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Probiotic Therapy for Prevention of Necrotizing Enterocolitis in Preterm Infants – A Review

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Abstract

Purpose: Preterm infants are prone to systemic infections due to increased intestinal permeability to potentially pathogens resulting from immature intestinal function, frequent use of broad-spectrum antibiotics, delay in initiating enteral feeding, infection control procedures and sterilization of milk. Very Low Birth Weight infants, particularly Extremely Low Birth Weight infants are at higher risk due to abnormal pattern of colonization, which may contribute to the pathogenesis of neonatal Necrotizing Enterocolitis (NEC). Dietary intervention through probiotic supplementation is widely adopted for the prophylaxis of NEC and nosocomial infections throughout the world.

Design/Methodology/Approach: This review paper is based upon systematic review of randomized controlled trials, meta-analyses, research papers and books related to the short and long-term administration of single or mixed probiotic cultures for the prevention of NEC only in preterm infants. Clinical trials and cohort studies concerning manipulation of the intestinal microbiota in premature infants are also included. Evidence based data published in the English language retrieved from three databases Pub Med, Science Direct and Cochrane Reviews, published in The Cochrane Library from 2000-2016, using a combination of key words like necrotizing enterocolitis, probiotics and preterm infants have been considered.

Findings: All probiotic strains are not equally efficacious for preventing NEC and application of probiotic combinations may be advantageous. Due to heterogeneity of probiotic formulations exclusive administration of probiotics in premature infants is not recommended and should be introduced along with breast milk as routine clinical practice for neonatal health care.

Originality/Value: Probiotic foods have been found effective in modulating gastrointestinal flora to prevent NEC but safety aspects must be evaluated prior to consideration of probiotic therapy for preterm infants and neonates.

Keywords: Probiotic therapy; necrotizing enterocolitis; preterm infants; dietary intervention

Introduction

Breast milk is considered the most ideal food for infants owing to its nutrition attributes, immune factors, growth factors, digestive enzymes, hormones, bioactive factors such as antibodies, Immunoglobulin M, Immunoglobulin G and IgA and antibacterial proteins/peptides such as lysozyme and lactoferrin [1-3]. Human milk is also equally suitable for the management of premature infants and mother's own milk should be the first choice. Mother's milk does not alone provide optimal nutrition and requires appropriate fortification to meet the growth and neuro-developmental requirements [4-6].

Reviewed literature revealed that preterm infants are prone to systemic infections due to increased intestinal permeability to potentially pathogens resulting from immature intestinal function, frequent use of broad-spectrum antibiotics, delay in initiating enteral feeding, infection control procedures and sterilization of milk [7]. Abnormal pattern of colonization in Very Low Birth Weight (VLBW) infants with birth weight <1500g and particular in Extremely Low Birth Weight (ELBW) infants with birth weight <1000g are at higher risk and may contribute to the pathogenesis of neonatal Necrotizing Enterocolitis (NEC), an acquired Gastrointestinal (GI) disease associated with significant morbidity and mortality. NEC infected infants develop intestinal injury, which permits bacteria and bacterial by-products to cross the mucosal barrier and disseminate to the bloodstream via the lymph system, resulting in sepsis, shock, multi-system organ failure and potentially death [8, 9].

Incidences of NEC in premature infant can be reduced by manipulating the composition of the intestinal microbiota and expression of gut microbial genes through most promising interventions like human milk, probiotics and lactoferrin [10]. Amongst modern therapeutic strategies, the probiotic approach of modulating the gut flora to re-establish the normal health has gained much creditability due to their capability for colonizing the gut, restoration of normal microflora, re-establishment of the intestinal barrier function, induction of homeostasis of immune system, normalization of the digestive functioning, providing several trace nutritive elements anti-inflammatory action to the host improvement in feeding intolerance, prevention of sepsis and NEC [11-17]. Dietary intervention through probiotic supplementation is widely adopted worldwide for prophylaxis of NEC and nosocomial infections [18].

Diverse commercial probiotic products offered to VLBW infants in neonatal intensive care unit (NICU) are not capable

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of exhibiting protective effect against NEC and even certain probiotic products do not have declaration regarding probiotics or contains active organisms [19-22]. It can thus be interpreted that all probiotic products available in the market and all probiotic cultures are not equally effective against NEC prevention. In the present review, attempt has been made to highlight the health benefits of probiotics for NEC prevention and its safety concern for preterm infants.

Colonization of Gut

At birth the intestinal flora of human is sterile and is subsequently colonized by vaginal and faecal flora of mothers during birth [23, 24]. Development of the intestinal microbiota of infants is characterized by rapid and large changes in microbial abundance, diversity and composition and is influenced by medical, cultural and environmental factors such as mode of delivery, diet, familial environment, diseases and therapies used [25]. A balance between commensal and pathogenic bacteria is of utmost importance for normal function, immunology and homeostasis in the healthy intestine and any disruption of this balance may lead to disease conditions [26].

Gut colonization pattern of preterm infants is different from normal infants and is influenced by nutritional, immunological and environmental factors [27, 28]. Predominance of gut with beneficial flora like *Bifidobacterium, Lactobacillus* and *Bacteroides* in normal infants and potentially pathogenic bacteria such as Enterobacteriaceae and Clostridium species in preterm infants were reported [29-32]. Preterm, especially ELBW infants lack transplacental transfer of maternal antibodies and are at greater risk for aberrant colonization due to non-vaginal births, exposure to abnormal environmental pathogens at intensive care unit, delayed and/or sterile feeding, prolonged antibiotic exposure, greater infection control practices lack of typical skin contact with maternal flora as well as alterations in typical exposure to breast milk [27,29, 33, 34]. Preterm infants lack adequate intestinal commensal or "healthy" bacterial flora and abnormal pattern of colonization in preterm infants may contribute to the pathogenesis of NEC. Various pathways for early patterns of microbial colonization are enumerated below [27, 30].

- Enhancement of the mucosal protective barrier
- Modification of systemic immune response
- Competitive exclusion of less desirable microbe
- Protein and carbohydrate degradation
- Vitamin and butyrate production
- Mucosal differentiation

Probiotics for Preterm Infants

Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit on the host [35]. This definition is widely accepted and adopted by the International Scientific Association for Probiotics and Prebiotics [36]. Dani et al. suggested restriction of growth of pathogens by colonization of the intestine with non-pathogenic and normal resident bacterial species (probiotics) of gut bacteria in preterm and term infants [37]. Probiotics may promote intestinal function, maturation and defense against potential harmful pathogens and most systematic reviews reported probiotic to be safe and efficacious and can be recommend for routine administration in the preterm infants [17, 38, 39].

Raguz *et al.* reported shorter stay time in intensive care, early full peroral intake of milk and shorter time of treatment with anti-ulcer medicine due to administration of probiotics in premature infants [40]. Introduction of probiotics resulted in lower mortality and lower frequency of infection reduces the risk of Late-Onset Sepsis (LOS) in premature infants [41, 42, 43]. Rijkers, et al. categorized the diverse health benefits extended by probiotics into three groups [44].

- Probiotic microorganisms act directly within the GI tract through direct interaction with the intestinal microbiota or by enzymatic activities.
- Probiotic microorganisms interact directly with the intestinal mucus layer and epithelium thereby influencing the intestinal barrier function and the mucosal immune system.
- Probiotic microorganisms can have effects outside the GI tract such as on the systemic immune system and other organs.

Demonstrated health benefits for specific probiotic strains of genera: *Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus, Pediococcus, Leuconostoc, Bacillus, Escherichia coli* have been reported [45]. Rouge *et al*. reported that supplementation of *Lactobacillus rhamnosus* GG and *Bifidobacterium longum* BB536 failed to colonize in ELBW infants and may not improve the gastrointestinal tolerance to enteral feeding in VLBW infants [46]. Reviewed literature and research findings indicated that all probiotic cultures and their dosages are not effective in preventing NEC in preterm neonates (Table 1). Meta analysis of randomized controlled trials indicated that probiotic supplementation was associated with a significant decrease in risk of NEC and mortality in preterm VLBW infants. AlFaleh and Anabrees reported that probiotic supplementation was associated with significantly reduction in the incidence of severe NEC (typical RR 0.35, 95% CI 0.24 to 0.52) and mortality (typical RR 0.55, 95% CI 0.40 to 0.74) [75]. Another Meta analysis showed a significantly decreased risk of NEC in preterm VLBW infants (RR=0.47; 95%CI: 0.35-0.62; *P<0.001*) as well as risk of mortality (RR=0.63; 95%CI: 0.51-0.78; *P<0.01)* due to probiotic supplement [76]. A significant decrease in incidence of NEC (risk ratio, RR = 0.55, 95% confidence interval, 95% CI, 0.39–0.78; p = 0.0006) and mortality (RR = 0.72, 95% CI, 0.61–0.85; P < 0.0001) but no evidence of significant decrease in the risk for sepsis (RR = 0.86, 95% CI, 0.74-1.00; p = 0.05) could be noted in premature neonates receiving prophylactic probiotics [77]. Recently, in a randomized controlled trial, preterm neonates fed with oral probiotics containing *Saccharomyces boulardi, L. rhamanosus, Lactobacillus acidophilus, B. longum and Streptococcus thermophilus* along with breast milk exhibited a greater decline in both incidence (2.7 vs. 9.3 %) and severity (Stage 1: 2 vs. 3.3% and Stage 2: 1 vs. 9%) of NEC in contrast to neonates fed exclusively with breast milk [72].

Table -1: Effect of probiotic dosages on necrotising enterocolitis in preterm neonates

Dosage of Probiotic organisms	Observations	References
Lactobacillus GG (10^8cfu/twice daily)	No effect on NEC	47
L. acidophilus ($2.0x10^8$cfu/day) *B. infantis* ($2.0x10^8$cfu/day)	Reduced NEC	48
L. rhamnosus GG ($6.0x10^9$cfu/day)	Reduced NEC	37
B. infantis ($0.35x10^9$ cfu/day) *S. thermophilus* ($0.35x10^9$ cfu/day) *B. bifidus* ($0.35x10^9$ cfu/day)	Reduced NEC	49
L. acidophilus ($2.0x10^8$cfu/day) *B. infantis* ($2.0x10^8$cfu/day)	Reduced NEC	50
L. acidophilus (10^8cfu/ml)	No significant effect on NEC	51
L. acidophilus (10^9cfu/twice daily) *B. bifidus* (10^9cfu/twice daily)	Reduced NEC	52
B. bifidus ($2.5x10^9$cfu/twice daily) *B. longum* ($2.5x10^9$cfu/twice daily) *B. infantis* ($2.5x10^9$cfu/twice daily) *L. acidophilus* ($2.5x10^9$cfu/twice daily)	Reduced NEC	53
L. rhamnosus GG *+B. longum* ($1x10^8$cfu)	No effect on NEC	46
L. rhamnosus GG ($6.0x10^9$ cfu/day)	Reduced NEC	54
Lactobacillus sporogenes ($3.5x10^8$cfu/day)	Reduced NEC	55
L. casei ($3.5x10^7$ to $3.5x10^9$ cfu/day) *B. breve* ($3.5x10^7$ to $3.5x10^9$ cfu/day)	Reduced NEC	56
B. lactis BB 12 ($2x10^9$cfu/kg for 6 weeks)	Reduced NEC	57
L. reuteri DSM 17938 ($5.5x10^7$/d cfu/day)	Reduced NEC	58
L. rhamnosus GG ($0.5×10^9$ + *B.infantis* ($0.5×10^9$ daily)	No effect on NEC	59
L. acidophilus ($1.0×10^9$)+*L. reuteri* ($4.4×10^8$)+*L. casei* ($1.0×10^9$)+*L. planatarum* ($1.76×10^8$) + *B. Infantis* ($2.76×10^7$)+*S. thermophillus* ($6.6×10^5$ cfu/day)	No effect on NEC	60
Saccharomyces thermophilus + B.infantis + B. bifidum	Reduced NEC	41
Saccharomyces boulardii ($5.0x10^9$ cfu/day)	No significant effect on NEC	61
L. rhamnosus LCR35 ($2x10^8$cfu/twice daily)	Reduced NEC	62
Saccharomyces boulardii ($5×10^8$ cfu/kg/ twice daily)	No effect on NEC	63
B. infantis ($3x10^8$ cfu/day), *S. thermophilus* ($3.5x10^8$ cfu/day), *B. lactis* ($3.5 x10^8$ cfu/day)	Reduced NEC	64
B. breve BBG-001 ($2.1\text{-}5.3x10^8$ cfu/day)	Reduced NEC	65
L. acidophilus + B. Infantis ($1 x10^9$/d for 14 days)	No effect on NEC	18
L. rhamnosus GG , *B. breve, B. bifidum,B. infantis*, *B. longum* ($2x10^9$ cfu/day until 34 weeks)	Reduced NEC	66
Bovine Lactoferrin + *L. rhamnosus* GG ($3×10^9$ cfu /day)	Reduced NEC	67
L. reuteri DSM 17938 ($1x10^8$cfu/daily)	Reduced NEC	68
L. acidophilus (10^9cfu/twice daily) *+B. bifidum* (10^9 cfu/twice daily)	No effect on NEC	69
L. acidophilus (10^9cfu/day) *B. infantis* (10^9cfu/day)	Reduced NEC	70
B. lactis ($5.0x10^9$ cfu/day)	Reduced NEC	71
Saccharomyces boulardi 250 mg, *L. rhamanosus* ($2.4x10^8$cfu/ twice daily) *L. acidophilus* ($2.4x10^8$cfu/ twice daily) *B. longum* ($2.4x10^8$cfu/ twice daily) *S. thermophilus* ($2.4x10^8$cfu/twice daily)	Reduced NEC	72

L. acidophilus ($6x10^9$cfu/day) *Bifidobacterium ssp.* ($6x10^9$cfu/day)	Reduced NEC	73
B. breve BBG ($1.6x10^8$-$1.6x10^9$/day until 36 weeks)	Reduced NEC	74

Recommended probiotics for administration in preterm infants are *Lactobacillus reuteri, Lactobacillus casei, L. rhamnosus GG, L. acidophilus, B. infantis, Lactobacillus* GG, *Bifidobacterium breve, Lactobacillus paracasei subsp. paracasei* [77, 78]. In order to reduce NEC and mortality in preterm infants, it is advisable to add routine prophylaxis with dual-strain probiotics such as a combination of *L. casei* and *B. breve, Bifidobacterium infantis, Lactobacillus* and *Bifidobacterium lactis* or *L. acidophilus* and *Bifidobacterium* spp. [56, 79, 80]. The Latin American Expert group consensus recommends the use of *B. breve*, mixtures of *Bifidobacterium* and *Streptococcus, L. rhamnosus* GG, *L. acidophilus* and *L. reuteri* DSM 17938 for the prevention of NEC [81].

Mechanism of Prophylactic Effect of Probiotics on NEC

Postulated mechanisms of probiotics that can be put forward towards prevention of development of sepsis and NEC in preterm infants are:

- Enhanced barrier to migration of bacteria and their products across the mucosa [82, 83]
- Competitive exclusion of potential pathogens [84]
- Modification of host response to microbial products [85]
- Augmentation of IgA mucosal responses
- Enhancement of enteral nutrition that inhibits the growth of pathogens and upregulation of immune responses [86, 87]
- promoting colonisation with beneficial organisms
- modulating the immune system to the advantage of the host [35, 88]
- binding sites and substrate in the bowel, which increases the production of anti-inflammatory cytokines, decreases the production of pro-inflammatory cytokines and reduces intestinal permeability [27, 89]

Safety of Probiotics for Preterm Infants

In general, the microorganisms used in the production of food fermentation have a long history of safe use and are often referred to as "food grade" or Generally Recognized as Safe (GRAS) microorganisms [90]. Probiotics extends numerous health benefits but theoretically they may have diverse types of side effects such as systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gene transfer interference or alteration of commensal microflora by exogenous probiotic cultures and sepsis, fungemia and GI ischemia [91-95]. FAO/WHO recommends that probiotic strains must be characterized for the following tests for recognition as GRAS [96].

- Determination of antibiotic resistance patterns
- Assessment of certain metabolic activities (D-lactate production, bile salt deconjugation)
- Assessment of side-effects during human studies
- Epidemiological surveillance of adverse incidents in consumers (post-market)
- If the strain under evaluation belongs to a species that is a known mammalian toxin producer, it must be tested for toxin production.
- If the strain under evaluation belongs to a species with known hemolytic potential, determination of hemolytic activity is required

ESPGHAN Committee on Nutrition declared that administration of commercially prepared probiotic/probiotic formulas is safe for healthy infants and more data is required for its routine use in healthy infants and for VLBW infants [97]. Based upon the level of evidence American Pediatric Surgical Association Outcomes and Clinical Trials Committee recommended routine supplementation of probiotics in premature infants but made no formal recommendations regarding the formulation, timing or duration of supplementation, however administration of at least one probiotic formulation at least for a period of 2 weeks, initiated from the first week of life is suggested [98]. Probiotics have been recommended as a routine therapy for preterm neonates and an initial dosage of $1.5x10^9$cfu/day for ELBW neonates until they reach enteral feeds of 50–60 ml/kg/day followed by an augmentation in dosages to $3x10^9$ cfu/day [99].

A meta-analysis of RCTs indicated shorter time to full enteral feeds, fewer episodes of feed intolerance, better weight gain and growth velocity, decreased transition time from or gastric to breast feeds and increased postprandial mesenteric flow reduced duration of hospitalization, lower incidence of late-onset sepsis with no adverse effects of probiotic supplementation. Current evidence indicates that probiotic supplementation did not increase the incidence risk of sepsis or mortality and is safe and effective in reducing the risk of LOS in preterm neonates in NICU [43, 100-103].

Reviewed literature and Meta analysis of randomized controlled trials revealed that controversies exist for safety and efficacy of probiotics for preterm infants especially in ELBW infants. Probiotics have been found to be well tolerated by preterm low birth weight neonates but based upon evidence and efficacy and safety routine use of probiotics in ELBW infants is not recommended [43, 57, 103-107]. Recently, Sawh *et al.* concluded that administration of probiotics may prevent severe NEC in infants with a birth weight < 2500 g but did not recommend for babies with a birth weight < 1000 g [107]. Reviewed literature suggested administration of probiotics in premature infants for prevention of NEC, however the current evidence are not conclusive due to the heterogeneity of probiotic

formulations (single or multiple-strains of probiotics), diverse doses (10^5 to 10^{10} cfu/ml) and duration of treatment [108]. Based upon reviewed literature routine use of probiotics in the preterm infant is not be recommended due to many uncertainties such as the mechanisms of action of probiotics, health effects of employed probiotics, forms of microbial adaptations and ecological consequences [109].

Millar et al. delineated various uncertainties relevant to administration of probiotics in the preterm infant as pathogenesis of NEC, impact of probiotics on early development, ecological consequences of widespread use of probiotics, microbial adaptations consequent on use of probiotics, risk groups for adverse outcomes, optimum dose and timing of intervention, impact of unintended cross-colonisation on outcome and interactions with other preventive interventions [21]. Evidence suggests that probiotics are safe but may have an adverse immunologic effect and critically sick infants in intensive care units, postoperative and hospitalized patients and patients with immune-compromised complexity were at greater risk [95, 110]. van den Nieuwboer, et al. suggested intense analysis of safety aspects prior to consideration of probiotic therapy for preterm infants and neonates [111]. Following approaches are suggested to assess the safety of a probiotic strain.

- Assessment of pathogenicity and infectivity, deleterious metabolic activities, excessive immune response and potential gene transfer [112]
- Studies should focus on the intrinsic properties of the strain
- Studies on the pharmacokinetics (survival, activity in the intestine, dose–response relationships, faecal and mucosal recovery) of the strain
- Studies for interactions between the strain and the host [113]
- An individual risk-benefit assessment is required
- Safety and efficacy of each probiotic strain has to be proven separately [57].

Future Research Requirements for Probiotic Recommendation for Preterm Infants

- Long term gut colonization or impairment of the natural diversity of the gut microbiota due to probiotic intervention at an early age needs to be addressed [114].
- Large trials are needed to evaluate the short and long-term safety of probiotics and effect on the composition and development of the intestinal microflora especially during the first months of life is emerging as probiotics can alter immune responses and microbial-epithelial cross talk [22, 76, 115,116].
- Determination of optimal dose, duration and selection of probiotic agents (species, strain, single or combined, live or killed) used for supplementation is emerging [77,100,103]
- Strain specific efficacy of probiotics to be determined for application in ELBW infants [39,117].
- Clinical trials are necessary to evaluate adverse effects of probiotic in higher risk subjects such as immune compromise, premature infants or patients with short bowel syndrome, central venous catheters and cardiac valve disease [118].
- Emergence of a standard methodology for assessing the intestinal flora and its mandatory adoption for conducting related studies and definite treatment protocols is required to arrive upon a conclusive result [74, 116].
- Research indicated that the probiotic mechanism of action can be translocated, thus increasing the risk of developing subsequent sepsis and bacteraemia, therefore determination of the optimal dosage for the best effect without side-effects, is essential [119].
- Health benefit claims of probiotic foods are still not conclusive and further studies are required to confirm its safety especially for preterm infants [109].

Conclusion

Preterm infants lack adequate intestinal commensal or "healthy" bacterial flora and abnormal pattern of colonization in preterm infants may contribute to the pathogenesis of NEC. Probiotics may promote intestinal function, maturation and defense against potential harmful pathogens and most systematic reviews reported probiotic to be safe and efficacious and can be recommend for routine administration in the preterm infants but not for ELBW infants. Breast milk is the most ideal food even for preterm infants and oral feeding with probiotics along with breast milk would exhibit a greater decline in both incidence and severity of NEC in contrast to neonates fed exclusively with breast milk.

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