



## Efficacy of probiotics to prevent necrotizing enterocolitis in low birth weight preterm neonates.

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## INTRODUCTION

Necrotizing enterocolitis (NEC) is considered a severe intestinal inflammatory disease among newborns.<sup>1</sup> Exact pathogenesis of NEC is not fully known but it might be linked with inapt innate immune response or higher inflammatory responses related to immature intestine.<sup>2</sup> In developed countries, incidence of NEC among neonates is estimated to be around 2%.<sup>3</sup> In Pakistan, incidence of NEC is calculated to be around 14% among preterm newborns which represent alarming figures.<sup>4</sup>

Probiotics have been widely utilized for the promotion of health and support while its useful role for NEC is being widely studied.<sup>5</sup> Many researchers have highlighted improvement of mucosal defense related to human intestine with the use of probiotics.<sup>6</sup> Probiotics have living microorganisms which reside in the gut and contribute beneficial effects. Some of

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**ABSTRACT... Objective:** To compare the efficacy of probiotics in prevention of necrotizing enterocolitis (NEC) among low birth weight (LBW) preterm neonates. **Study Design:** Randomized controlled trial. **Setting:** Department of Pediatric Medicine, Unit-II, Services Hospital, Lahore. **Period:** September 2019 to February 2020. **Material and Methods:** A total of 260 LBW preterm neonates were enrolled. All the neonates were allocated to 2 groups with equal number of cases (130 in each group). Group-A was given probiotics whereas placebo was administered in Group-B. All the cases were admitted and follow ups were made up until 7<sup>th</sup> day. Occurrence of NEC was recorded among both groups. **Results:** Out of a total of 260 LBW preterm neonates, 142 (54.6%) were male and 118 (45.4%) female. Overall, mean age was noted to be 1.48±0.50 days. Table-I shows that there was no statistical difference among neonates of both study groups in terms of age, gestational age and birth weight ( $p>0.05$ ). Five (3.8%) neonates in Group-A and 14 (10.8%) in Group-B were found to have NEC. Efficacy of treatment in Group-A was significantly higher in comparison to Group-B. **Conclusion:** Probiotics are effective in the prevention of NEC in preterm LBW neonates. Prophylactic usage of probiotics among preterm neonates is noted to be helpful in avoiding development of NEC.

**Key words:** Efficacy, Low Birth Weight, Necrotizing Enterocolitis, Probiotics, Preterm.

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the most commonly found microorganisms in the most frequently utilized probiotics are genera lactobacillus, bifidobacterium and saccharomyces. Most appreciated benefits of probiotics include modifications to intestinal permeability as well as increased mucosal IgA effects that increase synthesis of anti-inflammatory cytokines and protect mucosa from residing pathogens.<sup>7</sup> Researchers have also pointed out helpful effects of probiotics in minimizing incidence as well as severity of NEC. Children having very low birth weight (VLBW) using probiotics have been noted to have 100% prevention from developing NEC in comparison to 94.1% among controls ( $p=0.01$ ).<sup>8</sup> Another study reported that there was not much difference in terms of benefits associated with probiotics in comparison to controls for the prevention of NEC ( $p=0.51$ ).<sup>9</sup>

We planned this study with an aim to compare

efficacy of probiotics for the prevention of NEC among LBW preterm neonates. Our results are thought to assist reduction in NEC related mortality as well as morbidity. Probiotics are considered affordable choice and can help the community fighting against a severe form of disease like NEC in an affordable manner. Variations exist regarding potential benefits of probiotics among LBW preterm newborns. To the best of our knowledge, this will be 1<sup>st</sup> local research to compare the effectiveness of probiotics for the prevention of NEC among LBW preterm neonates. Our study will also provide local evidence in showing whether probiotics are helpful in the prevention of NEC or not among LBW preterm newborns.

## MATERIAL & METHODS

This randomized controlled trial (RCT) was conducted at the Department of Paediatric Medicine, Unit-II, Services Hospital, Lahore, from September 2019 to February 2020. Approval from Institute's Ethical Review Board was sought. Informed consent was sought from parents/guardians of all the cases. No support from any pharmaceutical company was taken in this study.

A sample size of 260 (130 in each group) was estimated considering 80% power of test, 5% significance level and anticipated efficacy of probiotics as 100% and 94.05% among cases and controls respectively<sup>8</sup> for the prevention of NEC among LBW preterm neonates.

Neonates of both genders, below 3 days of age, presenting with gestational age between 30-37 weeks (confirmed through antenatal maternal records) with birth weight below 1500 grams (as per medical record of newborns) were registered. Those having antifungal prophylactic treatment or mechanical ventilation, early onset sepsis (increased CRP above 6mg/dl) or having hepatic failure (aspartate transaminase, alanine aminotransferase levels above 3 folds than reference range) were excluded. Neonates having congenital anomalies, congenital heart disease or birth asphyxia or with persistent cyanosis or requirement of oxygen inhalation were also excluded.

Demographic characteristics of neonates like name, gender, age, gestational age as well as birth weight were recorded. All neonates were randomly divided among 2 equal groups (Group-A and Group-B) adopting lottery method. Among neonates in Group-A, probiotics (2gm x Pox x OD) were given while neonates in Group-B were given placebo. All neonates were admitted and enteral feeding (mother feed 10% o/w) was given whereas all study participants were followed up until 7 days of hospitalization. Occurrence of NEC was noted at the end of 7<sup>th</sup> day of treatment as presence of any four of the 5 signs and symptoms: i) feeding intolerance / vomiting  $\geq$  1 episodes per 24 hours, ii) abdominal distension (as per clinical examination), iii) grossly bloody stool, iv) changes in the color (pale yellow) of abdominal skin, v) X-ray abdomen (distended gut loops). All neonates who developed NEC were managed according to hospital protocol that included NPO, intravenous fluids, intravenous antibiotics and surgical intervention if needed. All study information was recorded on a specifically designed template and analyzed using SPSS version 24.0. For quantitative variables, mean and standard deviations were calculated whereas qualitative variables were represented in terms of frequencies and percentages. Chi-square test was utilized for the comparison of efficacy between study groups considering p value  $\leq$  0.05 as significant.

## RESULTS

Out of a total of 260 LBW preterm neonates, 142 (54.6%) were male and 118 (45.4%) female. Overall, mean age was noted to be  $1.48 \pm 0.50$  days. Table-I shows that there was no statistical difference among neonates of both study groups in terms of age, gestational age and birth weight ( $p > 0.05$ ).

Table-II highlights that efficacy was observed in a total of 231 (92.7%) neonates whereas significantly more neonates in Group A were found show efficacy in comparison to neonates in Group-B ( $p = 0.032$ ).

Table-III shows efficacy of treatment with respect to age, gestational age, gender and

gestational age. Age did not seem to make any significant impact on efficacy among both study groups. Male neonates in Group-A were having significantly higher efficacy in comparison to neonates in Group-B (97.4% vs. 87.9%, p=0.027). Efficacy among female neonates was also better

in Group A in comparison to Group-B (94.4% vs. 90.6%, p=0.436) but it did not reach statistical significance. (Table-III)

Table-IV shows efficacy of treatment with respect to birth weight.

Characteristics	Group-A (n=130)	Group-B (n=130)	P-Value
Age in days (Mean±SD)	1.50±0.50	1.45±0.50	0.421
Gestational Age in weeks (Mean±SD)	34.01±1.39	34.08±1.33	0.679
Birth Weight in grams (Mean±SD)	1245.12±137.66	1243.63±155.29	0.935

**Table-I. Characteristics of study participants (n=260)**

Efficacy of Treatment	Group-A (n=130)	Group-B (n=130)	P-Value
Yes	125 (96.2%)	116 (89.2%)	0.032
No	5 (3.8%)	14 (10.8%)	

**Table-II. Efficacy of treatment among both study groups (n=260)**

Efficacy	Age					P-Value	
	1-Days		P-Value	2-Days			P-Value
	Group-A	Group-B		Group-A	Group-B		
Yes	63(96.9%)	64(88.9%)	0.071	62(95.4%)	52(89.7%)	0.223	
No	2(3.1%)	8(11.1%)		3(4.6%)	6(10.3%)		
Efficacy	Gender					P-Value	
	Male		P-Value	Female			P-Value
	Group-A	Group-B		Group-A	Group-B		
Yes	74(97.4%)	58(87.9%)	0.027	51(94.4%)	58(90.6%)	0.436	
No	2(2.6%)	8(12.1%)		3(5.6%)	6(9.4%)		
Efficacy	Gestational Age					P-Value	
	32-33 Weeks		P-Value	34-36 Weeks			P-Value
	Group-A	Group-B		Group-A	Group-B		
Yes	51(98.1%)	41(87.2%)	0.036	74(94.9%)	75(90.4%)	0.276	
No	1(1.9%)	6(12.8%)		4(5.1%)	8(9.6%)		

**Table-III. Efficacy of treatment with respect to Age, Gender and Gestational Age (n=260)**

Birth Weight (grams)	Groups	Efficacy		P-Value
		Yes (n=141)	No (n=19)	
1000-1100	A	22(91.7%)	2(8.3%)	0.892
	B	29(90.6%)	3(9.4%)	
1101-1200	A	31(96.9%)	1(3.1%)	0.732
	B	19(95%)	1(5%)	
1201-1300	A	27(100%)	0(0%)	0.019
	B	22(81.5%)	5(18.5%)	
1301-1500	A	45(95.7%)	2(4.3%)	0.287
	B	46(90.2%)	5(9.8%)	

**Table-IV. Efficacy of treatment with respect to Birth weight (n=260)**

## DISCUSSION

Necrotizing enterocolitis has been a widely researched topic in the recent decades. Role of probiotics for the avoidance of NEC has been studied all around the world in systemic reviews and meta-analyses but variation and controversy surrounds definitive conclusions.<sup>10,11</sup> This study was aimed at providing local experience from Pakistan in the shape of a RCT.

In the present study, we found only 3.8% neonates using probiotics to have NEC in comparison to 10.8% in the control group and the difference between both study groups was significantly better favoring Group-A ( $p=0.032$ ). Age did not seem to have any significant impact in terms of efficacy among both study groups. Yang Y et al in their meta-analysis about the role of probiotics for the prevention of NEC noted that probiotics were noted to significantly minimize the risk of NEC among preterm neonates while gestational age did not seem to affect the outcomes.<sup>12</sup> They also found that probiotics were not shown to enhance the risk of sepsis or deaths among treated neonates. Probiotics were also found not to have any adverse effects on usual feeding or growth of the neonates. These results are favoring our findings about the efficacy of probiotics among LBW preterm neonates for the prevention of NEC. Braga TD observed probiotics to impart significant efficacy for the prevention of NEC along with improving intestinal motility as well.<sup>13</sup> In their double blind RCT, No case of NEC occurred in their study among VLBW preterm neonates using probiotics. Dilli D also noted significantly reduced rates of NEC occurring ( $P<0.001$ ) among neonates using probiotics (4.0%) when compared to prebiotics (12.0%) and placebo (18.0%).<sup>14</sup> Deshpande G et al in their meta-analysis evaluating 11 RCTs observed 2176 newborns using probiotics with gestational age less than 34 weeks to have significantly less all-cause mortality and NEC occurring.<sup>11</sup>

Some researchers have also reported conflicting results which are different from current findings. Demirel G et al in their study found that efficacy of probiotics for the prevention of NEC was not significantly better than the comparator groups (4.4%

vs. 5.1%,  $p=1.0$ ).<sup>15</sup> Rouge C et al also noted not much difference among neonates of probiotic and control groups in the prevention of NEC (4.4% vs. 2.0%).<sup>9</sup>

Increased understanding about the role of probiotics among neonates has attracted many neonatologists round the world. Probiotics are also described as “commensal or protective bacteria” which accompany numerous benefits contributing to minimize the risk for the development of NEC among premature newborns.

Our study had few limitations as well. As we only noted short term efficacy of probiotics in the present study, we are still unable to confirm the long-term safety and effects of probiotics on immune as well as gastrointestinal functioning among neonates. Different types of probiotics using different strains around the world might result in inconsistent findings so further RCTs involving different sets of populations are required to further confirm the finding of this present study.

## CONCLUSION

Probiotics were found effective for the prevention of NEC among low birth weight preterm neonates. Prophylactic usage of probiotics among preterm neonates is noted to be helpful in avoiding development of NEC.

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2	Farrukh Saeed	Study concept, Supervision, Proof Reading.	
3	Shahla Tariq	Methodology, Literature Review.	
4	M. Azhar Farooq	Discussion, Data interpretation.	
5	Sanauallah Khan	Drafting, Literature Review.	
6	Syeda Faiza Akhter	Data Collection, Introduction.	