ORIGINAL ARTICLE

Frequency of Necrotizing Enterocolitis in Preterm Infants Treated with Prophylactic Probiotics Versus Controls

WAHEED AHMAD[1], ALLAH NAWAZ SULTAN[2], IRFAN YOUNAS[3], MUHAMMAD ALI[4], MUHAMMAD NAVEED[5], MUHAMMAD BILAL SAFDAR[6]

[1]Senior Registrar, Pediatrics, University of Lahore Teaching Hospital, Lahore
[2]Senior Registrar, Pediatrics, Sharif Medical City Hospital, Lahore.
[3]Senior Registrar, Pediatrics, The Children's Hospital, Lahore
[4]Fellow Pediatrics Gastroenterology, The Children's Hospital, Lahore
[5,6]Assistant Professor of Pediatrics, University College of Medicine, The University of Lahore
Correspondence to: Dr. Waheed Ahmed, Email: w_a272002@yahoo.com, Ph: 03363398906

ABSTRACT

Objective: The objective of the study was To determine the frequency of necrotizing enterocolitis in preterm infants treated with prophylactic probiotics versus controls.
Study Design: Randomized Controlled Trial (RCT)
Settings: Department of Pediatrics and Neonatology University of Lahore Teaching Hospital, Lahore.
Methodology: The study was started after approval from the ethical review committee. Preterm patients in neonatal period of life, admitted in neonatal ICU were included in the study. Written informed consent was taken from parents / Guardians. Patients were divided in two groups randomly on basis of lottery method. In group A patient was given prophylactic probiotics via oral drop. In Group-B patients were managed routinely without prophylactic probiotics. Standard management of necrotizing enterocoliis including NPO, iv fluids and iv antibiotics was started. Patients were monitored for development of necrotizing enterocolitis which was confirmed by presence of air in wall of intestine (pneumatosis intestinalis) in both groups within 10 days of admission.
Results: Comparison of frequency of necrotizing enterocolitis in preterm infants treated with prophylactic probiotics versus controls shows 4.71% (n=4) NEC in Group-A and 18.82% (n=16) in Group-B whereas 95.29% (n=81) in Group-A and 81.18% (n=69) in Group-B had no findings of NEC, p value was 0.004.
Conclusion: We concluded that the frequency of necrotizing enterocolitis in preterm infants treated with prophylactic probiotics is lower when compared with controls.
Keywords: Preterm infants, prophylactic probiotics, necrotizing enterocolitis

INTRODUCTION

Necrotizing enterocolitis is one of the common medical emergencies which involve the gastrointestinal tract, primarily affecting the premature neonates.[1] In necrotizing enterocolitis there is inflammation and necrosis of the walls of gastrointestinal tract including small and large intestines with translocation of the gas forming microorganism from gastrointestinal tract.[2]

The incidence of necrotizing enterocolitis has inverse relationship with gestational age and birth weight with overall incidence of 5 to 7 percent for all infants ≤35 weeks gestational age and weight less than 1500g at birth.[2] Necrotizing enterocoloitis is one of the most devastating diseases of neonates with high morbidity and mortality.[3] It is estimated that mortality from necrotizing enterocolitis ranges from 15 to 30 percent.[4] Necrotizing enterocolitis is a multifactorial disease with various risk factors; including prematurity, low birth weight, decreased immunity, ischemia/reperfusion injury, abnormal gut colonization, delay in enteral feeding of human milk and wide use of broad spectrum antibiotics.[3-4] Approximately 90% of infants with necrotizing enterocolitis are born preterm.[3] those who survive the high mortality of necrotizing enterocolitis are at increased risk of various complications including impaired neurodevelopment, short gut syndrome and strictures.[5]

The sign and symptoms of necrotizing enterocolitis varies, they may be subtle including feeding intolerance, slight distention of the abdomen, vomiting, diarrhea, irritability, apnea, bradycardia , changes in the appearance/activity of the infant or there may be systemic inflammation, bowel perforation and shock depending on the severity of the disease.[6] The diagnosis of necrotizing enterocolitis is usually made on the basis of sign and symptoms supported by hematological and radiological investigations. The presence of air in the walls of intestine is pathognomonic of necrotizing enterocolitis.[7]

Different prophylactic treatment modalities have been tried for prevention of necrotizing enterocolitis in premature newborns which include use of enteral antibiotics, feeding of mother's expressed breast milk and use of various growth factors and glucocorticoids.[8] Recently use of probiotics has been shown to decrease the incidence of necrotizing enterocolitis.

Upregulation of nitric oxide plays an integral role in development of epithelial injury in NEC. Some treatment strategies have been aimed at abrogating toxic effect of NEC. Cytoprotective effect of epidermal growth factor in breast milk, or fortification of infant formula with specific growth factor.[11]

Despite surgical treatment mortality remains high. surgical treatment is beneficial only at early stages.[12] So keeping all these things in view, probiotics are easy to use and having no complications of using it, Preterm babies are prone for sepsis so I also want to see role of probiotics in preventing sepsis as well. The risk of necrotizing enterocolitis was significantly reduced in a study group treated with prophylactic probiotics (2.5%) as compared to control group (15.1%).[1]

Rationale of my study is that since premature births are common in our society, an effective treatment modality should be adopted which reduces the incidence of necrotizing enterocolitis in preterm newborns to decrease the complications associated with the disease and to reduce the hospital burden.

METHODOLOGY

We included a total of 170 preterm neonates ≤35 weeks gestational age (male & females) (85 in each group), with birth weight less than 1500g and 5 mins APGAR score >7. We excluded all those with death within first 7 days of life, contraindication to oral probiotics: short gut syndrome, severe immunocompromised condition and life threatening co-morbids: severe respiratory distress, complex congenital heart disease. Written informed consent was taken from parents / Guardians.

Patients were divided in two groups randomly on basis of lottery method. In group A patient was given prophylactic probiotics via oral drop. In Group-B patients were managed routinely without prophylactic probiotics. Routine management including NPO, iv fluids and iv antibiotics.

Patients were monitored for development of necrotizing enterocolitis which was confirmed by presence of air in wall of intestine (pneumatosis intestinalis) in both groups within 10 days of admission. Frequencies and percentages were calculated for qualitative data like gender and NEC. Mean and standard deviation was calculated for quantitative data i.e. age of gestation and APGAR score, weight. Chi square test was applied to compare the difference between (frequency of NEC) in two group.

RESULTS

Gender distribution of the patients was done, it shows that 51.76% (n=44) in Group-A and 55.29% (n=47) in Group-B Male whereas 48.24% (n=41) in Group-A and 44.71% (n=38) in Group-B females. (Table No. 1)
Mean APGAR score at 5 minutes (Table No. 2)

Table 1: Gender Distribution (n=170)

Gender	Group-A (n=85)		Group-B (n=85)	
	No. of patients	%	No. of patients	%
Male	44	51.76	47	55.29
Female	41	48.24	38	44.71
Total	85	100	85	100

Table 2: Mean Apgar Score at 5 Minutes (n=170)

APGAR score	Group-A (n=85)		Group-B (n=85)	
	Mean	SD	Mean	SD
	8.56	1.06	8.81	1.18

Table 3: Comparison of Frequency of Necrotizing Enterocolitis in Preterm Infants Treated with Prophylactic Probiotics Versus Controls (n=170)

NEC	Group-A (n=85)		Group-B (n=85)	
	No. of patients	%	No. of patients	%
Yes	4	4.71	16	18.82
No	81	95.29	69	81.18
Total	85	100	85	100

P value=0.004

Comparison of frequency of necrotizing enterocolitis in preterm infants treated with prophylactic probiotics versus controls shows 4.71% (n=4) NEC in Group-A and 18.82% (n=16) in Group-B whereas 95.29% (n=81) in Group-A and 81.18% (n=69) in Group-B had no findings of NEC, p value was 0.004. (Table No. 3)

DISCUSSION

In our study, out of 170 cases (85 in each group), Male cases in A Group 51.76% (n=44) and in B Group 55.29%(n=47) remaining were females i.e. 48.24% (n=41) in A and 44.71% (n=38) in B Group, 51.76% (n=44) in Group-A and 58.82% (n=50) in Group-B were between 30-32 weeks whereas 48.24% (n=41) in Group-A and 41.18% (n=35) in Group-B were between 33-35 weeks, mean±sd was calculated as 32.87±1.54 weeks in Group-A and 32.53±1.57 weeks. Comparison of frequency of necrotizing enterocolitis in preterm infants treated with prophylactic probiotics versus controls shows 4.71% (n=4) NEC in Group-A and 18.82% (n=16) in Group-B whereas 95.29% (n=81) in Group-A and 81.18% (n=69) in Group-B had no findings of NEC, p value was 0.004.

Our study revealed that the risk of necrotizing enterocolitis was significantly reduced in a group treated with prophylactic probiotics (2.5%) as compared to control group (15.1%).[1]

Another study by Robinson J[12] in a study enrolled 24 eligible trials. These were variant regarding inclusion criteria i.e. gestational age/weight at birth, NEC baseline risk, dose, timing, feeding regimens and probiotics formulation. The data of metaanalysis, shows that supplementation of enteral probiotics produced good results with lower risk of severe NEC i.e. stage II or more and mortality as well. However, nosocomial sepsis was not found with significant reduction. Supplemention of probiotics did not show any systemic infection in the included trials. However, efficacy was found in both methods of probiotics preparation i.e. Lactobacillus alone or combined with Bifido bacterium. It was concluded that in preterm neonates mortality or severity of NEC is prevented with the help of enteral supplementation of probiotics.

Another study[13] revealed that enteral supplementation of probiotics prevents severe NEC.

Tanjina Chowdhury and others[14] are of the view that NEC was found significantly lower in trial group when compared with those of control group by calculating its incidence as 1.9% and 11.5% respectively, p value=0.04. Similarly full oral feeding was also achieved more earlier in study group, p=0.001. In addition hospital stay was shorter in study group. They finally revealed that supplementation of probiotics reduce the rate of NEC in preterm neoantes with low birth weight and results in faster full oral feeding with shorter hospital stay.

However, considering the above national and international studies, we are of the view that the frequency of necrotizing enterocolitis is lower in experimental group (receiving probiotics) as compare to control group in preterm infants.

CONCLUSION

We concluded that the frequency of necrotizing enterocolitis in preterm infants treated with prophylactic probiotics is lower when compared with controls.

REFERENCES

1. Hurter C, Dim MA, Gal P, Winer JE Ransom JL, Cain RQ et. al. Effect of routine probiotic. Lactobacillus reuteri DSM 17938, use on rates of necrotizing enterocolitis in neonates with birthweight < 1000 grams: sequential analysis. BIV1C Pediatr 2012 ;12:142.
2. Sa.wh SC„ Deshpande 5, Jansen 5, Reynaert CJ. Prevention of necrotizing enterocolitis with probiotics: a systematic review and meta-analysis. Peed 2016;4:e2429
3. Aceti A, Gori D, Barone 0, Callegai ML, Di Mauro A, Fanhni MP et al. Probiotics for prevention of necrotizing enterocolitis in preterm infants: systematic review and meta-analysis. Ital J Pediatr. 2015;41:89.
4. Zhou P, Li Y, Ma LY. The Role of Immunonutrients in the Prevention of Necrotizing Enterocolitls in Preterm Very Low Birth Weight Infants. Nutrients 2015;287(9):7256-70.
5. Patel nil, Denning pw, Intestinal microbiota and its relationship with necrotizing enterocolitis. Pediatr Res 2015;78:232-8.
6. Neu J. Probiotics and necrotizing enterocolitis. Clin Perinatol. 2014;41:967-78.
7. Kamali K, Hosseini SR, Ardakani SM, Farnoodi MR. Complementory value of Sonography in Early Evaluation of Necrotizing Enterocolitis. Pol J Radiol 2015;9:80:317-23.
8. Choi YY. Necrotizing enterocolitis in newborns: update in pathophysiology and newly emerging therapeutic strategies. Korean J Pediatr 2014;57:505-13.
9. Yang Y, Guo Y, Kan Q, Zhou XG, Zhou XY, Li Y. A meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Braz J Med Biol Res 2014;47:804-10.
10. Ofek Shlomai N, Deshpande G, Rao S, Patole S. Probiotics for preterm neonates: what will it take to change clinical practice? Neonatology 2014;105:64-70
11. Baucells BJ, Mercadal Hally M, Alvarez Sanevez AJ, Figueras Aley J. Probiotic association in the prevention of necrotizing enterocolitis and reduction of late onset sepsis and neonatal mortality in preterm infants. An Pediatric (Bare) 2016
12. Robinson J. Cochrane in context: probiotics for prevention of necrotizing enterocolitis in preterm infants. Evid Based Child Health 2014 Sep;9(3):672-4.
13. Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2011;(3):CD005496.
14. Chowdhury T, Muhammad Manajjir Ali. Efficacy of Probiotics Versus Placebo in the Prevention of Necrotizing Enterocolitis in Preterm Very Low Birth Weight Infants: A Double-Blind Randomized Controlled Trial. Journal of the College of Physicians and Surgeons Pakistan 2016; 26(9):770-4.