The Prophylactic Role of Probiotics for Preterm Infants/Neonates

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ABSTRACT

Necrotizing enterocolitis (NEC) is a major morbidity and cause of mortality in preterm neonates. Probiotics seem to have a beneficial role in preventing NEC, which is confirmed in meta-analyses of randomized controlled trials (RCTs). We therefore aimed to review and confirm the efficacy of probiotics in preterm neonates obtained in observational studies. To assess the effects of prophylactic probiotics in preterm infants.

Keywords: Prophylactic, Probiotics, Preterm Infants.

INTRODUCTION

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in neonates, mostly affecting premature neonates [1]. Advances in neonatology and modern neonatal intensive care units, the incidence of NEC has increased, with improved survival of smaller and more premature infants [2]. Premature infants are in the unique situation of having an immature digestive system along with a concurrent need for multiple antibiotics and formula feedings, which can all lead to feeding intolerances and a predisposition toward necrotizing enterocolitis (NEC). It has been assumed that probiotics can be used as a treatment for infants with NEC, and early clinical studies have shown a certain degree of success. Probiotics are viable non-pathologic bacteria that colonize the intestine and modify the intestinal microflora with beneficial effects for the host that may improve immunity. Notwithstanding, in spite of an incredible measure of research several issues are still hampering our understanding of this disease, and NEC continues to be a major cause of death in preterm infants [3]. It has been suggested that pathogenesis must be multifactorial and may involve an overactive response of the immune system to cause an insult that might be ischemic, infectious, related to the introduction of enteric feeds or a response to translocation of normal enteric bacteria [4]. This overactive inflammatory response may lead to harmful effects. Accordingly, there is a critical role for both medical and surgical management in the treatment of NEC once it occurs, but prevention could have the most dramatic impact on overall morbidity [4]. Such a preventive measure could be the enteral administration of probiotics. The term probiotics is defined as 'live microorganisms which when administered in adequate amounts confer a benefit for the host' [5]. The beneficial mechanisms of probiotics are unknown but include changes in intestinal permeability, enhanced mucosal IgA responses and increased production of anti-inflammatory cytokines [1]. The immature immune system of premature neonates cannot control the outgrowth of pathogenic bacteria. According to the benefits of probiotics, feeding premature infants with these bacteria may populate their intestines with normal flora and prevent an overgrowth of pathogenic flora that contributes to the development of NEC [6]. Several systematic reviews of randomized controlled trials (RCTs) on prophylactic probiotics for preterm infants have discovered beneficial effects on NEC and mortality [1, 7]. In spite of such convenient results, concerns about the effectiveness of prophylactic probiotics still remain unevaluated. Thus, we needed to investigate any conceivable gainful impacts of probiotics in observational studies beyond the effects previously observed in RCTs. We therefore aimed to carry out a systematic review on observational (nonrandomized) studies to evaluate the efficacy of probiotic supplementation outside strictly controlled settings.

Probiotic Use in Neonates

The word probiotic is Greek and means for life whereas antibiotic means against life. The

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term probiotic was first used in 1974 in the sense of its current usage, as organisms and substances which contribute to intestinal microbial balance. Over time, the definition of probiotics has expanded to mean a living microbial food supplement that beneficially affects the host animal [8]. In the neonatal intensive care unit (NICU), the term probiotic should refer to "life," and the arduous journey the premature infant needs to make on the road to recovery.

Probiotics are viable non-pathologic bacteria that colonize the intestine and modify the intestinal micro flora with beneficial effects for the host that may improve immunity [9]. The best way for an infant to get probiotics is from its mother's milk. Infants should be breastfed for the first six months of life, if possible. However, formula is sometimes needed for all or part of a baby's diet. Manufactures are producing baby formulas supplemented with probiotics and prebiotics. Adding probiotics offers important health advantages to babies who are bottle-fed. Many paediatricians consider yoghurt an excellent option for babies who are eating solid foods.

Consequences of antibiotics in NICU infants

The NICU population is routinely exposed to antibiotic therapy. Premature infants often receive antibiotics as early as the first day of life. Some new-borns are on prophylactic oral antibiotics for hydronephrosis or recurrent urinary tract infections. Antibiotics alter the gut flora, and can result in diarrhoea or constipation, as well as foster the development of thrush or cutaneous candidal infections [10]. Sick new born and premature infants treated with antibiotics are at risk for colonization with aggressive and drug-resistant bacteria, which may pose a greater risk of NEC and its complications. Infants who have been on antibiotic therapy for longer periods of time were noted to have the fewest number of different bacteria present in their intestinal system. A decrease in the number of normal flora is believed to be a risk factor for NEC. A probiotic given with the prescribed antibiotic theoretically may reduce the effect of microbial alteration and any adverse effects on stool consistency and frequency. Although a few studies have been conducted regarding prevention of antibiotic-associated diarrhea through the use of probiotics in older patients [11].

Necrotizing Enterocolitis

Bacterial infection and colonization of the premature intestinal tract play a role in both the predisposition to and pathogenesis of NEC. NEC is the most common gastrointestinal emergency in premature infants. Although mortality rates among infants with NEC have decreased as a result of improved supportive and surgical care, effective preventative strategies are lacking. The causes of NEC are multifactorial. Prematurity, formula feeding, intestinal ischemia and bacterial colonization are presumed prerequisites for NEC [12]. The key risk factors of NEC result in intestinal necrosis through inflammation.

The colon of newborn infants is sterile at birth, but is rapidly colonized soon after birth [13]. Identified microorganisms that colonize the preterm newborn intestine include mainly coliforms, enterococci and bacteroides species [12]. Bifidobacteria, commonly found in the term newborn gut, are not detected in very low birth weight (VLBW) infants receiving breast milk during the first two weeks after birth. Bifidobacterium and Lactobacillus could be found in the stool of less than 5 percent of preterm infants within the first month of life [13]. The combination of an increase in potentially pathogenic microorganisms together with a decrease in normal flora found in preterm neonates is speculated to be one of the factors that make these infants more at risk for overgrowth of potentially pathogenic species and the development of NEC [12].

Another study suggests that premature, formula-fed infants are at higher risk for NEC due to decreased Bifidobacteria. Normally, Bifidobacteria colonization lowers luminal pH, which decreases the growth of more pathogenic organisms. Additionally, Bifidobacteria may stimulate the production of inflammatory mediators including IL-1, IL-6 and TNF-alpha [14] ,which are safety mechanisms to protect against NEC.

Breast milk, formula and intestinal colonization

Breastfed infants have higher concentrations of protective Bifidobacteria and Lactobacillus in their gastrointestinal tracts, whereas Streptococcus faecalis, Staphylococcus, E. coli

and Clostridia are found in higher levels in formula-fed infants. Premature infants who receive breast milk have fewer episodes of late-onset sepsis, NEC, diarrhea and urinary tract infections, and are less likely to require antibiotic therapy.

Evidence suggests that a lack of breastfeeding along with increased antibiotic use have separate but interactive negative effects on gut flora diversity. Human breast milk also contains three components that inhibit colonization by harmful bacteria: (1) secretory immunoglobulin A, which is produced by the maternal immune system against enteric pathogens that had previous exposure; (2) fatty acids that destroy viruses and act against other pathogens when released from the triglycerides of milk in the stomach of the infant; and (3) lactoferrin, the major protein in human milk, which is active against a broad spectrum of pathogenic bacteria [15].

Probiotics combined with prebiotics

Many preparations of probiotics are containing various microbial strains individually and in combination. Some products include a prebiotic, a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon.to enhance probiotic survival and efficacy. Prebiotics are mainly oligosaccharides that usually stimulate the growth of Bifidobacteria. Some examples of prebiotics include fructooligosaccharides (FOS), inulin, transgalactosylated oligosaccharides and soybean oligosaccharides. Products containing both probiotics and prebiotics are described as symbiotic [8].

How probiotics work

For effective results, probiotics must survive the acidic stomach environment and the alkaline conditions of the duodenum. Probiotics must also adhere to the intestinal mucosa of the colon. Some probiotics facilitate antigen transport to underlying lymph cells or reduce the ability of other pathogenic organisms to colonize the intestine either by producing acids that decrease the environmental pH or by secreting specific antibacterial substances [14]. Other probiotics increase the numbers of IgA and other immunoglobulin-secreting cells in the intestinal mucosa as well as stimulate the release of interferon. In adhering to the colonic mucosa, probiotics prevent the attachment of pathogenic bacteria. The phagocytic response of peritoneal macrophages and the trophic response of intestinal epithelial cells are improved by probiotic use. Probiotics also improve the environment of the microvillus by preventing mucosa permeability and bacterial translocation [14].

Benefits of probiotics

Probiotics are modestly effective at preventing antibiotic-associated diarrhea (AAD) in children, WebMD reported, citing a clinical report published in Pediatrics. Also, children with diarrhea from acute viral gastroenteritis saw relief an average of one day sooner when given a probiotic [8]. Prevention of food allergies, the first bacteria strains introduced into a baby's intestines have the best chance of gaining a foothold and establishing gut flora. Babies who are given beneficial bacteria soon after birth are able to colonize these probiotics in their intestines. This prevents the body from identifying certain foods as foreign substances and mounting an allergic response to them. Evidence also exists that probiotics may help reduce eczema, asthma and food allergies). For infants, potential benefits of probiotics include stimulation of the immune system, reduction of intestinal gas, improved absorption of essential nutrients, synthesis of vitamins and resistance to food-borne pathogens. These factors translate into prevention of bacterial sepsis, urinary tract infections and NEC and a decrease in *C. difficile* and Rotavirus infections. In preterm formula-fed neonates, probiotic use has resulted in improved feeding tolerance, bowel habits and gastric motility, as well as reduced crying time [16].

Premature infants have an immature immune system causing lower gastric acid production, lower concentrations of protective intestinal mucus, lower proteolytic enzyme activity and decreased gut motility. These factors contribute to increased risk for infection and inflammation due to translocation of pathogens. Probiotics can alter several key components of intestinal inflammation, including gut bacterial colonization, production of inflammatory mediator compounds, activation of the intestinal immune system and the integrity of the mucosal barrier [14].

Types of probiotics

The micro flora in the gut was thought to be caused by bacteria, namely clostridia, enterococci, lactobacilli, and Escherichia coli, but since then a number of new innovative techniques have been able to show that there are actually many more varieties of bacteria at work in the gut. There are several different kinds of probiotics, with each one being identified by its species, genus, and strain level. The following are some of the most commonly bacteria with their benefits:

Lactobacillus: Lactobacillus is a kind of bacteria than can be divided into 50 more species; they are naturally found in the urinary, genital and digestive systems. They can be incorporated into the body by consuming fermented foods like yoghurt or dietary supplements. Lactobacillus has been in use for treating a number of diseases in the infant's body. the most well-known types of Lactobacillus are Lactobacillus GG which, when given to infants suffering from irritable bowel syndrome, reduced the frequency as well as severity of abdominal pain, has been effective in the management of acute pediatric diarrheal disease and reduces *Candida* colonization in neonates. *Lactobacillus GG* has also been associated with reduced atopic dermatitis in infants when administered to pregnant women prenatally and during the first six months of the infant's life [17]. *Lactobacillus acidophilus* has been shown to prevent infectious diseases and favorably alter the intestinal microflora balance, thereby inhibiting the growth of harmful bacteria, promoting good digestion, boosting immune function and increasing resistance to infection. *Lactobacillus casei* increases levels of circulating IgA in infants infected with rotavirus, thereby shortening the duration of diarrhea

Bifidobacteria: when it comes to this particular genus, it has approximately 30 species and makes up most of the healthy bacteria in our colon. They are known to have a significantly high presence in the intestinal tract right from the days of birth, notably in breastfed infants.

Species most commonly used as probiotics include Bifidobacteria bifidum, Bifidobacteria lactis, Bifidobacteria longum, Bifidobacteria thermophilum, Bifidobacteria breven, and Bifidobacteria infantis.

Bifidobacteria have shown to be effective against glucose intolerance and reduce blood lipid levels. Bifidobacteria infantis has shown to improve the symptoms of abdominal pain, bloating and incomplete evacuation of gas. Bifidobacterium bifidum strengthens gastrointestinal immunity especially in children. *Bifidobacteria lactis increases the levels of good cholesterol and glucose tolerance* [18].

Prophylactic administration of *Bifidobacteria infantis* and *Lactobacillus acidophilus*was shown to reduce both the incidence and severity of NEC in premature neonates in one study [19].

Probiotics as prevention

The administration of probiotics to VLBW infants (<1,500 g) in the NICU is currently being studied as a means to prevent NEC by preventing colonization from pathogenic flora and establishing a normal nonpathogenic microenvironment in the premature gut. Probiotic supplementation has resulted in a reduction in the incidence of NEC-like intestinal lesions in several animal models. *Bifidobacteria* supplementation resulted in intestinal colonization and subsequent reduction in NEC-like lesions in a neonatal rat model of intestinal ischemia/reperfusion. In another animal study using quail, supplementation with *Bifidobacteria* prevented the development of cecal lesions resembling NEC.

In a randomized study of 367 VLBW infants, the probiotic group received *Lactobacillus acidophilus* and *Bifidobacterium infantis* with breast milk twice daily until discharge [18]. Infants in the control group were fed with breast milk alone. Death or NEC Bell stage 2 occurred in 9 (5 percent) of 180 infants in the probiotic group and in 24 (13 percent) of 187 infants in the control group. The probiotic group was noted to have only 1 percent of NEC greater than Bell stage 2 versus 5.3 percent in the control group, and no cases of severe NEC (Bell stage 3) versus 6 cases in the control group. The authors concluded that probiotics fed entirely with breast milk significantly reduced the incidence and severity of NEC in VLBW infants [19].

In a study of 1,237 neonates in a Bogota, Colombia NICU, prophylactic *Lactobacillus*

acidophilus and *Bifidobacterium infantis* were administered to all neonates to determine if the incidence of NEC would decrease. The infants in the treatment group received one-fourth of a capsule of a probiotic agent preparation daily. Stool color of infants in the treatment group changed from coffee and green tones to light yellow after receiving the probiotic. Feeding intolerance and diaper dermatitis also decreased for neonates who received probiotic therapy. The incidence of NEC in neonates treated with probiotics was reduced to one-third the number of cases compared with the control group. A significant decrease in NEC-associated mortality (from 25 to 7 cases) was also noted. NEC was predominantly seen in low birth weight infants in both the probiotic group and in the non-probiotic group [20].

The beneficial effects of probiotics may be more important in infancy than in late childhood or adulthood. Eventually, administration of probiotics to women late in pregnancy may be more effective than lifelong administration of the organisms. The use of probiotics antenatally for pregnant women on antimicrobial therapy must be taken into consideration. Probiotic additives are being added to infant milk formulas due to increasing evidence that breastfed infants' intestinal tracts are colonized faster, and have fewer gastrointestinal infections than bottle-fed infants. Probiotics may eventually be added to the food supply the same way that breads and cereals are currently enriched.

Infants with a family history of milk protein allergy may also benefit from the use of probiotics. It may be beneficial to have mothers with known milk protein allergy to be supplemented with probiotics during pregnancy. Another consideration would be to have children routinely supplemented with probiotics while on antimicrobial therapy. This would also benefit the high-risk NICU population who are exposed to antibiotics early in life, and on multiple occasions. Other uses for probiotics in preterm neonates may also include the prevention of fungal colonization and *Candida*-related disorders [21].

Implications for nursing practice

In order to use the administration to be feasible for neonates, probiotics ought to be produced in a form that allows oral administration in relatively small volumes. Minimum one type of probiotic supplement is available in liquid drops for infant use. Most probiotics should be kept refrigerated at 40°F to preserve the viability of the micro-organism, though a few forms are known to be stable at room temperature. Because antibiotics may inactivate the live bacteria in probiotics, the timing of probiotic and antibiotic doses will require to be appropriately spaced. Neonatal nurses must document tolerance of feedings for infants given probiotics, as well as note improvement in any diaper dermatitis, thrush or *Candida* infections.

Probiotic alterations of commercial formula preparations have been reported to influence the development of intestinal *Bifidobacteria* colonization by supplementation with oligosaccharides, FOS, lactulose and lactoferrin [14].

Risks of probiotics

Allergenic sensitization has not been observed thus far in grown-ups or children who have taken probiotics. Significant worries for infants incorporate the prompt or long-term toxicity of promoting particular bacteria in the intestine and early or lengthy modification of the microbial system. Heat-killed probiotics may be safer because the dose of killed bacteria can be more carefully controlled in patients with poor intestinal motility such as premature infants. Infections with the organisms in the probiotic product are theoretically possible if bacterial overgrowth occurs. Fungal infections, sepsis and a trend toward nosocomial infections have been accounted for when certain probiotics have been used in immune compromised or basically sick patients.

Specific agents and specific doses of such agents with proven efficacy need to be studied further. Additionally, safety guidelines for the use of probiotics have not been established by the FDA. Currently, the greatest evidence of safe use in infants and children, including high-risk populations, has been shown to be the *Bifidobacteria* species [17].

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