Original Article

Evaluation of Synbiotics in the Prevention of Ventilator-Associated Pneumonia: A Randomized, Triple-Blind, Placebo-Controlled Clinical Trial

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Abstract

Background: Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections. The role of probiotics in preventing VAP is still questionable. This study aimed at evaluating the effect of synbiotic FamiLact 2plus on the prevention of VAP in patients admitted to the intensive care unit (ICU). **Methods:** A total of 80 mechanically ventilated patients were included and divided into two groups of 40. Group 1 received FamiLact 2plus, and group 2 received placebo. The outcome variables were compared, including the incidence of VAP, the time interval between the onset of ventilation and VAP, the duration of mechanical ventilation, and the length of stay in the ICU. **Results:** VAP is documented in four patients (10%) in group 1 and 11 patients (27.5%) in group 2 (P = 0.045). The length of stay in the ICU in group 1 was significantly shorter than in group 2, and the time interval between the start of intubation and the onset of VAP in group 1 was longer than in the placebo group. During the intervention, 15 patients in group 1 (37.5%) and 26 patients in group 2 (65%) developed diarrhea, which was a significant difference (P = 0.02). **Conclusions:** Synbiotic is associated with a reduction in the incidence of VAP as well as a reduction in ICU stay and delayed VAP.

Keywords: *Incidence, mortality, pneumonia, probiotics, synbiotics, ventilator-associated pneumonia*

Introduction

Ventilator-associated pneumonia (VAP) is an important, common, and serious nosocomial infection that affects 250,000 patients annually in the United States.[1,2] VAP is more common in patients who have had mechanical ventilation for at least 48 hours.[1,3] Studies have shown that although the intensive care unit (ICU) accounts for only 5–15% of hospital beds, more than 30% of nosocomial infections are related to these wards.[4] Among the microbial agents known for causing VAP, *Staphylococcus aureus* and gram-negative organisms are more common than other microorganisms.[5]

Although many advances have been made in supportive care, antibiotic therapy, and mechanical ventilation, VAP remains a major problem for patients admitted to the ICU.[6] In addition to antibiotic therapies for VAP, supportive treatments are extremely important. In this regard, preventing pulmonary aspiration can play an important role in preventing VAP. In addition, preventing the colonization of bacteria in the upper gastrointestinal tract reduces the risk of lung infection if aspirated.[7,8] Pulmonary micro-aspiration can be one of the most important risk factors for VAP incidence. If bacteria colonize the proximal part of the gastrointestinal tract and assume the aspiration of these secretions, VAP development increases.[9] The gastrointestinal tract is colonized by bacteria of the natural flora, and with the use of antibiotics, the natural flora of the gastrointestinal tract changes, and hence, the risk of VAP increases.[10,11]

Probiotics are beneficial microorganisms that help modulate the natural flora of the gastrointestinal tract. Probiotics have been shown to be effective in preventing diseases, such as inflammatory bowel disease, antibiotic-induced diarrhea, Clostridium difficile colitis, hepatic encephalopathy, and allergies.[12] FamiLact 2plus, which is available in the market as an oral capsule, is a synbiotic (a combination of probiotics and prebiotics) and consists of eight strains of bacteria (probiotics) and fructooligosaccharides (prebiotics). These

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bacteria include *Lactobacillus acidophilus*, *Lactobacillus casei, Lactobacillus rhamnosus*, *Lactobacillus salivarius, Lactobacillus reuteri*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *and Bifidobacterium bifidum*.[13] Probiotics can reduce the risk of infection through local and systemic effects such as inhibiting the growth of pathogenic microorganisms, enhancing the function of the gastrointestinal mucosa, reducing bacterial translocation, and optimizing the host's immune deficiencies.[14-17] Although probiotics have been shown to play a role in balancing the gastrointestinal flora, their exact role in reducing infectious complications such as VAP remains unclear. This study was performed to investigate the effect of using synbiotic FamiLact 2plus on the prevention of VAP in patients admitted to the ICU.

Methods

Trial designs and participants

This single-center randomized, triple-blind, placebo-controlled clinical trial was performed on ICU hospitalized patients who have had mechanical ventilation in Al-Zahra Hospital, affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, from November 2020 to October 2021. The trial was approved by the Ethics Committee of Isfahan University of Medical Science (Grant No.: IR.MUI.MED.REC.1399.756). It was conducted according to the Declaration of Helsinki and subsequent revisions and was registered at the Iranian Registry of Clinical Trials (unique registration number: IRCT20200825048515N45). Written informed consent was obtained from all patients or their companions.

Patients were selected from those who were admitted to ICUs of the hospital for any reason using the convenience sampling method and in order of admission time to the ICU if the inclusion criteria were met based on an intensive care specialist's opinion and also observing the exclusion criteria. The inclusion criteria were as follows: 1) hospitalization in the ICU; 2) undergoing mechanical ventilation; 3) no active lung infection; 4) not having myasthenia gravis, amyotrophic lateral sclerosis (ALS), and Guillain–Barré; and 5) lack of immunodeficiency status or use of immunosuppressive drugs. The exclusion criteria included separation of the patient from the mechanical ventilator before 48 hours and intolerance to intestinal feeding (need for intravenous feeding).

Treatment protocol and variables examined

Demographic and clinical information of patients, including age and gender, underlying lung diseases, and vital signs such as blood pressure, heart rate, weight, and height, was measured and recorded. Patients were randomly assigned to two groups: drug (1) and placebo (2) using random allocation software. For group 1, oral FamiLact 2plus (synbiotic) capsule (Zist Takhmir Company, Iran), one capsule every 12 h (two capsules daily) for 2 weeks, was prescribed, and for group 2, placebo capsule (Zist Takhmir Company, Iran) was prescribed with the same dose and duration. The blinding was as follows: the drug and placebo, prepared by the manufacturer with the same package and appearance that were coded with A and B and provided to the ICU nurse to be randomly assigned according to the code determined for each patient in the randomization process to dissolve the capsule with the relevant code in water and gavage to the patient through the nasopharyngeal tube. The physician in charge of evaluating the outcome of the study, the nurse, the patient, his companion, and the person in charge of statistical analysis of the information were unaware of the type of capsule prescribed (type of intervention) until the final analysis of the data. During the study, all patients received standard care, including preventive measures to prevent VAP (hand washing, patient position, and suction of secretions if needed), antibiotics if needed, and intestinal feeding of 30 kcal/kg. All patients were examined daily for VAP symptoms and signs. Regarding the clinical examination, chest X-ray, and laboratory findings based on American College of Chest Physicians (ACCP) criteria, the diagnosis of VAP was reported as a new or progressive infiltration in the CXR with two or three symptoms[18]:

1. Temperature lower than 35°C or higher than 38.5°C
2. Leukopenia lower than 3000 or leukocytosis higher than 10000
3. Purulent sputum or increased pulmonary secretion

After the diagnosis of VAP, a sample of patients' lung secretions was sent for culture, and other consequences were recorded in the patients, such as the interval between the onset of ventilation and VAP, the duration of mechanical ventilation, the length of stay in the ICU, and the frequency of diarrhea. The outcome variables were compared after determination in each group at the end of the intervention, including the number of VAP cases, the time interval between the onset of ventilation and VAP, the duration of mechanical ventilation (connection to the ventilator), the length of stay in the ICU, and the number of incidences of diarrhea.

Statistical analysis

The data were analyzed using SPSS software version 25 at a 5% error level and using an independent-samples t-test, Chi-square, and Fisher's exact test. $P < 0.05$ was considered significant.

Results

During the study, 102 patients were evaluated for inclusion criteria of which 87 met them. Three patients in the drug group and four patients in the placebo group were excluded from the study due to premature death, leaving the study, and the treatment service giving up continuing the study. Therefore, 80 patients were divided into two groups of 40: group 1 (synbiotic) and group 2 (placebo).

Tables 1 and 2 show the basic demographic and clinical parameters of patients in both groups. There was no significant difference between the two groups in terms of these indicators (P > 0.05).

Outcome variables

Four patients in the placebo group (10%) and 11 patients (27.5%) in the drug group of groups 1 and 2, respectively, developed VAP, which was statistically significant (P = 0.045).

Table 3 shows the comparison of other variables between the two groups. The length of stay in the ICU in the drug group was significantly shorter than in the placebo group, and the time interval between the start of intubation and the onset of VAP in the drug group was significantly longer in the placebo group than in the drug group. Although the duration of ventilation was shorter in group 1 than in group 2, this difference was not statistically significant.

Regarding the results of endotracheal culture, the results of 12 and 14 patients in the drug and placebo groups were positive, respectively, but this difference was not statistically significant. Also, during the intervention, 15 patients in group 1 (37.5%) and 26 patients in group 2 (65%) developed diarrhea, which was statistically significant (P = 0.02).

Table 1: Comparison of basic quantitative demographic and clinical parameters between the two groups

Parameter	Mean	Standard deviation	Group	*P*
Age (year)	Placebo	46.07	17.75	0.06
	Drug	38.90	15.83	
BMI	Placebo	25.48	3.15	0.88
	Drug	25.58	2.91	
Systolic blood pressure	Placebo	105.05	10.84	0.62
	Drug	106.26	10.73	
Diastolic blood pressure	Placebo	70.05	8.87	0.77
	Drug	69.39	11.25	
Heartbeat	Placebo	81.02	12.73	0.58
	Drug	79.40	13.42	

Table 2: Comparison of basic demographic and clinical qualitative parameters between the two groups

Parameter	Group		*P*
	Placebo	Drug	
Gender (male/female)	(17/23) (42.5%/57.5%)	(24/16) (60%/40%)	0.26**
Smoking	7	4	0.33*
COPD	9	5	0.43*
Diabetes mellitus	13	7	0.46**
Heart			
MI	4	4	0.99*
CHF	2	2	
IHD	1	1	
Dialysis			
Hemodialysis	1	1	0.99*
Peritoneal	1	0	
History of surgery			
Orthopedics	5	10	0.61*
Heart	4	3	
Visceral	3	2	
Urology	1	0	

*Fisher's exact test, **Chi-square test

Table 3: Comparison of outcome variables between the two groups

Parameter	Group	Mean±SD	*P*
Duration of stay in ICU (days)	Placebo	7.6750±1.43915	0.03
	Drug	7.0250±1.18727	
Ventilator connection time (hours)	Placebo	61.0750±9.78850	0.06
	Drug	57.4250±7.66908	
Time to VAP (days)	Placebo	3.1111±0.92796	0.02
	Drug	4.5000±0.57735	

Discussion

This study showed that the use of synbiotic FamiLact 2plus is associated with a significant reduction in the incidence of VAP and length of stay in the ICU and also a significant increase in the time required for the onset of VAP. Since VAP is an important cause of infection and its spread, causing illness and death in the hospital, and increasing hospital stays and higher medical costs, serious measures must be taken to prevent and treat it. Preventing colonization of pathogens in the upper and lower gastrointestinal tracts is one of the methods to prevent VAP; recently, the use of probiotics has been suggested. In fact, probiotic bacteria increase the antimicrobial peptides of host cells, regulate the composition of the intestinal flora, and reduce the overgrowth of pathogenic bacteria. Accordingly, this mechanism may have an effective and safe role in the prevention or treatment of VAP in ICU patients.[18]

Studies have shown that infectious complications such as pneumonia are less common in critically ill and surgical patients treated with probiotics.[19-21] Mahmoodpoor *et al*.[22] found the administration of probiotic product can decrease the length of ICU and hospital stay in intubated patients. Although the rate of diarrhea was lower in the drug group than in the placebo group, contrary to this study, this difference was not statistically significant, which may be due to the type of probiotics used and the related strains. A systematic review and meta-analysis by Liu *et al*.[23] showed the beneficial effect of probiotics in reducing nosocomial pneumonia. Golparvar *et al*.[24] considered the use of probiotics as an important step in reducing the incidence of VAP and improving factors such as blood pH, PCO_2, and WBC count in patients admitted to the ICU.

However, some studies have suggested that probiotics are ineffective in causing VAP; Gu *et al*.,[25] for example,

believed that the evidence from their review and meta-analysis suggests that probiotics have no beneficial effect on mechanically ventilated patients.

Differences in the type of probiotics (in terms of bacterial strains and colony count), sample size, definition of VAP (with or without microbiological approval), and the patients' conditions (surgery, trauma, etc.) can cause differences in the results.

The present study did not evaluate the mortality rate and the disease severity using one of the standard scoring systems (such as APACHE II) to homogenize the patients in the two groups. However, the study enjoys strengths such as triple-blind design and the use of a new synbiotic product (instead of a probiotic product).

Conclusion

The use of synbiotic FamiLact 2plus is associated with a reduction in VAP incidence in patients admitted to the ICU, reduction in ICU stay, and delayed VAP. Further controlled studies with larger sample sizes are necessary to confirm these effects.

Authors' contributions

F.K acquired data. M.N analyzed and interpreted the data. F.K wrote the first draft of the manuscript. R.S and A.H revised the manuscript. All authors have read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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