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ORIGINAL ARTICLE

Advantages of Probiotics in Ventilator Associated Pneumonia Prevention in Children.

Tarek Abd El-rahman Atiyyah[1], Rania Ahmed Ghonaim[2], Neveen El Sayed Ibrahim Boraey[1] , and Dalia Abdullatif AbdulRahman[1]

1Department of Pediatrics, Faculty of Medicine , Zagazig University, Zagazig, Egypt
2Department of Clinical Pathology, Faculty of Medicine , Zagazig University, Zagazig, Egypt

Corresponding author
Neveen El Sayed Ibrahim Boraey
Department of Pediatrics, Faculty of Medicine , Zagazig University, Zagazig, Egypt

E-mail:
romu_3600000@yahoo.com

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is the most common health care-associated infection in intensive care units (ICU).Its appearance causes an increase in stay, mortality and economic costs. Probiotics are non-pathogenic micro-organisms that have beneficial effects on human health. We aimed from this work to evaluate the role of probiotic in ventilator association pneumonia prevention.

Methods: This was prevention clinical trial study which performed during the period from March 2019 to January 2020 is carried out in Pediatric Department at Zagazig University Hospitals. This study included 80 children that were divided into 2 groups: Probiotic group (40 children). Non-probiotic group (40 children).All subjects in the study were subjected to: Full history. Full General examinations. Laboratory examinations: Patients were randomized to probiotic therapy received Lactobacillus LB corresponding to Lactobacillus delbrueckii and Lactobacillus fermentum 10 billions twice /daily in form of 2 sachets / day throw nasogastric tube till discharge or death.

Results: the incidence of VAP among all the studied 80 patients was 44 cases (55 %) most of them were in the control group (72.5%).There was statistically significant difference between the studied groups regarding VAP incidence (lower among probiotic group). There was statistically non-significant difference between the studied groups regarding duration of ICU stay or mechanical ventilation.

Conclusion: Using probiotic therapy**,** In this era of increasing incidence of hospital acquired life threatening infections, may be effective and safe in prevention of VAP but has no effect on duration of MV or ICU stay.

Key words: Probiotic; Ventilator association pneumonia; Prevention.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common health care-associated infection in intensive care units (ICU).Its appearance causes an increase in stay, mortality and economic costs. The traditional diagnostic criteria are clinical, radiological and microbiological. Around them there were growing controversies; thus, for example, the poor reliability of radiological criteria has been recognized in intensive care unit (ICU) patients where there may be other situations (such as atelectasis or pulmonary edema), other than an inflammatory condensation and that share radiological signs [**1].** The prevalence of VAP ranges broadly from 9 to 27%; this variability might be attributed, at least partially, to the lack of a "gold standard" for diagnosis, differences in infection control practices, different case-mix and variable underlying diseases. Ventilator-associated pneumonia (VAP) is also one of the causes of the increase in the cost of healthcare, with estimated mean attributable costs ranging from around $11,000 to 40,000 USD . Reported all-cause mortality ranges widely from 20 to 50% [**2]**
The pathogenesis of VAP is complicated; however it typically involves the colonization of upper aero digestive tract with pathogenic bacteria and the leakage of contaminated or pharyngeal secretions into the lung [**3].**
These micro-organisms contribute to the maintenance of intestinal microbial balance and

enhance the host immune system. Probiotics are commonly found in dairy products such as yoghurt, milk and kefir, and also non-dairy products such as vegetables, fruits, fish and meat [**4].** Probiotics are non-pathogenic micro-organisms – in particular *Lactobacillus* and *Bifidobacterium* – that have beneficial effects on human health such as enhancement of the host immune system and maintenance of intestinal microbial balance. Probiotics are usually given the generally regarded as safe (GRAS) status. However, since probiotics can have side-effects that include systemic infections, altered metabolism and gene transfer of antibiotic resistance from probiotic bacteria to pathogens, they should also be administered to immune-depressed children with care [5**]**.

In recent years, several studies suggest that orally administered probiotics may conduce to the prevention of VAP **[6].** However, the conclusions on this topic are still controversial [**7].** This study aimed to find out if probiotics can prevent ventilator associated pneumonia in mechanically ventilated children or not.

METHODS

This was a prevention clinical trial study which performed during the period from March 2019 to November 2019 is carried out in Pediatric intensive care unit and clinical pathology department at Zagazig University Hospitals. This study included 80 critical ill children who were divided into 2 groups: Probiotic group (40children), Non-probiotic group (40children) who did not receive probiotics. Inclusion criteria: All critical ill children aged more than one month up to 12 years old who are likely to require mechanical ventilation more than 48 hours due to any other cause rather than respiratory infection.Exclusion criteria: Immunosuppression patients, Cancer patients, Short bowel syndrome.

Written Informed consent was taken from the patient parents to participate in the study. The permission for the study was received from the Pediatrics Departments of Zagazig University Hospitals after the permission of the Institutional Review Board (IRB). The research was carried out in compliance with the Code of Ethics of the World Medical Association (Decleration of Helsinki) for studies involving humans.

Each Patient was subjected to complete history taking including (age, sex, cause of PICU admission, cause of mechanical ventilation (MV), duration & ICU stay (Days), duration of M.V (Days), Full General examinations. Laboratory investigations complete blood count (CBC) , c reactive protein (CRP), total bilirubin, Albumin, liver and kidney functions and electrolytes, arterial blood gases arterial blood gases (ABG) and bleeding profile). Chest x.ray done routinely to ensure lung ventilation and prober tubal position. Tracheal aspirate for culture and sensitivity after (5-7) days of MV. Throat swab for culture and sensitivity.

Patients were randomized to probiotic therapy received Lactobacillus LB corresponding to Lactobacillus delbrueckii and Lactobacillus fermentum 10 billions twice/daily till discharge or death. The contents of one sachet containing 10 billions of Lactobacillus were suspended in sterile, water – based surgical lubricant and administered as a slurry to the oropharynx, the contents of a second sachet containing 10 billions of Lactobacillus were suspended in sterile water and given through the nasogastric tube. Patients continued to receive active intervention until extubation, tracheostomy placement, or death. Patients were received all routine care, including VAP-preventive measures as per hospital protocols and antibiotic therapy as deemed necessary, under the direction of their admitting physicians throughout the study. Institutional VAP-prevention measures were remained unchanged throughout the study period and are described further in the online supplement.

The diagnostic criteria for VAP was defined in patients who were mechanically ventilated for more than or equal to 48 hours with presence of three or more of the following findings: Radiographic evidence of new, persistent or progressive pulmonary infiltrates. Fever more than 380c with no other recognized cause. Blood Leukocytosis (more than 12000/mm3) or Leukopenia (less than 4000/mm3). Positive culture from endotracheal aspirate. Change in sputum amount, color or character with positive sputum culture. Apnea, tachypnea, nasal flaring with retraction of chest wall or grunting, wheezing, rales or cough.

STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Chi square test and fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare continuous quantitative data of two groups, Mann whitney test (for non-normally distributed data) and independent sample t test (for normally distributed data) were used. The level statistical significance was set at 5% (P<0.05).

Highly significant difference was present if p≤0.001.

RESULTS

This study showed that there was statistically non-significant difference between the studied groups regarding gender, age or weight **(Table 1)**.

There was statistically significant difference between the studied groups regarding VAP (lower among probiotic group). Probiotic use significantly protects against incidence of VAP. VAP incidence density was calculated as follows: (Number of cases with VAP/Number of ventilator days) x 1000= VAP rate per 1000 ventilator days. VAP incidence density in probiotic group= 15/359 X 1000= 41.78 VAP rate per 1000 ventilator days. VAP incidence density in Non-probiotic group= 29/363 X 1000= 79.89 VAP rate per 1000 ventilator days **(Table 2).**

There was statistically significant difference between the studied groups regarding presence of non-sterile tracheal aspirate. There was statistically significant difference between the studied groups regarding presence of klebseilla pneumonia. There was statistically non-significant difference between the studied groups presence of other organisms **(Table 3)**

There was statistically significant difference between the studied groups regarding respiratory failure. There was statistically non-significant difference between the studied groups regarding cause of admission or other causes of ventilation **(Table 4).**

There was statistically non-significant difference between the studied groups regarding outcome (lower mortality among probiotic group). Probiotic use non-significantly reduces mortality risk (crude OR=0.73) **(Table 5)**

Table(1): Comparison between the studied groups regarding demographic characteristics and body weight

Demographic characteristics	Groups		Test	
	Probiotic group	**Non-probiotic group**	χ^2/Z	**P**
	N=40 (%)	**N=40 (%)**		
Gender: Female Male	 **15 (37.5)** **25 (62.5)**	 **18 (45)** **22 (55)**	**0**	**>0.999**
Age (years) Mean ± SD Range	 **3.11 ± 3.19** **2.25 (0.5- 13)**	 **2.65 ± 3.06** **1.15 (0.5 – 12)**	**-0.51**	**0.61**
Body weight (kg) Mean ± SD Range	 **12.25 ± 8.23** **11 (3 - 35)**	 **11.71 ± 7.47** **10 (4.8 – 35)**	**-0.053**	**0.958**

Table (2): Comparison between the studied groups regarding incidence of VAP

VAP	Groups		Test		COR (95% CI)
	Probiotic group	**Non-probiotic group**	χ^2/Z	**p**	
	N=40 (%)	**N=40 (%)**			
No **Yes**	25 (62.5) 15 (37.5)	11 (27.5) 29 (72.5)	9.899	0.002*	0.23 (0.09 – 0.59)

*p<0.05 is statistically significant COR Crude

Table (3): Comparison between the studied groups regarding tracheal aspirate

Tracheal aspirate	Groups		Test	
	Probiotic group	Non-probiotic group	χ^2	P
	N=40 (%)	N=40 (%)		
Sterile	25 (62.5)	11 (27.5)	9.899	0.002*
Non-sterile Acenitobacter E. coli Klebseilla pneumonia Pseudomonas	15 (37.5) 3 (7.5) 2 (5) 10 (25) 0 (0)	29 (72.5) 6 (15) 5 (12.5) 16 (40) 2 (5)	 Fisher Fisher 5.895 Fisher	 0.063 0.082 0.015* 0.111

*p<0.05 is statistically significant

Table (4): Comparison between the studied groups regarding cause of admission and ventilation

ITEMS	Groups		Test	
	Probiotic group	Non-probiotic group	χ^2	P
	N=40 (%)	N=40 (%)		
Cause of admission:				
Cardiac	**8 (20)**	**6 (15)**	**0.346**	**0.556**
CNS	**14 (62.5)**	**18 (62.5)**	**0.833**	**0.361**
Renal	**7 (17.5)**	**6 (15)**	**0.092**	**0.762**
GIT	**4 (10)**	**5 (12.5)**	**Fisher**	**>0.999**
Sepsis	**1 (2.5)**	**1 (2.5)**	**Fisher**	**>0.999**
Neuromuscular	**3 (7.5)**	**1 (2.5)**	**Fisher**	**0.615**
Respiratory	**4 (10)**	**8 (20)**	**Fisher**	**0.348**
Cause of ventilation:				
Cardiac failure	**5 (12.5)**	**7 (17.5)**	**0.392**	**0.531**
Respiratory failure	**27 (67.5)**	**35 (87.5)**	**4.588**	**0.032***
Renal failure	**3 (7.5)**	**1 (2.5)**	**Fisher**	**0.615**
Neurologic	**4 (10)**	**5 (12.5)**	**Fisher**	**>0.999**
Septic shock	**1 (2.5)**	**0 (0)**	**Fisher**	**>0.999**

*p<0.05 is statistically significant
odds ratio CI Confidence interval

Table (5) : Comparison between the studied groups regarding outcome:

Outcome	Groups		Test		COR (95% CI)
	Probiotic group	Non-probiotic group	χ^2	p	
	N=40 (%)	N=40 (%)			
Death	22 (55)	25 (62.5)			0.73 (0.3 – 1.79)
Discharge	18 (45)	15 (37.5)	0.464	0.494	

COR Crude odds ratio CI Confidence interval

DISCUSSION

There was statistically non-significant difference between the studied groups regarding gender, age or weight.This agreed with study done by **Banupriya et al. [4]** who aimed to study the effect of probiotics on VAP in pediatric populations. 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 48h were eligible for inclusion in the study. Patients were randomized into two groups. Children in the intervention group received probiotic preparation. The control group did not receive probiotic. They found that, there is no statistically significant difference between the studied groups regarding gender, age or weight. Baseline characteristics of both probiotics and control groups were comparable and no significant difference was observed between any parameter in the two groups ($p > 0.05$). 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.

This study showed that, there was statistically non-significant difference between the studied groups regarding cause of admission or other causes of ventilation.These results were in agreement with **Mahmoodpoor et al.** [5] who found that, there was statistically non-significant difference between the studied groups regarding cause of admission or other causes of ventilation.

This study showed that, regarding causes of admission of the studied cases. CNS, cardiac, renal and respiratory causes were the most frequent etiologies.

This disagreed with **El-Kinany et al.** [8] who aimed to evaluate the pre-PICU management at Alexandria University Children's Hospital and its association with the survival rate of the cases. A cross-sectional study was conducted on 40 patients during 12 months period at PICU of Alexandria University Children's Hospital. They found chest infection was the most common cause for admission in PICU.

This disagreed also with **Yang et al. [9]** who found that, diseases of the respiratory system was the major cause for admission in PICU.This disagrees also with]**Taori et al. [10**] who found that, cardiovascular diseases was the major cause for admission in PICU.Furthermore **Shahab et al. [11]** in the United States found that respiratory conditions 485(22.8%) were the most common

reasons for admission in PICU.This was in disagreement with **Randolph and McCulloh, [12]**, whom found that diarrheal diseases are major cause of admission in PICU in infants and children. This study showed that, regarding causes of ventilation of the studied cases, respiratory causes was the most common.These results were in agreement with other published studies on pediatric subjects, as the most common indications were respiratory causes that represented 60%–75% of ventilated subjects [13] (**Wolfler et al., 2011**).

In this study, regarding microorganisms associated with Tracheal aspirate in all the studied groups, klebsiella was the most common organism.This study showed that, there is statistically significant difference between the studied groups regarding presence of klebseilla pneumonia.*Klebsiella* was significantly reduced in the probiotics group compared to the control group.Probiotics showed significant reduction of VAP caused by*Klebsiella* (25 % in the probiotics group vs 40 % in the control group, $p = 0.01$)This study showed that, there was statistically non-significant difference between the studied groups regarding duration of ICU stay or mechanical ventilation.This agreed with **Bo et al. [14]**.These results were in disagreement with **Banupriya et al. [4]** who found 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 ventilation in the probiotics group was 6.24 days compared to 10.35 days in the control group ($p = 0.001$).This study showed that, the incidence of VAP among all the studied 80 patients was 44 cases (55 %). **Amanati et al. [15]** who aimed to identify of VAP incidence and mortality rate in PICU: They found that, VAP developed in 22.9% of critically ill children undergoing mechanical ventilation**.** This study showed that, there was statistically significant difference between the studied groups regarding VAP (lower among probiotic group). Probiotic use significantly protects against incidence of VAP.41.78 VAP rate per 1000 ventilator days among Probiotic group vs 79.89 VAP rate per 1000 ventilator daysamong non probiotic group, $p = 0.002$). Also **Zeng et al. [7]** found that, the incidence of microbiologically confirmed VAP in the probiotics group was significantly lower than that in the control patients (36.4 vs. 50.4 %, respectively; $P = 0.031$).**Branch-Elliman et al. [16]** developed a cost-benefit model to determine the most cost-effective strategy for prevention of VAP and examined a total of 120 unique combinations of VAP prevention strategies. They documented that the application of prophylactic probiotics and subglottic endotracheal tubes was cost-effective for prevention of VAP from the perspective of societal and hospital.The effect of probiotics in critically ill patients has been evaluated in several studies **[17, 18, 19]**. They all supported that the use of probiotics could reduce the risk of infection for critically ill patients, including VAP. Therefore, the application of probiotics for VAP prevention should be recommended in clinical practice in the current healthcare circumstance.This study showed that, there was statistically non-significant difference between the studied groups regarding outcome (lower mortality among probiotic group). Probiotic use non-significantly reduces mortality risk.This agreed with **Banupriya et al.** [4] who found that, probiotics had failed to show any effect on mortality. There was no statistically significant difference in mortality between the two groups ($p = 0.407$). Also **Zeng et al. [7]** found that, the administration of probiotics did not result in any improvement in the mortality.A result which is consistent with previously reported data. Many other evolving factors other than VAP, such as organ failure, may contribute to the death of critically ill patients. A possible explanation of our finding is that mortality attributable to VAP is likely to be much lower than initially believed, as suggested by **Bekaert et al. [20]** who reappraised attributable mortality of VAP and found that only 4.4 % of the deaths at 30 days and 5.9 % of those at 60 days could be attributable to VAP. Similarly, other complications which develop during the ICU stay, such as muscle weakness, pressure ulcer, pulmonary embolism and hyperactive delirium, also increase the duration of mechanical ventilation **[21]**.

CONCLUSION

We concluded that using probiotic therapy**,** In this era of increasing incidence of hospital acquired life threatening infections, may be effective and safe in prevention of VAP but has no effect on duration of MV or ICU stay.

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