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Effects of Probiotics on Prevalence of Ventilator-Associated Pneumonia in Multitrauma Patients: A Randomized Clinical Trial

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Abstract

Background: Probiotics may have a role in preventing ventilator-associated pneumonia (VAP) by inhibiting the natural flora from transforming into pathogenic flora.
Objective: We sought to assess the effects of probiotics on the prevalence of VAP in multitrauma patients hospitalized in a neurosurgical intensive care unit (ICU).
Methods: This randomized clinical trial was performed from 2018 and 2019 with the participation of 150 patients hospitalized in the Neurosurgical ICU. After randomizing the participants (using the permutable blocking method) into the intervention (probiotic) and control (placebo) groups, the interventions were implemented. Each participant received one capsule every 12 hours by gavage and their VAP symptoms were evaluated and recorded. Data were assessed via SPSS-22 and then compared using the chi-square, independent t-test, Fisher's exact test, and repeated measures ANOVA.
Results: The prevalence of VAP was significantly lower in the intervention group than in the control group (p=0.001). A significant difference was observed between the two groups in pH (p=0.029) and WBC (p=0.042). The between-group difference in other variables was not significant.
Conclusion: Probiotics are effective in reducing the prevalence of VAP in trauma patients hospitalized in ICU.

Keywords: Ventilator-associated pneumonia, Trauma, Probiotic, Lactocare.

Introduction

Ventilator-Associated Pneumonia (VAP) emerges in patients undergoing mechanical ventilation (people with an endotracheal tube).[1] According to statistics, VAP affects 250,000 people per year and the prevalence of ventilator-associated pneumonia in Iran is also reported to be about 70%.[2] It is a nosocomial infection with a higher prevalence among the patients, who are submitted to mechanical ventilation (MV) for at least 48 hours. Studies have shown that although 5-15% of all hospital beds are allocated to ICUs, accounting for more than 30% of nosocomial infections, which raises a major health concern.[3,4]

VAP is a common, costly, and serious complication in ICU patients and the leading cause of nosocomial infections. Among the known microbial causes of this complication, Staphylococcus aureus and gram-negative bacteria are the most common microorganisms.[5]

Despite several recent progress in supportive care, antibiotic treatments, and mechanical ventilation, VAP has remained a major problem in ICU patients.[6] Studies have attributed this complication to various risk factors, such as age over 60 years, male gender, brain trauma, chronic lung disease, increased duration of mechanical ventilation, pulmonary aspiration, sinusitis, paralysis of the limbs, having nasogastric tube, low endotracheal tube cuff pressure, temporary transfer out of the ICU, and delayed extubation.[7,8] Pulmonary aspiration may be one of the most important risk factors of VAP. The VAP possibility greatly increases with the colonization of bacteria in the proximal part of the digestive system and aspiration of these secretions.[9]

It has been shown that the highest VAP rate occurs on the fifth day of mechanical ventilation. There are still many disagreements among specialists about the clinical and microbiological diagnosis of VAP, identification of its risk

factors, prevention indicators, and experimental treatment.[10]

In addition to antibiotic treatments for VAP, supportive therapies are extremely important. In this regard, pulmonary aspiration prevention can play a more important role in VAP prevention.[11] It is also noteworthy that bacterial colonization prevention in the upper part of the digestive system reduces the risk of infection at aspiration. The digestive system is colonized by natural flora bacteria. Using medication, especially antibiotics, or having stress can change the natural flora of the digestive system, and thereby increase the risk of VAP.[12]

Probiotics are beneficial microorganisms, which can contribute to the adjustment of the natural flora of the digestive system. It has been proved that they have a role in preventing various diseases such as inflammatory bowel disease, antibiotic-induced diarrhea, Clostridium difficile colitis, hepatic encephalopathy, and allergy. Lactocare, available in the market in the form of oral capsules, is a symbiotic of probiotics and prebiotics. Lactocare consists of 1010 colony forming units (CFU), which itself contains seven species of probiotic bacteria in an insulin base. These bacteria include *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophiles, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum,* and *Lactobacillus bulgaricus.*[13,14] Since probiotics are living microorganisms that colonize the oropharynx and digestive system and prevent the natural flora from transforming into pathogenic flora, they may be effective in preventing VAP;[15] however, the mechanism of its effects is still unknown. Therefore, this study aimed to investigate the effects of probiotics on the prevalence of VAP in multitrauma patients hospitalized in the neurosurgical ICU.

Materials and Methods

This single blind randomized clinical trial was performed between 2018 and 2019 in the ICUs of Imam Reza and Shohada Hospitals (Tabriz-Iran). For this reason, 150 ICU patients in these centers were enrolled based on the inclusion and exclusion criteria. The inclusion criteria were ICU patients submitted to mechanical ventilation (MV) for at least 48 hours. The exclusion criteria were insensitivity to probiotics (based on the clinical record), death during the intervention, discontinuation of mechanical ventilation in less than 48 hours, history of infectious diseases, history of lung diseases, urinary tract infections, febrility, bedsores, cancer, receiving immune suppression medicines, receiving chemotherapy drugs, and transfer to other departments. The ICU of the Imam Reza Hospital, affiliated with the Tabriz University of Medical Sciences, was selected for data collection and intervention.

The estimated sample size was 150 based on a similar study,[16] power of 80%, confidence interval of 95%, α=0.05, ß=0.2, impact factor of 0.2, and sample loss of 5%. The participants were selected using convenience sampling from the ICUs of the aforementioned hospitals and then randomized into the intervention and control groups. In this single-blind study, the statistical specialist was completely blinded to the groups.

The participants were randomized in either the intervention or placebo groups, using the permutable blocking method with a block size of 4. For this purpose, four possible states of the blocks (BAAB, ABBA, BABA, AABB, ABAB, and BBAA) were first listed and a random number from 0 and 1 was assigned to each block, based on which the participants were assigned to the intervention (A) and placebo (B) groups. This process continued until the required sample size was achieved.

At the beginning of the study, the patients received two daily Lactocare capsules (Zist Takhmir Company-Tehran-Iran) with 20 cc of distilled water through NG tube once every 12 hours (9 o'clock in the morning and evening - at least two hours after the last NG tube). In the control group, the starch capsule was administered as a placebo (twice per day - once every twelve hours - at 9 o'clock in the morning and evening - at least two hours after the last NG tube).

The body temperature, blood pressure, heart rate, partial pressure of carbon dioxide (PCO_2), pH, blood oxygen saturation level (SPO20) of arterial blood pH, WBC count, and neutrophil percentage of each patient were measured and recorded at 8 am every morning. While intensive care was provided, the auscultation of lungs was performed by an anesthesiologist and the results were recorded as clear, coarse, generalized rattling, and reduced localized voices. In the case of susceptibility to pneumonia, a chest x-ray (CXR) was performed base on the clinical pulmonary infection score (CPIS). The set number of breaths was recorded based on synchronized intermittent mandatory ventilation full support (SIMV) with a rate of eight or more, or its equivalent in other ventilation support methods, such as partial ventilation support (lower support) and spontaneous

(ventilation with an endotracheal tube or tracheostomy tube using T-Piece or oxygen mask). All requests for culture and antibiogram reports were recorded by the medical team.

The positive VAP indicators included the diagnosis of pneumonia by an infectious disease specialist after 48 hours under mechanical ventilation 4, positive sputum culture after 48 hours of mechanical ventilation, fever, leukocytosis with a left shift along with another symptom including consolidation in CXR, increase in the pulmonary secretion, foul-smelling pulmonary secretions, increased need for respiratory support without systemic problems or metabolic disorders. All patients received the VAP routine and preventative measures according to the hospital policy. These measures included bed positioning at an angle of 3-45, using chlorhexidine mouthwash, oropharyngeal secretion suctioning, endotracheal cuff pressure control, and using sterile gloves for all nursing procedures, hand washing, and hygiene procedures.

Ethical considerations included obtaining informed written consent from the patient's first-degree relatives, free intervention, coordination with the attending physician, no counseling fee and providing routine procedures for all patients. Also, the code of ethics was obtained from Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.499) and registered in the Iranian clinical trial system (IRCT20190325043107N18).

After collecting data by the researcher, they were inputted into SPSS-22 (IBM Corporation, Armonk, NY) by a statistical consultant. Quantitative data were presented in the form of mean and standard deviation. Qualitative data were shown in the form of numbers and percentages. The chi-square test, Fisher's exact test, independent t-test, and repeated measures ANOVA were employed for quantitative variables at different times. A p-value of less than 0.05 was statistically significant.

Results

A total of 319 patients were hospitalized in the ICU over this period. Among them, 150 patients were enrolled in this study. The participants were randomized into two equal-size groups. In the intervention group, one participant was excluded due to death and one due to transfer to another department. In the control group, one person was excluded due to early ventilator disconnection (in less than 12 hours after the start of the intervention). Finally, 73 participants remained in the intervention group and 74 participants in the control group (Figure-1).

Demographic information of the participants did not show any significant between-group difference in the age (p = 0.309), gender (p = 0.119), Glasgow Coma Scale (p = 0.409), cause of trauma (p = 0.709), and body mass index (p = 0.400). However, the number of people with a history of drug abuse was significantly higher in the intervention group than the control group (p=0.044) (Table-1).

Studies on the length of hospital stay (p=0.119) and ICU stay (p=0.219), pulmonary sounds (p=0.149), and the existence of consolidation (p=0.509) did not show any significant between-group difference (Table-2). The results also showed a significantly lower prevalence of VAP in the intervention group than the control group (p = 0.001). According to Table-2, there was no significant difference in culturing pulmonary secretions (p=0.059) and antibacterial resistance in the antibiogram (p=0.339) between the intervention and control groups.

The blood test results indicated that the intervention group had the highest stability in all variables. According to the t-test results, changes in four consecutive days indicated a statistically significant between-group difference in the pH (p=0.029) and WBC (p=0.042); whereas, the between-group difference was not significant in other variables (Table-3).

Discussion

This study aimed to investigate the effects of probiotics on the prevalence of VAP in patients with multitrauma hospitalized in neurosurgical ICU. The results suggested that the probiotic capsule could reduce the incidence of VAP. Moreover, the blood pH level was significantly improved in the intervention patients compared to the control patients (without receiving probiotics). VAP in the ICU occurs due to various factors, including the normal flora of the digestive system. In this study, the use of probiotics and normalization of the altered flora of the digestive system reduced the incidence of VAP. In a meta-analysis, Siempos et al. (2010) reviewed five studies into the effects of probiotics on the incidence of VAP. They found that this medicine reduced the incidence of VAP, which is consistent with the findings of the present study.[17] In a meta-analysis by Su et al. (2020), they investigated the preventive effects of probiotics in 14 clinical trials in reducing the prevalence of VAP and concluded that the use of probiotics could significantly reduce its incidence.[18]

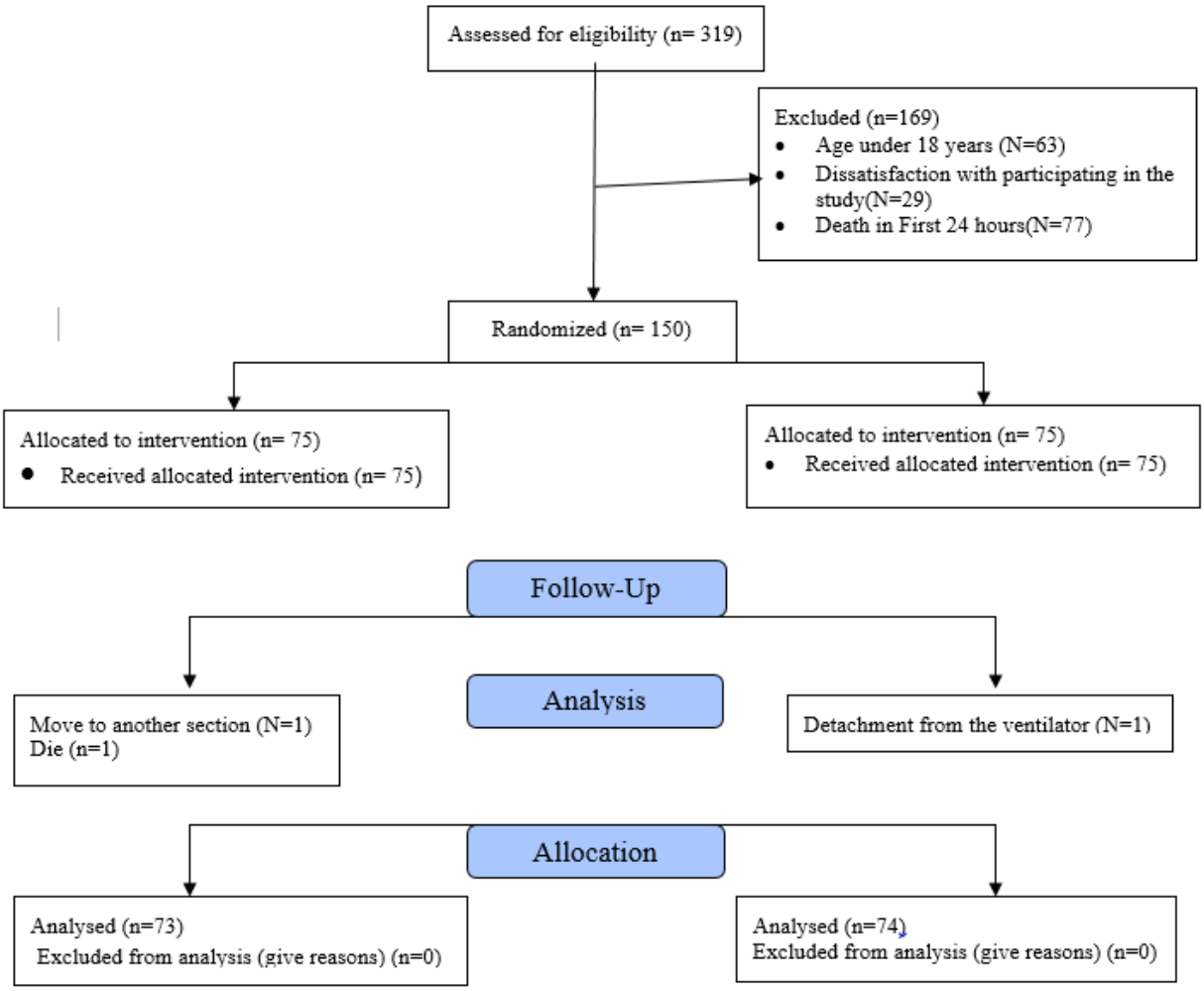

Figure-1. The flow Chart of the Recruitment and Retention of Participants

Table-1. Comparison of demographic information of participants

Variables		Groups (N=147)		P value
		Intervention Group (N=73)	Control Group (N=74)	
Age (Mean ±SD)		52.18±04.10	53.02±03.99	0.309
Sex N (%)	Male	49 (67.12%)	52 (70.27%)	0.119
	Female	24 (32.88%)	22 (29.73%)	
GCS (Mean ±SD)		6.22±01.15	6.51±01.10	0.409
Diagnosis N (%)	Traffic	59 (80.83%)	60 (81.09%)	0.709
	Non-traffic	14 (19.17%)	14 (18.91%)	
Underlying disease N (%)	Yes	53(72.60%)	50(67.56%)	0.211
	No	20(27.40%)	24(32.44%)	
BMI (Mean ±SD)		25.10±02.10	25.59±02.03	0.400
Opium use N (%)	Yes	12 (16.44%)	5 (06.75%)	0.044
	NO	61 (83.56%)	69 (95.25%)	

GCS: Glasgow Coma Scale BMI: Body mass index

Table-2. Comparison of lungs conditions, length of stay, and prevalence of pneumonia in ICU patients

Variables		Groups (N=147)		P Value
		Intervention Group (N=73)	Control Group (N=74)	
Pulmonary hearing	low	48(65.75%)	45(60.81%)	0.149
	Crackles	25(34.25%)	29(39.09%)	
Consolidation	Yes	31(42.46%)	32(43.25%)	0.509
	No	42(57.54%)	42(56.75%)	
Duration of use of mechanical ventilation (Day)		08.19±01.21	08.00±01.51	0.219
Duration of hospitalization in the intensive care unit		13.35±01.45	14.88±01.79	0.119
VAP	Yes	9(12.32%)	33(44.59%)	0.001
	No	64(87.68%)	41(55.41%)	
Cultivation of lung secretions	Positive	15(20.54%)	20(27.03%)	0.059
	Negative	58(79.46%)	54(72.97%)	
Presence of antibacterial resistance in antibiogram	Positive	10(13.69%)	12(16.21%)	0.339
	Negative	32(43.83%)	30(40.54%)	
	Unknown	32(43.83%)	31(41.89%)	

Table-3. Comparison of blood tests on different days of intervention between the two groups

Variables		Groups (N=147)		P Value
		Intervention Group (N=73)	Control Group (N=74)	
Ph	First Day	07.23±00.05	07.24±00.03	0.315
	Second day	07.29±00.06	07.22±00.04	0.218
	Third Day	07.35±00.10	07.24±00.05	0.119
	Fourth Day	07.40±00.12	07.25±00.08	0.098
	P Value	0.029		
PCO2	First Day	39.80±01.45	39.78±01.15	0.411
	Second day	39.88±01.49	38.81±01.25	0.259
	Third Day	40.05±01.47	39.23±01.12	0.109
	Fourth Day	40.12±01.10	39.55±01.10	0.119
	P Value	0.219		
Hr	First Day	89.12±02.29	88.14±02.45	0.501
	Second day	85.15±02.33	83.15±02.36	0.452
	Third Day	86.29±02.78	84.95±02.87	0.369
	Fourth Day	88.10±02.44	89.30±02.59	0.359
	P Value	0.258		
SBP	First Day	125.12±05.12	129.14±02.23	0.215
	Second day	141.25±06.59	158.79±04.59	0.088
	Third Day	136.49±05.36	149.96±03.33	0.098
	Fourth Day	138.62±05.81	148.22±03.05	0.102
	P Value	0.219		
DBP	First Day	69.10±02.10	71.14±02.65	0.259
	Second day	88.49±03.85	85.29±02.29	0.209
	Third Day	80.89±03.59	85.33±02.23	0.119
	Fourth Day	79.59±02.25	76.59±02.10	0.216
	P Value	0.119		
Temp	First Day	38.12±01.10	38.40±01.50	0.215
	Second day	38.30±01.15	39.02±01.90	0.098
	Third Day	38.40±01.06	39.36±01.25	0.077
	Fourth Day	38.15±01.12	39.70±01.12	0.065
	P Value	0.054		

WBC	First Day	96.12±08.10	98.10±08.22	0.115
	Second day	95.20±08.23	102.25±09.59	0.059
	Third Day	98.39±08.02	110.12±10.36	0.040
	Fourth Day	97.14±08.15	115.36±10.15	0.031
	P Value	0.042		
Neutrophil	First Day	72.12±03.14	72.35±01.45	0.202
	Second day	73.10±03.26	79.35±01.45	0.111
	Third Day	74.26±03.81	65.35±01.45	0.069
	Fourth Day	75.15±03.11	85.35±01.45	0.079
	P Value	0.230		

Bonten examined the prophylactic effects of antibiotics and finally recommended the use of such new methods as probiotic therapy for VAP prevention. They also mentioned the effectiveness of Lactocare, used in this study, in preventing this complication.[19] Their findings were consistent with the results of the present study.

The present study also revealed that the use of probiotics could not significantly reduce the length of ICU stay as compared to the control patients. In this regard, the present study was consistent with the study of Mahmoodpoor et al. (2019), who found that probiotics could not reduce the length of ICU stay of VAP patients. The present study used a methodology similar to Mahmoudpoor et al., study. It seems that further studies with a greater sample size are required to achieve more accurate results regarding the efficacy of this medicine.[20]

The results also showed that among the respiratory parameters, only the pH and WBC were associated with significant changes, and the use of probiotics led to desired effects; whereas, no significant changes were observed in other parameters. It seems that the effects of this medicine resulted in a reduced incidence of VAP which, and also affected the pH and WBC stability. However, it needs more precise studies to establish why it did not result in significant changes in other parameters.

The present study was performed on a few trauma patients; therefore, the results cannot be generalized to other patients.

It is recommended performing this study with a larger sample size and patients with other diseases. On the other hand, due to the positive effects of probiotics in reducing the prevalence of VAP in trauma patients, it is recommended using this medicine for these patients.

Conclusions

In conclusion, probiotics are effective in reducing the incidence of VAP in trauma patients admitted to the ICU.

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Authors' Contribution

All authors pass the four criteria for authorship contribution based on the International Committee of Medical Journal Editors (ICMJE) recommendations.

Conflict of Interests

The authors declared no potential conflict of interests with respect to the research, authorship, and/or publication of this article.

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