Original Research Article

EFFECTIVENESS OF ORAL PROBIOTICS IN PREVENTION OF NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS

ABSTRACT

OBJECTIVE: To determine the efficacy of probiotics in prevention of necrotizing Enterocolitis in preterm infants

MATERIALS AND METHODS: This randomized controlled trial was conducted at pediatric Department of CMH Muzaffarabad AJK. All preterm bottle and NG feed neonates with age of more than 24 hours and both genders were included. All the study subjects were divided into two groups randomly as group-A and group-B. Group-A was given probiotics (named Bifidobacterium prophylactically, hiflora, / gutcare, one sachet per day) while in Group-B probiotics was not given. All the cases were taken under observation, if they need any critical or intensive care they were excluded from study and other treatments were given as per hospital protocol. Patients were followed for 7 days efficacy in both groups was measured in terms of no occurrence of NEC during one week. All related data was collected on study proforma.

Results The average age of the neonates of the Probiotic group was 11.77 ± 6.52 days and in control group was 13.41 ± 6.86 days. There were 42.1% boys and 57.9% girls were in Probiotic group, while 54% males and 46% females were in control group. In Probiotic group only 5(2.1%) cases developed NEC while in control group 28(11.9%) cases developed NEC, the frequency of NEC was statistically higher in control group, resulting the oral probiotic showed significant efficacy (p- 0.001).

Conclusion: Oral probiotics have been found to be efficacious, noninvasive, and beneficial in the prevention of NEC. Probiotics must be utilized to prevent necrotizing enterocolitis in preterm newborns in the future, in order to lessen the associated complications and infant mortality.

Keywords: Preterm infants, low birth weight, prevention, necrotizing enterocolitis, Probiotics

INTRODUCTION

Necrotizing enterocolitis (NEC) is a multifactorial illness caused by the combination between the loss of intestinal mucosa integrity and the host's responses to the damage or injury [1]. Mucosal injury, intestinal ischemia, ulceration, edema, and passage of bacteria or air through the wall, leading in mucosa and intestinal wall necrosis, are all factors [1]. This condition has become a global problem specifically in preterm birth and very low birth weight neonates, with highly variable incidence i.e. reported as 2.6% to 28%, and causing 1% to 5% of admissions to the neonatal intensive care unit (NICU) [2]. Probiotics have been investigated the most in newborn medicine during the last several years [3]. In premature neonates around the world, optimizing enteral nutrition is a top priority. In premature infants, probiotics have been shown to increase gut maturation and

function [4]. So far different preventive interventions have been studied by different authors to prevent and minimize the risk of NEC in cases of preterm birth and low birth weight [5]. So, the use of probiotic in premature infants for prevention of NEC include numerous benefits such as a decrease in the intestinal reservoir of the more pathogenic strains, improved enteral nutrition, and decreased reliance on intravenous nutrition, an enhanced gut mucosal barrier to the bacteria and products of the bacteria, increased expression of protective immunity, a decrease in the occurrence of sepsis, and antibacterial drugs use [6]. Few studies are done in order to see the reduction rate in NEC, as a study was done a decade ago and they reported that frequency of NEC lesser in cases who were given probiotic as compared to control group with significant difference.[7,8] A local study reported that NEC was developed in 4.7% cases of probiotic group while in control group 24.7% developed NEC.[9] The current study is done to see role of probiotics in pre-term neonates in terms of prevention of NEC incidence in our local population, as data on local population is limited in which the NEC was reported higher (in probiotic and control group)[9] when compared with other studies.[7,8] So, higher frequency of published in local population motivated us to do this study, the results of this study may helpful to and was implemented in future to decrease the risk of NEC. Moreover, in the probiotic's treatment, the symbiotic organisms can stimulate the intestinal barrier function's maturity, inhibit the growth of potentially harmful organisms, increase the generation of anti-inflammatory cytokines, antioxidant activities enhancement, and apoptosis regularities, among other benefits to the host at the cellular level.

MATERIALS AND METHODS

This randomized controlled trial was conducted at pediatric Department of CMH Muzaffarabad AJK during a study period of six months from April 2018 to Oct 2018. All preterm bottle and NG feed neonates with necrotizing enterocolitis with age of more than 24 hours and both genders were included. All the neonate on mechanical ventilator support, IUGR, birth asphyxia, neonates having need of oxygen inhalation, congenital cyanotic heart diseases and persistent cyanosis were excluded. The study was done receiving approval from the hospital's ethical committee. After taking informed consent from parents or attendants 470 cases meeting inclusion criteria were taken. All data was taken from inpatient department of pediatric medicine of CMH Muzaffarabad AJK. The basic information like age, sex and contact details was taken than their gestational and birth history was noted from their available medical record or from parents. All the study subjects were divided into two groups randomly as group-A and group-B. Group-A was given probiotics (named Bifidobacterium prophylactically, hiflora, / gutcare, one sachet per day) but in Group-B probiotics was not given. All the cases were under observation, if they need any critical or intensive care they were excluded from study and other treatments were given as per hospital protocol. Patients were followed for 7 days efficacy in both groups was measured in terms of no occurrence of NEC during one week. All related data was collected on given proforma by researcher himself. Using SPSS version 22, all data was entered and analyzed using same software.

RESULTS

The average age of the neonates of the Probiotic group 11.77 ± 6.52 days and in control group was 13.41 ± 6.86 days. Mean gestational age in Probiotic group was 32.07 ± 2.50 weeks and in control group the mean gestational age was 32.06 ± 2.61 weeks. Mean weight of babies was 2002.88 g in Probiotic group and in control group the mean weight of babies was 2042.47 ± 305.74 g. There were 226(48.1%) boys and 244(51.9%) were girls while in Probiotic group there were 99(42.1%) male and 136(579%) female cases whereas in control group there were 127(54%) male and 108(46%) female cases. **Table - 1**

In Probiotic group only 5(2.1%) cases developed NEC while in control group 28(11.9%) cases developed NEC, the frequency of NEC was statistically higher in control group, (p-0.001). **Table -2**

The frequency of NEC was statistically significant according to gestational age, gender and weight (p-0.001) as shown in t**able -3**

Table-1. Mean comparison of Age (days) in both study groups n=224

Variables		**Mean**	**S. D**	**Minimum**	**Maximum**
Age (years)	Probiotic	11.77	6.52	1.00	24.00
	Control	13.41	6.86	1.00	24.00
Gestational age (weeks)	Probiotic	32.07	2.50	28.00	36.00
	Control	32.06	2.61	28.00	36.00
Weight (g)	Probiotic	2002.88	292.43	1501.00	2498.00
	Control	2042.47	305.74	1501.00	2496.00
Gender	**Frequency (%)**				
		Probiotic	**Control**	**Total**	
	Male	99(42.1%)	127(54.0%)	226(48.1%)	
	Female	136(57.9%)	108(46.0%)	244(51.9%)	

Table-2. Comparison of NEC in both study groups n=224

Variable		**Study group**		**Total**	**p-value**
		Probiotic	**Control**		
NEC	***Yes***	5(2.1%)	28(11.9%)	33(7.0%)	0.0001
	No	230(97.9%)	207(88.1%)	437(93.0%)	
Total		235(100.0%)	235(100.0%)	470(100.0%)	

Table-3. Comparison of NEC in both study groups with respect to gestational age, gender and weight n=224

Variables		*NEC*	Study group		p-value
			Probiotic	**Control**	
Gestational age (weeks)	**28-32**	***Yes***	3(2.4%)	14(10.9%)	0.007
		No	123(97.6%)	115(89.1%)	
	32.1-36	***Yes***	2(1.8%)	14(13.2%)	0.001
		No	107(98.2%)	92(86.8%)	
Gender	**Male**	***Yes***	1(1.0%)	15(11.8%)	0.002
		No	98(99.0%)	112(88.2%)	
	Female	***Yes***	4(2.9%)	13(12.0%)	0.006
		No	132(97.1%)	95(88.0%)	
Weight (grams)	***1501-2000***	***Yes***	2(1.7%)	16(15.0%)	0.001
		No	115(98.3%)	91(85.0%)	
	2001-2499	***Yes***	3(2.5%)	12(9.4%)	0.025
		No	115(97.5%)	116(90.6%)	

DISCUSSION

In premature newborns, necrotizing enterocolitis (NEC) is among the most surprising and deadly infections. Till now, no one cause for NEC has been identified; nevertheless, most studies agree that the pathophysiology is multifaceted and has been linked to enteral feedings, intestinal ischemia, and viral reasons [10]. The ischemia or toxic event that causes damage to the juvenile gastrointestinal mucosa and loss of mucosal integrity is regarded to be the precursor to NEC. [10,11]. It is a significant and costly issue, particularly for newborn babies with a low birth weight (VLBW). It's critical to pay attention to respiratory condition, electrolyte balances, acid-base, and coagulation profile [12]. Depending on the severity of the condition, in NEC, the death rate of the newborns is 10 ->50% among those having birth less than 1500 g, compared to a mortality rate of 0-20% for neonates having birth weight more than 2500 g. In current study in Probiotic group only 5(2.1%) cases developed NEC while in control group 28(11.9%) cases developed NEC, the frequency of NEC was statistically higher in control group, p-value < 0.001. Few studies are done in order to see the reduction rate in NEC, as a study was done a decade ago and they reported that frequency of NEC lesser in cases who were given probiotic (in 1.84%) as compared to control group (6.45% infants) with significant difference (p-0.02) [7]. In current study we also found the NEC was less in treatment group as compared to placebo. Another study was done also reported significantly lesser NEC in probiotics group (1.1%) when compared to control group (5.3%), (p- 0.04) [8]. A local study reported that NEC was developed in 4.7% cases of probiotic group while in control group 24.7% developed NEC [9]. These statistics are in agreement to our findings too. Consistently in a prospective randomized controlled trial

study reported the probiotic group had a reduced risk of NEC only 2.7% compared to the control group as 9.3%, and the death rate was also significantly lower than the controls, hence premature infants, probiotic therapy has decreased the rate of necrotizing enterocolitis and its severity. [13] Another a systematic review was carried out to analyze the effectiveness of the probiotics in the prevention of NEC among preterm infants babies, and they observed that the probiotics significantly prevented the NEC in the very low birth weight preterm infants (p 0.00001); although, there is inadequate event till now regarding specific probiotic strain that should be used, as well as the effectiveness of the probiotics in high-risk populations like extremely-low-birthweight newborns, before widespread use.[14] Similarly, a meta-analysis found that the risk of NEC was much lower in the probiotic group, and that probiotic supplementation could dramatically reduce the risk of NEC in preterm newborns independent of gestational age or NEC stage [15]. Another meta-analysis was conducted in 2009 to evaluate the safety and effectiveness of prophylactic enteral probiotics against placebo or no therapy in preventing severe NEC and other morbidities among preterm newborns. Nine trials with a total of 1,425 infants were involved in the study. Enteral probiotic treatment dramatically reduced the frequency of the NEC severity and rate of the death, according to the findings of the study. The probiotics supplementary organism caused no systemic infection in the experiments. As a result of the study's findings, enteral probiotic supplementation reduces the incidence of severe NEC and mortality in preterm newborns [16]. There were several limitations as a small sample size and single center study and not followed the patients more than one week and not followed the patients those were admitted in NICU for the ventilation support. Hence large-scale studies should be done on this subject.

CONCLUSION

Oral probiotics have been found to be efficacious, noninvasive, and beneficial in the prevention of NEC. Probiotics must be utilized to prevent necrotizing enterocolitis in preterm newborns in the future, in order to lessen the associated complications and infant mortality.

Ethical Approval:
As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent
As per international standard, parental written consent has been collected and preserved by the author(s).

REFERENCES

1. Bernardo WM, Aires FT, Carneiro RM, de Sá FP, Rullo VEV, Burns DA. Effectiveness of probiotics in the prophylaxis of necrotizing enterocolitis in preterm neonates: a systematic review and meta-analysis. J de Pediatr 2013;89(1):18-24.

2. Chowdhury T, Ali MM, Hossain MM, Singh J, Yousuf A, Yasmin F, et al. Efficacy of probiotics versus placebo in the prevention of necrotizing enterocolitis in preterm very low birth weight infants: a double-blind randomized controlled trial. J Coll Physicians Surgeons Pak. 2016;26(9):770-4.
3. Dermyshi E, Wang Y, Yan C, Hong W, Qiu G, Gong X, et al. The "golden age" of probiotics: a systematic review and meta-analysis of randomized and observational studies in preterm infants. Neonatol. 2017;112(1):9-23.
4. Athalye-Jape G, Deshpande G, Rao S, Patole S. Benefits of probiotics on enteral nutrition in preterm neonates: a systematic review–. Am J Clinic Nutr. 2014;100(6):1508-19.
5. AlFaleh K, Anabrees J, Bassler D, Al-Kharfi T. Cochrane Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants. Evid Based Child Health. 2012;7(6):1807-54.
6. De Magistris A, Marcialis MA , Puddu M , Dessì A , Irmesi R, Coni E, et al. Embryological development of the intestine and necrotizing enterocolitis. J Pediatr Neonat Individual Med. 2016;5(2):e050213.
7. Lin H-C, Hsu C-H, Chen H-L, Chung M-Y, Hsu J-F, Lien R-i, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatr. 2008;122(4):693-700.
8. Lin H-C, Su B-H, Chen A-C, Lin T-W, Tsai C-H, Yeh T-F, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatr. 2005;115(1):1-4.
9. Hussain M, Jabeen S, Subhani RUH. Role of probiotics in prevention of nectrotizing enterocolitis in preterm low birth weight neonates. Pak J Med Health Sci. 2016;10:455-9.
10. Wójkowska-Mach J, Różańska A, Borszewska-Kornacka M, Domańska J, Gadzinowski J, Gulczyńska E, Helwich E, Kordek A, Pawlik D, Szczapa J, Heczko PB. Necrotising enterocolitis in preterm infants: epidemiology and antibiotic consumption in the Polish neonatology network neonatal intensive care units in 2009. PLoS One. 2014 Mar 21;9(3):e92865.
11. Cobb BA, Carlo WA, Ambalavanan N. Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. Pediatrics. 2004;113(1):50-3
12. Ganapathy V, Hay JW, Kim JH. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. Breastfeeding Med. 2012;7(1):29-37.
12. Meha T, Jaiswal AK, Raja A, Sinha AK. Role of oral probiotics in prevention of necrotising enterocolitis in preterm neonates in a tertiary care centre in Northern India. IJCP. 2016;3(4):1293-6.
14. Aceti A, Gori D, Barone G, Callegari ML, Di Mauro A, Fantini MP, et al. Probiotics for prevention of necrotizing enterocolitis in preterm infants: systematic review and meta-analysis. Ital J Pediatr. 2015;41(1):89
15. Yang Y, Guo Y, Kan Q, Zhou X, Zhou X, Li Y. A meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Braz J Med Biol Res. 2014;47(9):804-10
16. AlFaleh K, Anabrees J, Bassler D. Probiotics reduce the risk of necrotizing enterocolitis in preterm infants: a meta-analysis. Neonatology. 2009;97(2):93-9.