, boost the

IgA mucosal reaction, progress mucosal obstacle, decrease mucosal permeability, motivate intestinal mucosal lactase activity, improve anti-inflammatory cytokines & produce wide range of anti-microbial materials like bacteriocins, microcins, reuterin, hydrogen peroxide and hydrogen ions.<sup>16-17</sup>

It is reported that ENC can effect around 15% preterm neonates while 7% term neonates and is major cause of admissions in NICU. Mortality due to NEC is about 25–30% cases. Remaining about 25% who survived, have to go through prolonged consequences of gastrointestinal tract. The frequency of NEC decreases as gestational age increases and preterm birth ( $<37$  weeks) is the main and important risk factor of NEC.<sup>18</sup>

Thus we included total 220 neonates presented in NICU and conducted a randomized trial with the mean gestational age of neonates was 32.19±2.90 weeks. The mean weight of neonates was 1581.97±472.60grams (1.582±0.473kg).

Thus we compared the two groups to check the efficacy of probiotics and placebo to prevent NEC. But we obtained insignificant results. The neonates who were randomized to placebo, 10 (9.1%) neonates developed NEC while neonates randomized to probiotics, 7(6.4%) neonates developed NEC and this was insignificant ( $p$ -value $>0.05$ ). Thus our study result has shown that there is no difference in developing NEC whether probiotics are given or not. Results of our study coincides with that of another study showing no differences were detected in terms of NEC risk reduction although it was observe that a clear trend in the reduction of NEC frequency in the cases: 6 (8%) versus 12 (16%) in the control group ( $p$ -value $>0.05$ ).<sup>19</sup>

Recent evidence collected through therapeutic trials proposed that probiotics are efficient in reducing the frequency of NEC among preterm neonates while they are currently the most promising way to avoid this deadly syndrome. But, the data regarding safety and optimal dosing of probiotics is limited, which contraindicate the extensive clinical use in preterm neonates.<sup>20</sup>

Rising evidence proposed the important role of gut colonization in neonate during development of immune system. The likelihood to alter the coloniza-

tion inside the gut by using probiotic supplementation during childhood may help to avert atopic diseases. Data of 17 trials, including 4755 neonates (2381=probiotics and 2374=controls), were used in meta-analysis. Neonates given probiotics showed significantly less risk of eczema (RR:0.78 [95% CI:0.69-0.89],  $P<0.001$ ) than controls, specifically who were given mixture of probiotics (RR:0.54 [95% CI:0.43-0.68],  $P<0.001$ ). But insignificant difference was observed for asthma prevention (RR:0.99 [95% CI:0.77-1.27],  $P>0.05$ ), wheezing (RR:1.02 [95% CI:0.89-1.17],  $P>0.05$ ) & rhino-conjunctivitis (RR:0.91 [95% CI:0.67-1.23],  $P>0.05$ ). These results proposed that supplementation of probiotic can help to prevent infantile eczema, and proposed a new possible indication for the use of probiotic during pregnancy and infancy.<sup>21</sup>

Species of *Bifidobacterium* genus colonies are normally found in gut of a healthy human and variations in number and configuration of bacterium populations is one of greatest common characteristics found in gastrointestinal diseases. The prophylactic probiotics use, comprising bifido-bacteria strains, to preserve function of a healthy intestine is well-known. Probiotics are also recommended as therapeutic agents for gastrointestinal diseases.<sup>22</sup> The use of the following probiotics including *Lactobacillus rhamnosus* and *Saccharomyces boulardii* may be deliberated for management of acute gastroenteritis in pediatrics as an adjunct to standard rehydration therapy: *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*.<sup>23-24</sup>

## Conclusion

Thus through this study, we have proved controversy observed in literature and we did not find probiotics as beneficial for prevention of NEC. However probiotic therapy is cheap and safe. So whether probiotics are prescribed or not in neonates presenting in NICU, the results would be the same. In conclusion, results of this study do not support the beneficial role of probiotics in order to prevent NEC. So in future we will not prescribe probiotics as they may cause other additional problems.

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