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PROBIOTICS FOR PREVENTION OF NECROTIZING ENTEROCOLITIS : A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Necrotizing enterocolitis (NEC) is the most common serious acquired disease of the gastrointestinal tract in preterm infants. It is characterized by bowel wall necrosis, of various length and depth. Bowel perforation occurs in one third of the affected infants. Although 5% to 25% of cases occur in term infants, it is primarily a disease of preterm infants with the majority of cases occurring in very low birth weight infants (infants with birth weight < 1500 g).*

The aim: *This study aims to show about probiotics for prevention of nercrotizing enterocolitis.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 26 articles, whereas the results of our search on SagePub brought up 48 articles, on Google Scholar 5660 articles. The results of the search conducted for the last year of 2014 yielded a total 15 articles for PubMed, 35 articles for SagePub, and 4567 articles for Google Scholar. The result from title screening, a total 11 articles for PubMed, 16 articles for SagePub, and 8 for Google Scholar. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *The risk-benefit ratio depends on the incidence of NEC in a neonatal intensive care unit, and evidence has shown that preventive measures probiotic administration can result in a decrease in NEC.*

Keyword: *Probiotics, necrotizing enterocolitis, infants.*

INTRODUCTION

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. 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. 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.[1]

The pathogenesis of NEC remains incompletely understood. NEC most likely represents a complex interaction of factors causing mucosal injury. It is speculated that NEC occurs with the coincidence of two of the three pathologic events of intestinal ischemia, colonization of the intestine by pathologic bacteria, and excess protein substrate in the intestinal lumen. Bacterial colonization is necessary for the development of NEC. When compared to term infants, VLBW infants at risk of NEC have abnormal fecal colonization, demonstrate a paucity of normal enteric bacterial species, and have delayed onset of bacterial colonization. Nosocomial infection is also a frequent complication in VLBW infants.[2,3]

The prevalence is around 7% in preterm babies with a weight <1,500 g and has a mortality rate of 20–30%. NEC is predominantly seen in infants born at a gestational age younger than 32 weeks, and its incidence is inversely proportional to the gestational age. NEC usually develops between the second week and second month of life and rarely occurs in utero or prior to the first feeding. Many risk factors have been identified, including small for gestational age, premature rupture of membranes, assisted ventilation, sepsis, and hypotension. Other risk factors include formula feeding, exposure to acid suppression medication, and use of antibiotics. The latter category of modifiable risk factors alters the intestinal microbiome, which supports the hypothesis that dysbiosis is an important determinant factor leading to NEC. Consequently, probiotics are frequently used in neonatal intensive care units (NICUs). In the United States of America, out of 78,076 infants, 3,626 (4.6%) received probiotics. Probiotic use increased over the study period, from 1997 to 2016, and varied among NICUs.[4,5]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast probiotics for prevention of nercrotizing enterocolitis. It is possible to accomplish this by researching or investigating probiotics for prevention of nercrotizing enterocolitis. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about probiotics for prevention of nercrotizing enterocolitis. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " probiotics for prevention of nercrotizing enterocolitis." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Probiotics*"[MeSH Subheading] OR "*Necrotizing enterocolitis*"[All Fields] OR "*Benefit of probiotics*" [All Fields]) AND ("*Risk of necrotizing enterocolitis*"[All Fields] OR "* Causes of necrotizing enterocolitis *"[All Fields]) AND ("*Prevention of necrotizing enterocolitis*"[All Fields]) OR ("*Mechanism of necrotizing enterocolitis" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

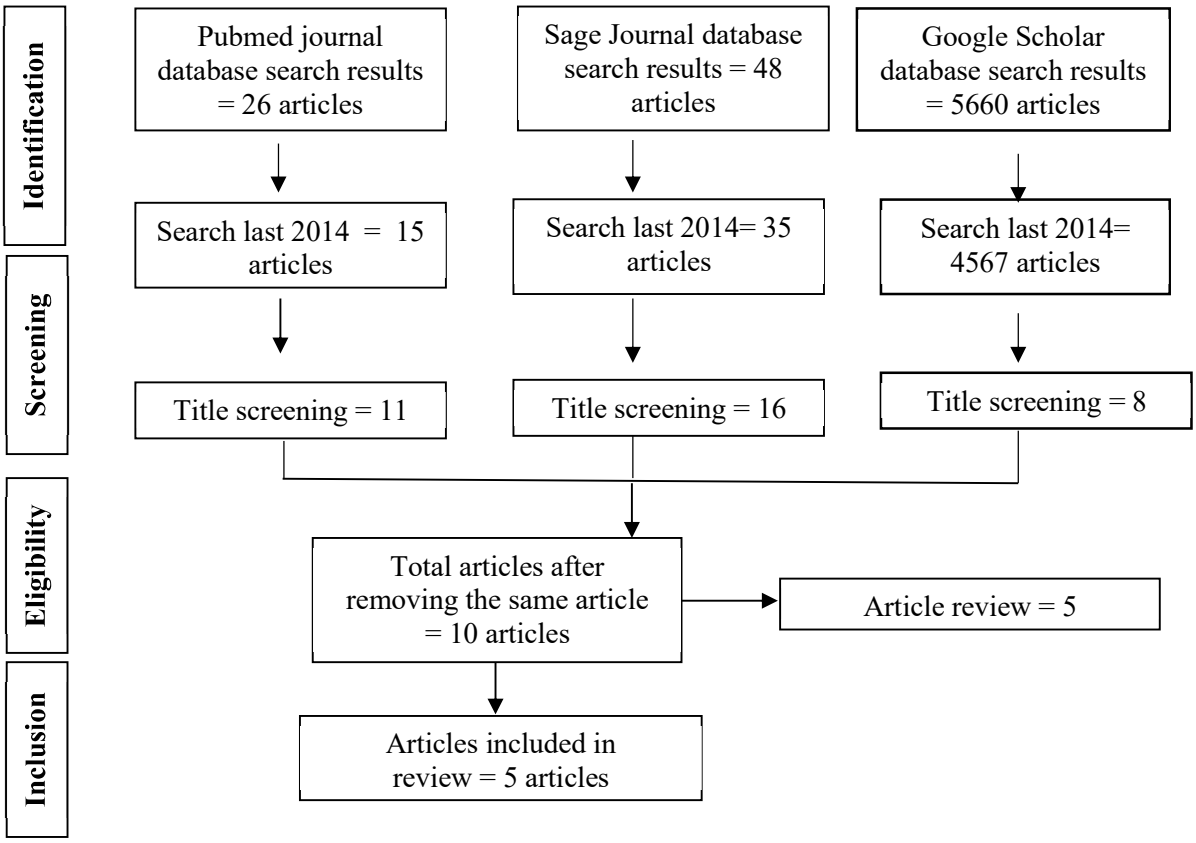

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 26 articles, whereas the results of our search on SagePub brought up 48 articles, on Google Scholar 5660 articles. The results of the search conducted for the last year of 2014 yielded a total 15 articles for PubMed, 35 articles for SagePub, and 4567 articles for Google Scholar. The result from title screening, a total 11 articles for PubMed, 16 articles for SagePub, and 8 for Google Scholar. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Meyer, MP *et al* (2020)[6] showed 38% reduction in cases of stage 2 or more NEC in NZ NICUs associated with the introduction of probiotics. This reduction was seen despite a very low background rate of severe NEC. We were able to compare results obtained with Infloran (*Lactobacillus acidophilus* and *B bifidum*) and *Lactobacillus GG* in combination with bovine lactoferrin and noted similar reductions with both regimes. At the same time cases of late onset sepsis were significantly decreased but in-hospital mortality was unchanged. There was one case of probiotic sepsis but no other unwanted effects from probiotics were apparent and their use is likely to be highly cost effective. These results are in keeping with the substantial evidence of benefit obtained from previous studies, provide support for routine probiotic use and indicate comparable results with the different combinations used in NZ NICUs.

Denkel, LA *et al* (2016)[7] showed large multi-center study adds data of more than 10,000 VLBW infants to the existing body of evidence that prophylactic enteral administration of dual-strain probiotics significantly reduces the incidences of

NEC, overall mortality, mortality following NEC and BSI. If these severe complications of preterm birth are to be reduced noticeably, the use of dual-strain probiotics should be considered in standard neonatal care, especially for ELBW infants.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Meyer, MP *et al*., 2020[6]	New Zealand	A randomized trial	4529	Four thousand five hundred and twenty nine infants were included and Pre and Probiotic groups were well-balanced with regard to gestation, birth weight and gender. The incidence of NEC in the Probiotic group was 1.6 and 2.7% in the pre group (corrected OR 0.62 CI 0.41–0.94). There was one case of probiotic sepsis. There was no significant difference between the Infloran and LGG/bLF combinations in regard to observed NEC rates. Late onset sepsis rates were significantly lower in the Probiotic group ($p < 0.01$). The multivariate regression model for NEC was derived initially from the significant univariate factors (see above). Many of the antenatal associations noted in appeared to be related to birth weight or gestation and were no longer significant in the multivariate model. Exposure to intra partum antibiotics was associated with NEC in the univariate model but there was missing data in 11.5% so this was not included in the multivariate analysis. Multiple imputation with 5 datasets was carried out for missing worst base excess data. Data on breast feeding at discharge was only available in 50% of cases, so this was not further analyzed.
Denkel, LA *et al*., 2016[7]	Germany	A multi-center interrupted time series analysis.	44	Of the 10,890 VLBW infants eligible for this study, 2.5% (n = 274) suffered from NEC. 4.6% of 4,683 ELBW infants (n = 215) developed NEC during the study period. The half-yearly incidences of NEC (per 100 VLBW or ELBW infants) decreased with routine use of dual-strain probiotics. The Cox proportional hazard regression identified routine probiotic treatment to be protective against NEC in VLBW and ELBW infants. Data from 10,890 preterm infants in 44 neonatal wards was included in this study.

				Incidences of NEC and BSI were 2.5% (n = 274) and 15.0%, (n = 1631), respectively. Mortality rate was 6.1% (n = 665). The use of dual-strain probiotics significantly reduced the risk of NEC (HR = 0.48; 95% CI = 0.38–0.62), overall mortality (HR = 0.60, 95% CI = 0.44–0.83), mortality after NEC (HR = 0.51, 95% CI = 0.26–0.999) and nosocomial BSI (HR = 0.89, 95% CI = 0.81–0.98). These effects were even more pronounced in the subgroup analysis of preterm infants with birth weights below 1,000 g.
Chowdury, T *et al*., 2016[8]	Bangladesh	A randomized double-blind control tria	102	In 108 neonates, development of NEC was significantly lower in the study group than that of control group [1 (1.9%) vs. 6 (11.5%); p=0.044]. Age of achievement of full oral feeding was significantly earlier in the study group than that in the control group (14.88 ±3.15 and 18.80 ±4.32 days; p < 0.001). Duration of hospital stay was significantly short in the study group compared to the control group (15.82 ±2.94 days vs. 19.57 ±4.26 days; p < 0.001). The distribution of the patients by development of NEC (stage II or III). NEC developed in 1 (1.9%) neonates in study group and 6 (11.5%) neonates in control group. Development of NEC was significantly less in study group than that of control group ($\chi 2$=4.050; p=0.044).
Arora, S *et al*., 2017[9]	India	A prospective randomized controlled interventional trial	150	The incidence of NEC was significantly lower in the test group compared with the control group (1 of 75 neonates vs 12 of 75 neonates; p=0.001). The severity of NEC, nosocomial sepsis and mean duration of hospital stay was significantly lower in the test group. Daily weight gain was significantly higher in the test group. There was no significant difference in mean age of onset of NEC, mortality and mean age to reach full feeds in two groups. NEC developed in only one neonate (1.33%) in test group as compared to 12 neonates (16%) in control group. In test

				group, staging of NEC was IA where as in control group, 8 cases (10.67%) were classified as stage IA, 3 cases (4%) as stage IIA and 1 case (1.33%) as stage IIIB. Over all incidence and severity was more in control group (p=0.016).
Amini, E *et al*., 2017[10]	Iran	Double blind randomized clinical trial (RCT)	115	The incidence of NEC and C-reactive protein (CRP) rise showed a significant difference between case and control groups (P = 0.02). In the case group, CRP increased in two patients. One suffered from sepsis and the other one had feeding intolerance that was treated with continuing probiotic administration. In the control group, CRP increased in 9 patients. In four neonates the reason for it was not clear, one case had many WBCs in U/A, one had Staphylococcus epidermidis in B/C, one had Klebsiella in U/C, one had Candida albicans in U/C, and one had occult blood in stool, Base excess showed an average decrease of 3.1. NEC and/or enteral dysmotility was seen in 5 infants in the case group and 14 infants in the control group; in 4 out of 5 infants in the case group the ailment improved with continuing the probiotic feeding (P = 0.013).

Chowdury, T *et al* (2016)[8] showed Probiotic supplementation reduced the frequency of necrotising enterocolitis (NEC) in preterm neonates with very low birth weight. It was also associated with faster achievement of full oral feeding and shorter duration of hospital stay.

Arora, S *et al* (2017)[9] showed the incidence of NEC was significantly lower in the test group compared with the control group (1 of 75 neonates versus 12 of 75 neonates ; p = 0.001). The severity of NEC, nosocomial sepsis and mean duration of hospital stay was significantly lower in the test group. Daily weight gain was significantly higher in the test group. There was no significant difference in mean age of onset of NEC, mortality and mean age to reachfull feeds.

Amini, E *et al* (2017)[10] showed positive effects of probiotics on preventing and treating NEC, which is a serious disease in ELBW and VLBW neonates. We showed that probiotics could be administered in divided doses in breast milk feeding intervals. Many RCTs have found that probiotics can be used as a routine therapy for preterm infants, So we focused on a suitable type of probiotics, its dosage, and its administration interval to prevent NEC.

DISCUSSION

Necrotizing enterocolitis (NEC) is the leading cause of neonatal death but a poorly understood disease. It frequently occurs in preterm infants, especially those with very low birth weight. The mortality and morbidity in very low birth weight infants are 10–30% and 5–10%, while the mortality is as high as 30–50% in neonates with extremely low birth weight. As the most common gastrointestinal emergency in neonates, it is categorized into three stages according to clinical symptoms. The typical initial symptoms include feeding intolerance, increased gastric residuals, abdominal distension, and bloody stools, which rapidly deteriorate to intestinal perforation, peritonitis with or without pneumoperitoneum, systemic hypotension, and coagulopathy, resulting in ischemic necrosis (tissue death) of the intestinal mucosa.[11,12]

Inflammatory reactions of neonates with NEC would cause delayed neurodevelopment in the neonate, and 25% of neonates with NEC would progress to brain malformation or serious neurodevelopmental problems. NEC increases the

duration of intravenous nutrition in infants, potentially increasing the risk of infectious complications and extending the duration of hospitalization. Therefore, early prevention and early diagnosis of NEC are crucial.[11]

Research has focused on the role of gut microbiota and its manipulations, such as the use of probiotics, on disease and health status. Probiotics are live–microorganisms which, when ingested in adequate amounts, confer a health-benefit to the host through an interaction with gut microbiota. The intestinal microbiota undergoes dynamic changes during childhood. Gut colonization in preterm infants occurs differently than in healthy term newborns, and preterm infants frequently have delayed and aberrant acquisition of the "normal" digestive flora.[13,14]

Recent studies performed in preterm foetuses and infants demonstrated that amniotic fluid and meconium are not sterile, suggesting an intrauterine origin of gut microbiota; after birth, the preterm infant's immature intestine is exposed to an unique environment and to several iatrogenic manipulations, including the use of broad-spectrum antibiotics. The subsequent intestinal *dysbiosis* is recognized as a risk factor for NEC: actually, it has been shown that preterm infants with NEC have reduced bacterial gut diversity and different bacterial strains compared to healthy control. In this perspective, provision of probiotics to preterm infants has the potential to "normalize" the abnormal colonization pattern, thus preventing the occurrence of the disease.[13]

CONCLUSION

The risk-benefit ratio depends on the incidence of NEC in a neonatal intensive care unit, and evidence has shown that preventive measures probiotic administration can result in a decrease in NEC.

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