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Original Research Article

Study of role of oral probiotics in patients on ventilator in paediatric Intensive Care Unit at tertiary care center

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ABSTRACT

Background: The normal intestinal microbiota of critically ill patients is altered and replaced by pathogens. Any significant insult to the gut or alteration to its microbiota plays a role in promoting systemic inflammation and infection in the critically ill population. Probiotics may affect other body sites in addition to the GI tract , and they can have applications in a variety of populations, including healthy individuals, children, elderly, immunocompromised and genetically predisposed individuals. These studies the effect of probiotics in pediatric population on mechanical ventilation in a tertiary care hospital.
Methods: Present study was conducted in a PICU of a tertiary care teaching hospital in children aged 12 years or less admitted to PICU and who were likely to need mechanical ventilation for more than 48 h were recruited.
Results: In present study 25 patients were recruited in each group i.e. case (probiotics) group and control group. Most common age group among case group was 6-8 years (44 %), while 9-12 years (36 %) was most common age group in control group. Mean age was comparable in both groups (7.6±3.5 years in case group and 7.9±4.1 years in control group). In both groups septic shock and pneumonia were most common diagnosis followed by admission due to miscellaneous cause. In both groups mechanical ventilation was used due to respiratory failure and shock. Outcome was compared in both groups. Authors noted a statistically significant difference in duration of ICU stay, duration of hospital stay and duration of mechanical ventilation, between case 7 control group ($p<0.05$). In terms of overall mortality, authors did not noted any significant difference among groups.
Conclusions: Authors noted a statistically significant difference in duration of ICU stay, duration of hospital stay and duration of mechanical ventilation, between case and control group ($p<0.05$).

Keywords: Children, Mechanical ventilation, Probiotics

INTRODUCTION

Probiotics are defined as 'live microorganisms that confer a health benefit on the host when administered in adequate amounts'.[1] Probiotics may affect other body sites in addition to the GI tract (such as the oral cavity, respiratory tract, urogenital tract and skin), and they can have applications in a variety of populations, including healthy individuals, children, the elderly, and immunocompromised and genetically predisposed individuals.[2]

The normal intestinal microbiota of critically ill patients is altered and replaced by pathogens for a number of reasons. Any significant insult to the gut or alteration to its microbiota is likely to play a role in promoting systemic inflammation and infection in the critically ill population. Guidelines on probiotics, produced by the World Gastroenterology Organization, states that gut microbiota may affect several non-gastrointestinal conditions. Numerous studies have shown that probiotics can reduce bacterial vaginosis, prevent atopic dermatitis in infants, reduce oral pathogens and dental caries, and

reduce incidence and duration of common upper respiratory tract infections.[3]

In addition to the widely recognized -beneficial health effects of probiotics, complications associated with their consumption (endocarditis, antibiotic resistance, lactobacillemia, bifidobacteremia and fungemia) appear to be rare.[4,5]

Although use of probiotics in other childhood conditions like acute infectious diarrhea, antibiotic associated diarrhea, necrotizing enterocolitis, etc. have been studied, with mixed results.[6,7] Present study was to study effect of probiotics pediatric population on mechanical ventilation in a tertiary care hospital.

METHODS

Present study was conducted in a PICU of a tertiary care teaching hospital. Study design was case-control, prospective type, study period was from June 2019 to October 2019. The study was approved by the institutional ethics committee. A written informed consent was obtained from the parents prior to inclusion of the subjects into the study.

Children aged 12 years or less admitted to PICU and who were likely to need mechanical ventilation for more than 48 h were recruited. Children with multiple trauma, known cancerous conditions, known allergies to probiotics, underlying immunodeficiency (HIV infected, children on steroids and other immunosuppressants), children with paralytic ileus, and children with gastrointestinal bleeding were excluded.

All children admitted to PICU were initially screened for the inclusion and exclusion criteria, patients satisfying all criterias were considered for present study. Case (the probiotics group) and control groups were decided on randomisation, based on number of admission, odd and even randomisation was done.

Children allocated to the probiotics group were administered one sachet twice a day mixed with milk or 5 ml of 5 % dextrose solution. Commercially available sachets containing Lactobacillus acidophilus 350 million cells, *Lactobacillusrhamnosus* 200 million cells, lactobacillus casei 150 million cells, *Lactobacillus plantarum* 150 million cells, *Lactobacillus bulgaricus* 150 million cells, Bifidobacteriumlongum 150 million cells, *Bifidobacteriuminfantis* 150 million cells, *Bifidobacteriumbreve* 150 million cells, *Streptococcus thermophilus* 200 million cells, *Saccharomyces boulardi* 50 million cells were used.

The control group did not receive either probiotics or any placebo. The throat swabs were sent to the microbiology laboratory for surveillance semi-quantitative culture of potentially pathogenic microorganisms (PPMOs) at admission and subsequently after 72 hours.

Clinical parameters like age, gender, indication for mechanical ventilation were assessed in two groups. The demographic and clinical characteristics of patients were compared in both groups. Risk factors like repeated intubations (at least two intubations), devices in situ like central venous catheter and urinary catheter, aspiration events, time taken for initiation of enteral feeds, and duration of ventilation were assessed and compared between both groups. Patients included in the study were examined daily.

All necessary routine and special investigations (biochemical/ serological/ radiological) were done whenever required. Patients were followed up till discharge from hospital. Outcome variables such as duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, and mortality studied in both groups. All statistical tests were conducted using the IBM Statistical Package for Social Sciences; version 25. Statistical significance was set at p-value <0.05. Statistical analysis was done using descriptive statistics.

RESULTS

In present study 25 patients were recruited in each group i.e. case (probiotics) group and control group.

Table 1: General characteristics.

Patient characteristics	Case (Probiotics) group	Control group
Age (in years)		
LESS than 5	6 (24%)	8 (32%)
6-8	11 (44%)	8 (32%)
9-12	8 (32%)	9 (36%)
(mean±SD) (in years)	7.6±3.5	7.9±4.1
Gender		
Boys	14 (56%)	13 (52%)
Girls	11 (44%)	12 (48%)
Diagnosis		
Septic shock	8 (32%)	7 (28%)
Intracranial infection	3 (12%)	2 (8%)
Pneumonia	6 (24%)	7 (28%)
Intracranial bleed	2 (8%)	1 (4%)
Status epilepticus	1 (4%)	2 (8%)
Miscellaneous	5 (20%)	6 (24%)
Indication for ventilation		
Respiratory failure	9 (36%)	8 (32%)
Coma	5 (20%)	3 (12%)
Shock	8 (32%)	9 (36%)
Cardiac arrest	3 (12%)	5 (20%)

Most common age group among case group was 6-8 years (44%), while 9-12 years (36%) was most common age group in control group. Mean age was comparable in both groups (7.6±3.5 years in case group and 7.9±4.1 years in control group). In both groups boys were more than girls. In both groups septic shock and pneumonia

were most common diagnosis followed by admission due to miscellaneous cause. In both groups mechanical ventilation was used due to respiratory failure and shock. (Table 1). Outcome was compared in both groups. Authors noted a statistically significant difference in duration of ICU stay, duration of hospital stay and duration of mechanical ventilation, between case 7 control group ($p<0.05$). In terms of overall mortality, we did not noted any significant difference among groups. (Table 2).

Table 2: Outcome characteristics.

Outcome characteristics	Case (Probiotics) group	Control group	p value
Duration of ICU stay (mean±SD in days)	6.5±5.12	11.26±6.87	0.001*
Duration of hospital stay (mean±SD in days)	11.92±6.19	18.01±9.95	0.001*
Duration of mechanical ventilation (mean±SD in days)	5.64±4.01	7.11±4.02	0.001*
Mortality	3 (12 %)	2 (8 %)	0.407

* p value less than 0.05 is considered significant

Table 3: Colonization of potentially pathogenic microorganisms.

Outcomes	Case (Probiotics) group	Control group	p value
Colonization at baseline			
Patients with Gram-negative PPMOs	3 (12%)	2 (8%)	0.25
Patients with Gram-positive PPMOs	3 (12%)	3 (12%)	0.21
Patients with polymicrobial PPMOs	2 (8%)	1 (4%)	0.32
Total	8/25 (32%)	6/25 (24%)	0.63
Eradication of colonization			
Patients with Gram-negative PPMOs	3 (12%)	2 (8%)	0.71
Patients with Gram-positive PPMOs	1 (4%)	1 (4%)	0.82
Patients with polymicrobial PPMOs	0	0	0
Total	4/25 (16%)	3/25 (12%)	0.35
Acquisition of colonization			
Patients with Gram-negative PPMOs	5 (20%)	7 (28%)	0.001*
Patients with Gram-positive PPMOs	2 (8%)	3 (12%)	0.004*
Patients with polymicrobial PPMOs	1 (4%)	1 (4%)	0
Total	8/25 (32%)	11/25 (44%)	0.31

(PPMOs Potentially pathogenic microorganisms)
(* p value less than 0.05 is considered significant)

The throat swabs were sent to the microbiology laboratory for culture of potentially pathogenic microorganisms (PPMOs) at admission and subsequently after 72 hours. Non-significant difference noted at baseline colonization (at admission) and eradication of colonization (no growth at 72 hr swab), 32% patients developed colonization with PPMO in case group while 44% patients developed colonization with PPMO in control group.

A significant difference in acquisition of colonization noted in patients with Gram-negative PPMOs and patients with Gram-positive PPMOs in case and control group (Table 3).

DISCUSSION

Increased colonization by pathogenic organisms and hence systemic invasion can occur with breakdown of gut microflora which normally prevent colonization by these pathogens. The 'gut origin of sepsis' hypothesis states that breakdown of the gut barrier appears to play a key role in the pathogenesis of sepsis and multiple organ dysfunction syndrome (MODS).[8]

Probiotics acts at multiple sites simultanrously. Probiotics may alter the local environment within the lumen of the gut, producing antimicrobial effects on pathogenic organisms. Lactic acid-producing and acetic acid-producing probiotics reduce the luminal pH resulting in an unfavourable milieu for pathogens.[9] Probiotics also exert a direct antimicrobial effect via the production of bacteriocins. Bacteriocins are proteins produced by bacteria that inhibit the growth and virulence of other pathogenic bacteria.[10] Probiotics have also been demonstrated to enhance intestinal barrier function. Intestinal barrier function is complex and its control involves cellular stability at a cytoskeletal and tight

junction level, as well as mucus, chloride and water secretion.[11] In addition, by competing with pathogens for nutrients and adhesion in a microbiological niche, probiotics can prevent replication by pathogens, a phenomenon known as colonisation resistance.[12]

A recent meta-analysis of probiotic prophylaxis for prevention of VAP in adults was inconclusive, with no observed effect on the prognosis for mechanically ventilated patients.[13,14] In another metaanalysis done by Siempos et al, which included five randomized controlled trials (RCTs), it was concluded that probiotics lead to significant reduction in the incidence of VAP.[15] Hojsak et al.[16] conducted a double-blind, randomized placebo-controlled trial of hospitalized children receiving Lactobacillus GG (n = 376) and placebo (the same post-pasteurized milk, deprived of Lactobacillus GG, placebo group, n = 366). They found a significantly reduced risk for respiratory tract and GI infections, in Lactobacillus GG group, compared with the placebo group.[16]

Another study of Hojsak et al, aimed to investigate the role of Bifidobacteriumanimalis; subsp.[16] lactis in preventing HCAIs. The incidence of nosocomial infections in children in developed countries is still high, ranging from 8% to 30%, and standard preventive measures, such as increased hygiene, are not sufficiently efficacious.[17] They organized a randomized, double-blind, placebo-controlled trial in 727 hospitalized children. The children were randomly assigned to receive placebo therapy (n = 365) or Bifidobacteriumanimalis subsp. Lactis in a dose of 109 CFU, once daily for the entire duration of the hospital stay (intervention group, n = 362). There was no statistical difference in primary outcome or incidence of common hospital acquired GI and respiratory tract infections between both groups and no statistical variation regarding the duration of HCAIs, the secondary outcomes.

Authors noted a statistically significant difference in duration of ICU stay, duration of hospital stay and duration of mechanical ventilation, between case and control group ($p<0.05$). In terms of overall mortality, we did not noted any significant difference among groups. Banupriya et al.[18] published an open-label randomized trial that included 25 children, aged 12 years or younger, who were likely to need mechanical ventilation for more than 48 hours. The intervention group received a probiotics mix of *L. acidophilus*, *L. rhamnosus*, *Lactobacillus plantarum*, *L. casei*, *Lactobacillus bulgaricus*, *Bifidobacteriumlongum*, *B. infantis*, *Bifidobacterium breve*, and *Streptococcus thermophilus* for 7 days or until discharge, whichever was earlier; the controls did not receive either probiotics or any placebo.

The authors found that probiotics resulted in a significant decrease in incidence of VAP, duration of pediatric ICU (PICU) and hospital stay, and mechanical ventilation. Several preventive strategies have been introduced to reduce VAP.[18] Also, the probiotic group had lower colonization rates with potentially pathogenic organisms (Klebsiella and Pseudomonas) (34.3% versus 51.4%; $p = 0.058$) and reductions of VAP caused by Klebsiella (4.2% versus 19.4%, $P = 0.01$) and Pseudomonas (4.2% versus 16.7%, $p = 0.03$). There were no complications due to the administration of probiotics.

A Cochrane review on probiotics for acute infectious diarrhea from 63 randomized and quasi-randomized placebo-controlled trials (56 of these studies recruited infants and young children) that comprised 8,014 participants from various geographical areas, in a wide range of settings, and tested different organism and doses, found that there was a diarrhea reduction following probiotic treatment compared with controls, although effect sizes were highly variable between trials.[19] Probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea in trials that used rehydration therapy alongside. Srinivasan et al, conducted a prospective study on children admitted to a PICU (n = 28) to establish clinical safety (invasive infection/colonization) of L. casei Shirota by bacteriologic surveillance in surface swabs and endotracheal aspirates (colonization) as well as blood, urine, and sterile body fluid cultures.[20] They found no evidence of either colonization or bacteremia with L. casei Shirota, and the preparation was well tolerated with no apparent side effects. Simakachorn et al, in an RCT involving 94 mechanically ventilated children (1 to 3 years), demonstrated that test formula containing a synbiotic blend (*L. paracasei* NCC 2461, *B. longum* NCC 3001, *Fructooligosaccharides*, inulin, and Acacia gum) was well tolerated.[21]

A meta-analysis of five randomized controlled trials concluded that the administration of probiotics, compared with control, was beneficial in terms of the incidence of ventilator-associated pneumonia, length of ICU stay, and colonization of the respiratory tract with Pseudomonas aeruginosa. There was no difference in ICU mortality, in-hospital mortality, duration of mechanical ventilation, and diarrhea.[22]

Current VAP prevention strategies aim to reduce colonisation of the oropharynx and upper gastrointestinal tract with pathogenic bacteria and prevent their subsequent aspiration. These measures include elevation of the head of the bed, silver-coated tracheal tubes, oral care, subglottic secretion drainage and use of sedation breaks and weaning protocols. Selective digestive tract decontamination using antibiotics in the oral cavity or whole gastrointestinal tract decontamination have been shown to reduce rates of VAP and mortality. Probiotic administration can be considered as a nonantibiotic option for the prevention of VAP through various local and systemic mechanisms that minimize the colonization by virulent species or modulate the host immune defense.[23]

CONCLUSION

Probiotics have the ability to restore the imbalance of intestinal microbiota and function in critically ill children and have been used for various indications. Authors noted a statistically significant difference in duration of ICU stay, duration of hospital stay and duration of mechanical ventilation, between case and control group ($p<0.05$).

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