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ORIGINAL

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Probiotic prophylaxis to prevent ventilator associated pneumonia (VAP) in children on mechanical ventilation: an open-label randomized controlled trial

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Take-home message: Children who received prophylactic probiotics had a significantly lower incidence of VAP compared to the control group. On multiple logistic regression analysis, use of prophylactic probiotics reduced the duration of ICU and hospital stays by an average of 2.1 and 3.3 days, respectively, after adjusting for the other confounders. No complications due to administration of probiotics were observed in the study.

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Abstract *Purpose:* Ventilator associated pneumonia (VAP) is one of the most common nosocomial infections in the pediatric intensive care unit (PICU). It is associated with increased mortality and prolonged hospital stay. Several preventive strategies have been introduced to reduce VAP. One novel intervention is prophylactic administration of probiotics. Studies on the effect of probiotics on VAP in pediatric populations are lacking. *Methods:* This was an open-label randomized controlled trial. A total of 150 children no older than 12 years admitted to the PICU were recruited from November 2011 to July 2013. Children who were likely to require ventilation for more than 48 h were eligible for inclusion in the study. Patients were randomized into two groups after stratification based on age groups. Children in the intervention group received probiotic preparation twice a day beginning from the day of ICU admission till 7 days or discharge from ICU, whichever was earlier. The control group did not receive any placebo. Children were examined daily for evidence of VAP and were followed up till discharge from hospital. Incidence of VAP, duration of hospital stay, and mortality were compared. *Results:* Children who received prophylactic probiotics had a lower incidence of VAP compared to the control group (17.1 % in the probiotics group vs 48.6 % in the control group, $p < 0.001$; 22 per 1,000 ventilated days vs 39 per 1,000 ventilated days, $p = 0.02$). On multiple logistic regression analysis, use of prophylactic probiotics decreased the incidence of VAP by 77 % and reduced the duration of ICU and hospital stays by an average of 2.1 and 3.3 days, respectively, after adjusting for the other confounders. No complications due to administration of probiotics were observed in the study. *Conclusion:* Prophylactic probiotics administration resulted in reduction of the incidence of VAP in critically ill children in a setting where baseline VAP rates are high. The intervention was found to be safe.

Keywords Probiotics · Children · Ventilator associated pneumonia

Introduction

Healthcare associated infections (HAI) represent a significant problem in the pediatric intensive care unit (PICU). Patients hospitalized in ICUs are 5–10 times more likely to acquire nosocomial infections than patients admitted to general wards [1]. HAI increase the morbidity and mortality and are associated with prolonged hospital stay [2]. VAP is one of the most common nosocomial infections in the PICU [1]. Crude ICU mortality rates in individuals with VAP have been reported to be 16–94 % compared to 0.2–51 % in individuals without VAP [3]. Several preventive strategies have been introduced to reduce VAP. One novel intervention is administration of prophylactic probiotics which has been well studied in adults. Probiotics restore non-pathogenic flora that compete with pathogens, modulate local and systemic immunity, and decrease intestinal permeability and thus can be beneficial in preventing nosocomial infections in critically ill patients [4, 5]. The role of the probiotics in preventing VAP in mechanically ventilated patients is inconclusive [6, 7]. 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 [8, 9]. In another meta-analysis done by Siempos et al. [10], which included five randomized controlled trials (RCTs), it was concluded that probiotics lead to significant reduction in the incidence of VAP. Although use of probiotics in other childhood conditions like acute infectious diarrhea, antibiotic associated diarrhea, necrotizing enterocolitis, etc. have been studied [11–13], studies on the effect of probiotics on VAP in pediatric populations are lacking.

Materials and methods

This non-blinded, non-placebo RCT was conducted in a PICU of a tertiary care teaching hospital from November 2011 to July 2013. The PICU catered for medical patients. It had 12 beds with 10 ventilators. The nurse to patient ratio was 1:4. Infectious diseases contributed to the predominant proportion (60 %) of the ICU admissions and most of the patients were admitted with severe sepsis. The study was approved by the institutional ethics committee (SEC 2011/4/85). The trial was also registered with the clinical trial registry (CTRI/2014/02/004381). Written informed consent was obtained from the parents prior to inclusion of the subjects into the study. All children aged 12 years or less admitted to PICU and who were likely to need mechanical ventilation for more than 48 h were recruited. The decision whether a child would require ventilation for more than 48 h was made by an experienced pediatric intensive care consultant on the basis of the clinical status and past experience with similar cases. Children with underlying immunodeficiency (HIV infected, children on steroids and other immunosuppressants), children with paralytic ileus, and children with gastrointestinal bleeding were excluded. The primary objective was to find out if prophylactic probiotics decrease the incidence of VAP in children admitted to the ICU. Assuming the power of the study as 80 % and 95 % confidence level with incidence of VAP among controls taken as 40 %, and 50 % expected reduction in the incidence of VAP as demonstrated in the study done by Morrow et al. [7], the sample size was estimated as 73 for each group using the OpenEpi software. To allow for 2.5 % attrition in each group due to possible deaths, the chosen sample size was 75 in each group.

Interventions

Probiotic capsules containing 2 billion CFU of *Lactobacillus*, 1 billion CFU of *Bifidobacterium*, and 300 million CFU of *Streptococcus thermophilus* were used in this study. One probiotic capsule contained a total of 3.3 billion CFU of probiotic organisms. Each capsule contained 700 million CFU of *Lactobacillus acidophilus*, 400 million CFU of *Bifidobacterium longum*, 400 million CFU of *Lactobacillus rhamnosus*, 300 million CFU of *Lactobacillus plantaris*, 300 million CFU of *Lactobacillus casei*, 300 million CFU of *Lactobacillus bulgaricus*, 300 million CFU of *Bifidobacterium infantis*, 300 million CFU of *Bifidobacterium breve*, and 300 million CFU of *Streptococcus thermophilus*. One capsule was administered twice a day mixed with milk (or 5 ml of 5 % dextrose solution if enteral feeding had not been started) and given through a nasogastric tube. A total of 6.6 billion CFU of probiotic organisms per day was administered to each child in the probiotic group for the initial 7 days or till discharge, whichever was earlier (Fig. 1).

Stratification and randomization

All children admitted to PICU during the study period were screened. Those who satisfied the inclusion criteria were recruited. Stratification was done on the basis of age groups (less than 1 year, 1–5 years, and over 5 to 12 years). On the basis of the 5-year data on proportion of children admitted to ICU according to age (from ICU statistics of previous 3 years, i.e., 2007–2010), the sizes of the strata were computed as 70, 40, and 40 children in the less than 1 year, 1–5 years, and over 5 to 12 year groups, respectively. Each group was then randomized into two groups—the probiotics group and the control group, according to a computer-generated random numbers list. Opaque, sealed, serially numbered envelopes were used for concealment of allotment. Children were randomized at admission to PICU. Only those who were expected to require more than 48 h of ventilation based

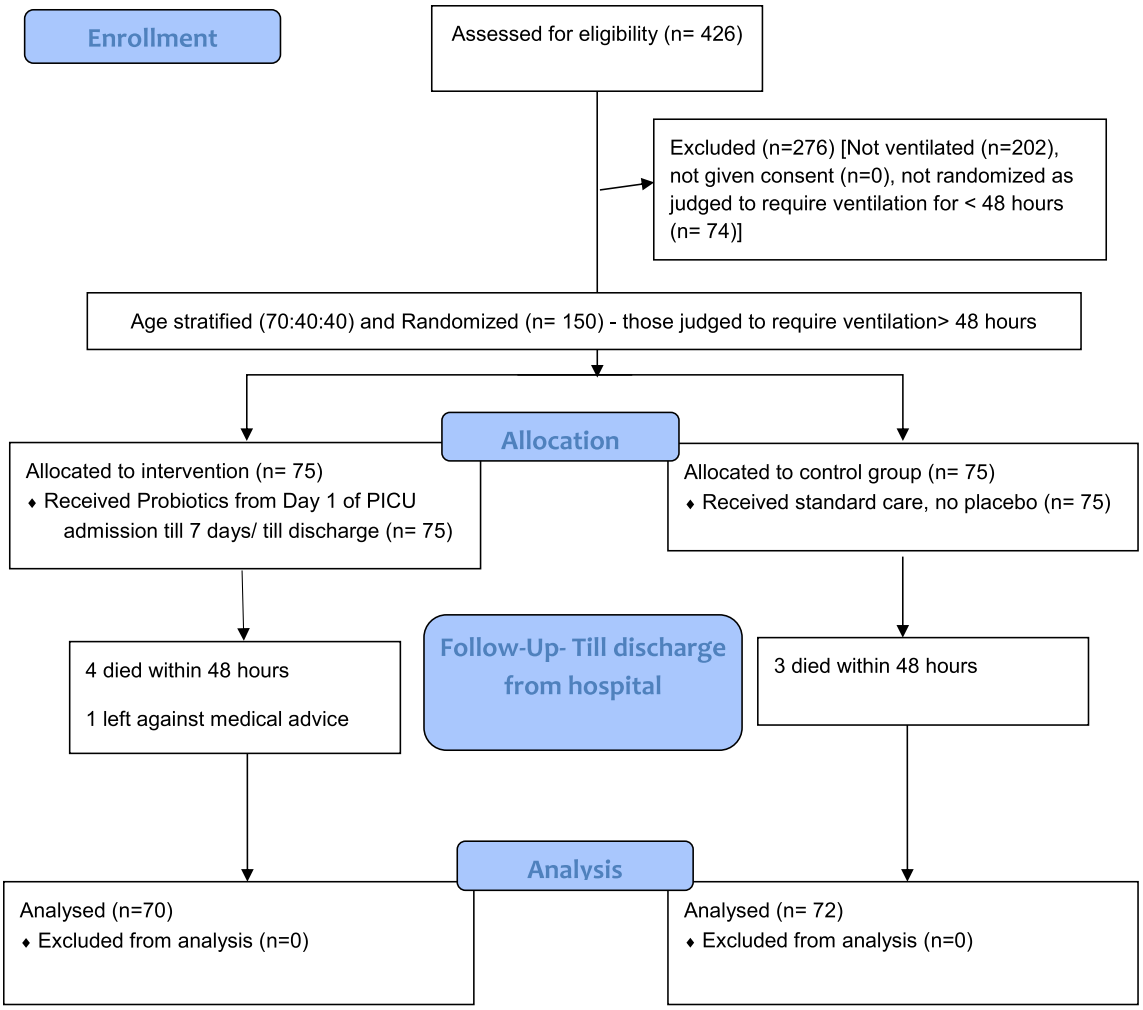

Fig. 1 CONSORT diagram of the study

on clinical judgement by an experienced person were randomized (as ventilator associated pneumonia (VAP) is defined as pneumonia developing more than 48 h after endotracheal intubation and initiation of mechanical ventilation [14]).

Clinical parameters like age, gender, indication for mechanical ventilation, PRISM score, and anthropometry based on World Health Organization (WHO) standards were assessed in two groups. The demographic and clinical characteristics of patients were compared in both groups. Pediatric risk of mortality (PRISM III) score was calculated for all children. Risk factors for nosocomial infections 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.

Children allocated to the probiotics group were administered probiotic capsules as per the study protocol. The control group did not receive either probiotics or any placebo. Patients included in the study were examined daily for any clinical evidence of VAP. Complete hemogram, blood cultures, or tracheal aspirate cultures were sent every third day or whenever there was clinical suspicion of VAP. Patients developing VAP were treated according to the standard unit protocols. Patients were followed up till discharge from hospital. Outcome variables studied in both groups were incidence of VAP, duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, and mortality. No changes were made in the methodology after commencement of the trial.

Study definitions

Ventilator associated pneumonia (VAP): for the study purpose, the diagnostic criteria for VAP were modified

from those established by the American College of Chest Physicians [15] as bronchoalveolar lavage, which is considered as a gold standard in the diagnosis of VAP, was not feasible.

VAP was defined as a new (developing more than 48 h after the start of mechanical ventilation or within 48 h of extubation) or persisting radiographic infiltrate (persisting radiographically for at least 72 h) that develops in conjunction with one of the following:

1. Radiographic evidence of pulmonary abscess formation (i.e., cavitations within pre-existing pulmonary infiltrates).
2. Two of the following: fever (increase in the core temperature of at least 1 °C and a core temperature of above 38.3 °C), leukocytosis (25 % increase in circulating leukocytes from baseline/a leukocyte count of greater than 10,000/mm^3), and purulent tracheal aspirate [Gram's stain showed more than 25 neutrophils per high-power field (×400 magnification)].
3. A positive blood or pleural fluid culture with the microorganisms recovered from blood or pleural fluid cultures being identical to the organisms recovered from cultures of respiratory secretions (tracheal aspirates). Blood and pleural fluid cultures had to be obtained within a period of 48 h before or after the clinical suspicion of VAP.

Results

Baseline characteristics of both probiotics and control groups were comparable and no significant difference was observed between any parameter in the two groups ($p > 0.05$) (Table 1). The mean age of children in the probiotics group was 2.9 ± 3.41 years and that in the control group was 2.93 ± 3.77 years, which was comparable. Indications for mechanical ventilation and clinical diagnosis at admission to ICU were also comparable between the two groups. There were no refusals of consent for participation in the study. Due informed consent was obtained without coercion from all parents of the children included in the study.

Table 1 Comparison of baseline characteristics between the two groups

Patient characteristics	Probiotics group ($n = 75$)	Control group ($n = 75$)
Age (in years) (mean ± SD)	2.9 ± 3.41	2.93 ± 3.77
Gender		
Male/female	48 (64 %):27 (36 %)	43 (57.3 %):32 (42.7 %)
PRISM score (mean ± SD)	11.61 ± 5.63	11.25 ± 6.58
Weight for height *Z* scores (children >1 month)		
Normal	23 (30.6 %)	21 (28 %)
Between −1 and −2 SD	15 (20 %)	12 (16 %)
Between −2 and −3 SD	13 (17.3 %)	15 (20 %)
Below −3 SD	8 (10.7 %)	12 (16 %)
Gestational maturity (children ≤1 month)		
Term	13 (17.3 %)	12 (16 %)
Preterm	3 (4 %)	3 (4 %)
System involved		
Neurologic	32 (42.7 %)	32 (42.7 %)
Respiratory	15 (20 %)	14 (18.7 %)
Sepsis	18 (24 %)	19 (25.3 %)
Cardiac	4 (5.3 %)	3 (4 %)
Renal	1 (1.3 %)	2 (2.7 %)
Gastrointestinal	3 (4 %)	1 (1.3 %)
Poisoning	2 (2.7 %)	4 (5.3 %)
Diagnosis		
Septic shock	15 (20 %)	9 (12 %)
Intracranial infection	16 (21.3 %)	17 (22.7 %)
Pneumonia	15 (20 %)	13 (17.3 %)
Intracranial bleed	6 (8 %)	6 (8 %)
Status epilepticus	3 (4 %)	2 (2.7 %)
Hypoxic ischemic encephalopathy	3 (4 %)	6 (8 %)
Neonatal sepsis	3 (4 %)	6 (8 %)
Miscellaneous	14 (18.7 %)	16 (21 %)
Indication for ventilation		
Respiratory failure	31 (41.3 %)	34 (45.3 %)
Coma	31 (41.3 %)	30 (40 %)
Shock	9 (12 %)	7 (9.3 %)
Cardiac arrest	4 (5.3 %)	4 (5.3 %)

All data are expressed as frequencies and percentages unless mentioned otherwise
p value less than 0.05 is considered significant

Children in the probiotics group had significantly lower incidence of VAP compared to the control group. Twelve children (17.1 %) in the probiotics group had VAP and 35 children (48.6 %) in the control group had acquired VAP ($p < 0.001$). The VAP rates were also significantly lower in the probiotics group compared to the control group (22 per 1,000 ventilated days vs 39 per 1,000 ventilated days, $p = 0.02$). Mean duration of ICU stay in the probiotics group was 7.7 days compared to 12.54 days in the control group ($p < 0.001$). Mean duration of hospital stay was 13.13 days in the probiotics group and 19.17 days in the control group ($p = 0.001$). There was no statistically significant difference in mortality between the two groups ($p = 0.407$). Mean duration of ventilation in the probiotics group was 6.24 days compared to 10.35 days in the control group ($p = 0.001$). The control group had higher colonization rates with potentially pathogenic organisms than the probiotics group (34.3 % patients in the probiotics group vs 51.4 % patients in the control group). Colonization rates with pathogenic *Klebsiella* and *Pseudomonas* was significantly reduced in the probiotics group compared to the control group. Probiotics showed significant reduction of VAP caused by *Klebsiella* (4.2 % in the probiotics group vs 19.4 % in the control group, $p = 0.01$) and *Pseudomonas* (4.2 % in the probiotics group vs 16.7 % in the control group, $p = 0.03$).

Risk factors for nosocomial infections were compared between the two groups and are shown in Table 2. There was a statistically significant higher number of children needing repeated intubations in the control group ($p = 0.027$). Re-intubation was done for indications like tube displacement, tube blockage, extubation failure due to poor sensorium, failure to maintain airway, or VAP. A greater number of children in the control group had prolonged central venous catheters in situ (more than 7 days) compared to children in the probiotics group (26.6 vs 10.6 %, $p = 0.021$). A total of 37 % ($n = 26$) children in the probiotic group required ventilation for more than 7 days as compared to 67 % ($n = 48$) children in the control group. Mean duration of ventilation in the probiotics group at the end of 7 days was 5.05 ± 2.15 days compared to 6.17 ± 2.14 days in the control group ($p = 0.001$). Other risk factors for nosocomial infections like aspiration of feeds, time to initiation of enteral feeds, parenteral nutrition, urinary catheterization, interventions, and antibiotic usage were comparable between the two groups (Table 2).

Table 2 Comparison of risk factors for nosocomial infections

Risk factors	Probiotics group ($n = 75$)	Control group ($n = 75$)	p value
No. of patients requiring ≥2 intubations	14 (18.7 %)	27 (36 %)	0.027*
Aspiration	2 (2.7 %)	4 (5.4 %)	0.670
Delayed initiation of feeds (>2 days)	14 (18.6 %)	17 (22.6 %)	0.686
Parenteral nutrition	1 (1.3 %)	3 (4 %)	0.612
Presence of central line	62 (82.6 %)	57 (76 %)	0.172
Prolonged indwelling central catheter (>7 days)	8 (10.6 %)	20 (26.6 %)	0.021*
Urinary catheterization	69 (92 %)	65 (86.6 %)	0.427
Procedures/intervention	35 (46.7 %)	33 (44 %)	0.869
Antibiotics prior to admission	68 (90.7 %)	66 (88 %)	0.791
Duration of ventilation at the end of 7 days (mean ± SD)	5.05 ± 2.15	6.17 ± 2.14	0.001*

All data are expressed as frequencies and percentages unless mentioned otherwise
* p value less than 0.05 is considered significant

Table 3 Comparison of outcome variables (univariate analysis)

Variable	Probiotics group ($n = 70$)	Control group ($n = 72$)	p value
Incidence of VAP	12 (17.1 %)	35 (48.6 %)	<0.001*
VAP rates (per 1,000 ventilated days)	22	39	0.02
Duration of ICU stay (mean ± SD)	7.7 ± 4.60	12.54 ± 9.91	<0.001*
Duration of hospital stay (mean ± SD)	13.13 ± 7.71	19.17 ± 13.51	0.001*
Duration of mechanical ventilation (mean ± SD)	6.24 ± 3.24	10.35 ± 8.87	0.001*
Mortality	17 (24.2 %)	23 (31.9 %)	0.407
Colonization rates	24 (34.3 %)	37 (51.4 %)	0.058
Mortality due to VAP	1 (1.4 %)	3 (4.2 %)	0.641

* p value less than 0.05 is considered significant

Multiple logistic regression analysis was done to overcome the effects of these confounding variables. Incidence of VAP was still found to be significantly lower in the probiotics group (Table 4) with adjusted relative risk of 0.227 (95 % CI 0.068–0.755). Probiotics decreased the duration of mechanical ventilation by a mean of 1.7 days, duration of ICU stay by a mean of 2.1 days, and duration of hospital stay by a mean of 3.3 days. In the logistic regression, we used the variable 'duration of ventilation at the end of 7 days'. We presumed that the effect of probiotic, if any, on the development of VAP will be best demonstrated in these 7 days (during which time it was administered to the child). We did not use total duration of ventilation as mechanical ventilation beyond 7 days by itself could be the effect rather than the risk factor for VAP.

Seventeen patients (24.3 %) died out of total 70 patients in the probiotics group and 23 patients (31.9 %) died out of total 72 patients in the control group (Table 3), but this difference was not statistically significant ($p = 0.407$). There were no adverse effects of the intervention in this study.

Discussion

This study mainly focused on evaluating the effect of probiotics on the incidence of VAP in pediatric ICU where studies are lacking. Although Honeycutt et al. [16] conducted a study on critically ill children in PICU at a children's hospital in North Carolina, that study was prematurely terminated because of safety concerns and lack of benefit in interim analysis.

Micro-aspiration of the pathogenic gram-positive and gram-negative bacteria, colonized on the oropharynx and gastrointestinal tract, is the main route of acquisition of VAP [17]. Also in a mechanically ventilated patient, bacterial adherence to the orotracheal mucosa is facilitated by reduced mucosal IgA, denuded mucous membranes, elevated airway pH, and increased number of airway receptors for bacteria [18]. Critical illness is often associated with significant proximal gut overgrowth of enteric organisms and alterations in intestinal barrier function predisposing to bacterial translocation across the gut resulting in sepsis [19].

Increased colonization by pathogenic organisms and hence systemic invasion can occur with breakdown of gut microflora which normally prevent colonization by these pathogens [20]. 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) [19]. Preventing carriage of potentially pathogenic microorganisms from the aero-digestive tract is an effective infection control strategy to reduce the occurrence of nosocomial infections in ICU. Therein lies the role of probiotics.

Probiotics are assumed to modulate the gut microbiota through several mechanisms—production of antimicrobial substances, competition for adhesion receptors, enhancing mucosal integrity, competition for nutrients, immunomodulatory properties of probiotics [4, 5], and stimulating the production of IgA by B cells [5]. Previous studies have proved that probiotics reduce the nasal and oropharyngeal colonization of pathogenic bacteria [21, 22] especially *Pseudomonas aeruginosa* [23].

There is a theoretical concern that probiotic strains may inhibit each other when given as a mixture. But in vitro studies have proved that a probiotic mixture is more effective at inhibiting pathogens than its component species given alone when tested at approximately equal concentrations [24].

There were no adverse effects of the intervention in this study. Probiotics are classified as generally regarded as safe (GRAS) by the Food and Agriculture Organization of the United Nations(FAO)/WHO. Studies in children have also found probiotics to be safe and beneficial [25, 26]. Several studies on probiotics have been conducted in preterm infants with no reported side effects [27–29]. The proposed theoretical risks, such as transmigration of probiotic organisms leading to probiotic induced sepsis, potential for antibiotic resistance transfer within the gastrointestinal tract from commensal or probiotic bacteria to other bacteria or potential pathogens [30], have not been found in the studies. Probiotics have been declared safe, even in immunocompromised populations such as premature neonates [31].

In this study, the probiotic group had a significant reduction in the incidence of VAP compared to the control group. This was comparable to those in previous studies [7, 32]. Multiple logistic regression analysis showed that probiotics decrease the risk of acquiring VAP by 77 %. The incidence of VAP was high in our study population. This could also be attributed to differences in diagnostic methods used for VAP. This study used modified American College of Chest Physicians' criteria for VAP which included both clinical and microbiological criteria but quantitative culture was not a prerequisite for the diagnosis. Many other studies have used microbiologically confirmed VAP (quantitative bronchoalveolar lavage culture with at least 10^4 CFU/ml). There was a significant reduction in the incidence of VAP caused by *Klebsiella* and *Pseudomonas* in the probiotics group which was similar to the observations in adult patients [7, 23]. Duration of ventilation was significantly longer in the control group as compared to the probiotic group. It may argued that this may serve as risk factor for VAP by itself. But we found that on analysis of duration of ventilation at the end of 7 days (during which the probiotic group received probiotics), the probiotic group had a significantly shorter duration of ventilation (Table 2). Differences in need for

Table 4 Comparison of outcome variables (logistic regression analysis)

Variable	Exp(*B*)	95 % CI for exp(*B*)		*p* value
		Lower	Upper	
Probiotics group	0.227	0.068	0.755	0.016*
Control group	Ref			
≥2 Intubations	11.336	3.190	40.285	<0.001*
<2 Intubations	Ref			
Prolonged indwelling central catheter (>7 days)	0.937	0.240	3.657	0.925
Indwelling central catheter for ≤7 days	Ref			
Duration of ventilation at the end of 7 days	0.356	0.217	0.585	<0.001*

repeated intubations, duration of ventilation, duration of ICU stay, and duration of central line could have been due to the significantly higher incidence of VAP in the control group. Multiple logistic regression was done including these possible confounders in the model. Probiotic use had a significant individual impact in reducing the incidence of VAP (Table 4).

Children in the probiotics group had a shorter duration of ICU stay and shorter duration of hospital stay, even after adjusting for the other confounders on the multiple logistic regression analysis. Previous studies in adults were not able to show a significant reduction in the duration of ICU and hospital stay [6, 10]. A recent meta-analysis of studies on the role of probiotics in VAP in adults concludes that probiotic prophylaxis in prevention of VAP is inconclusive [8]. One reason for this difference between adults and children could be the variable effects of probiotics on the microbiota in the gut. It is a well-known fact that the microflora of the child's gut is dynamic and attains a composition similar to that of the adult only at 2 years of age [33]. Use of probiotics also resulted in a reduced duration of mechanical ventilation by 1.7 days. But probiotics had failed to show any effect on mortality. The study was not adequately powered for finding differences in mortality. There were no refusal of consent for participation in the study. Cultural differences among different populations may be a reason for the high degree of participation.

The merits of our study include a large sample size adequately powered to assess the primary outcome, i.e., the effect of probiotics on VAP. This was the first study to examine the role of probiotics on VAP in critically ill children. Despite this the study is not without limitations. First, this study was conducted as an open-label trial. The non-blinded design could have given room for bias, but meticulous efforts were taken to overcome any potential bias. The sample size meant that the study was not powered enough to analyze the secondary outcome parameters. These data come from a single center and cannot be extrapolated to entire ICU populations. Hence further large multicenter trials would be needed.

Conclusions

Use of probiotics was associated with a significant reduction in the incidence of VAP especially in a setting where baseline VAP rates are high. It was also found to be safe. Although the costs were not evaluated in the study, it is likely that the reduction in duration of ventilation, ICU stay, and hospital stay associated with the use of probiotic therapy would be associated with significant cost savings in a setting where baseline VAP rates are high. In this era of increasing incidence of nosocomial infections and antimicrobial resistance, rather than pursuit of newer antibiotics, search for novel non-antibiotic strategies like probiotics for prevention of nosocomial infections would be more fruitful. Thus its routine use as a prophylaxis for VAP in critically ill children can be advocated. Though the cost of probiotics remains a concern, this study indirectly proves that it is a cost effective measure as it reduces expenses by reducing duration of ICU and hospital stays. However, larger multicenter trials, with cost-effectiveness analysis, are needed in different settings to further establish the efficacy of probiotics.

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Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. This article does not contain any studies with animals performed by any of the authors.

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