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Research Article

EARLY PROBIOTICS IN PREVENTING VENTILATOR-ASSOCIATED PNEUMONIA AFTER MULTIPLE TRAUMA

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ABSTRACT

Objective: Using probiotics in preventing ventilator-associated pneumonia (VAP) remain controversial due to different intensive care unit (ICU) populations included in such studies. The aim of this study is to evaluate the role of probiotics in prophylaxis of VAP after multiple trauma.

Methods: Sixty-five adult multiple trauma patients on mechanical ventilator (expected ≥48 h) after admission to the Critical Care Medicine Department, Alexandria Main University Hospital from June to November 2018. Patients were randomly assigned using computer sheet into two groups; probiotics group (32 patients received one Lacteol Forte® sachet through orogastric/nasogastric tube 3 times daily during their ICU stay) and control group (33 patients received similar regimen of placebo sachets). All patients were followed up and subjected to all possible strategies of the diagnosis of microbiologically confirmed VAP.

Results: Sixty-five patients were enrolled with a mean of age (39.48±7.692) years, 80% of them were male. Regarding the incidence of VAP, it was 18.46% of all patients without statistically significant difference between probiotics group (15.63%) and control group (21.21%) (p=0.751).

Conclusion: Routine use of early probiotics in mechanically ventilated multiple trauma patients was not associated with lower incidence of VAP, duration of MV, or ICU mortality.

Trial Registration: Alexandria University, IRB No: 00007589 FWA No: 00015712
Keywords: Critical, Mechanical Ventilation, Pneumonia, Probiotics.

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is "a type of nosocomial pneumonia which occurs more than 48 h after intubation." It is usually suspected when new or progressive infiltrate or clinical findings as fever ≥38°C, leukocytosis or leukopenia, and purulent secretions in contrast to hospital-acquired pneumonia, which occurs ≥ 48 h after admission without mechanical ventilation (MV) [1,2].

Globally, the prevalence of VAP is ranged between 10 and 20% of mechanically ventilated patients [3]. In recent research, the estimated overall mortality was about 13% [4]. *Pseudomonas aeruginosa* and Methicillin-resistant *Staphylococcus aureus* are the most prevalent organisms in VAP [5].Multiple factors are involved in the its pathogenesis including altered host immunity, oropharyngeal colonization, and factors associated with ventilator itself [2,6]. Although extensive studies for years, clear preventive strategies are still eluding VAP [7].

The World Health Organizations' Food and Agriculture Organization defined probiotic as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [8]. Different probiotic species or combination appears effective in decreasing the risk of diarrhea due to clostridium difficile and other antibiotic-related diarrhea [9]. In two systematic reviews, prophylactic probiotics were found to reduce VAP but not mortality in intensive care unit (ICU) settings [10,11]. However, these two reviews were limited by clinical heterogeneity. These two reviews recommended that future studies should be conducted to find a benefit in trauma patients specifically [11,12].

The aim of this study is to evaluate the role of probiotics in VAP prophylaxis in critically ill patients after multiple trauma.

METHODS

After approval of the medical ethics committee of Alexandria Faculty of Medicine, an informed consent was taken from the patient's next of kin.

This study included 65 adult multiple trauma patients on mechanical ventilator (expected ≥48 h) who were admitted to the Critical Care Medicine Department, Alexandria Main University Hospital from June 2018 to November 2018.

All enrolled patients were adults (>18 years) mechanically ventilated with expected ventilation for ≥48 h with no evidence of pneumonia at admission and not receiving antibiotics (at least 5 days before). All patients with previous MV >12 h, enteral medication contraindications, pregnancy, history of bronchiectasis, cystic fibrosis, or witnessed pulmonary aspiration either prior or at intubation were excluded from the study.

Patients were examined at time of enrollment with complete history taking, physical examination, diagnosis, routine laboratory investigations, and chest X-ray. In this double blinded trial, patients were randomly assigned using computer sheet into two groups; probiotics group (32 patients received one Lacteol Forte® sachet through orogastric/nasogastric tube 3 times daily during their ICU stay) and control group (33 patients received similar regimen of placebo sachets). Lacteol Forte® sachet contains "*Lactobacillus* LB, corresponding to *Lactobacillus delbrueckii* and *Lactobacillus fermentum* (10 billion)."

All enrolled patients were followed up during their ICU stay. Protocol of treatment was not changed during the study time. The same VAP preventive strategy was used over the study time if no contraindication. This strategy includes bed elevation, oral care, sedation interruption, stress ulcer, and deep vein thrombosis prophylaxis. Primary outcome was the diagnosis of VAP (using clinical, invasive diagnostic strategy, and surveillance for ventilator-associated events). Secondary outcomes were MV days and all cause in ICU mortality.

Statistical analysis of the data [13]

Data were fed to the computer and analyzed using IBM SPSS software package version 24.0 [14]. Qualitative data were described using

number and percent. Quantitative data were described using mean, standard deviation, and median. Significance of the obtained results was judged at the 5% level. Chi-square test was used for categorical variables to compare between different groups. Fisher's exact or Monte Carlo correction was a correction for Chi-square when applicable. Student's t-test was used for normally quantitative variables. Mann–Whitney U-test was used for abnormally quantitative variables.

RESULTS

In this study, two studied groups (probiotic and control) were studied. The mean of age of all patients was 39.48±7.692 years. About 80% of participants were males. There were no statistically significant differences between the two studied groups in their age (p=0.918) or sex (p=0.367).

At initial assessment, both groups were presented with nearly similar hemodynamics. There were no statistically significant differences between them in their mean arterial pressure (p=0.869), heart rate (p=0.610), temperature (p=0.162), or respiratory rate (p=0.224).

Regarding inflammatory markers, there were no statistically significant differences between them in their levels of C-reactive protein (p=0.156), procalcitonin (p=0.171), or white blood cells count (p=0.553) (Table 1).

Regarding the main study outcome (the incidence of VAP), it was 18.46% of all enrolled patients during their ICU stay. It was lower in probiotic group (15.63%) than control group (21.21%) but without statistically significant difference (p=0.751) (Fig. 1). Regarding the secondary outcomes, there were no statistically significant differences between the two groups in their duration of MV (p=0.182) or ICU mortality (p=1.000) (Table 2).

DISCUSSION

In this study, the incidence of VAP was investigated during ICU stay of two comparable groups of patients (n=65) after multiple trauma on MV. It was found to be 18.46%. Using prophylactic probiotic early (15.63%) was not associated with lower incidence than placebo (21.21%) (p=0.751) or different outcomes as duration of MV (p=0.182) and ICU mortality (p=1.000).

In contrast, Gu *et al*. meta-analysis of five randomized controlled trials (RCTs) showed that probiotics were associated with lower incidence of nosocomial infections by 35% generally. Specifically, it was associated with lower VAP and ICU stay with no difference in mortality [12].

Furthermore, Bo *et al*. meta-analysis showed that there is no enough evidence to draw conclusions on the efficacy of routine use of probiotics to decrease incidence of VAP or mortality in ICU patients. However, only

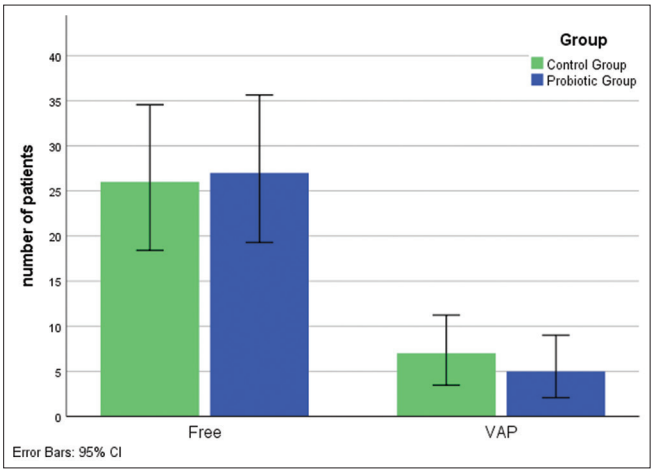

Fig. 1: The incidence of ventilator-associated pneumonia of the two studied groups

Table 1: Baseline characteristics of all enrolled patients

	Overall (n=65)		Probiotic group (n=32)		Control group (n=33)		p value
	No.	%	No.	%	No.	%	
Male	52	80	24	75	28	84.8	0.367
Female	13	20	8	25	5	15.2	
Age (years)	39.48±7.692		39.08±7.113		39.88±7.905		0.918
MAP (mmHg)	85.62±9.846		86.40±12.644		84.83±8.979		0.869
HR (beats/min)	102.74±14.127		103.66±14.779		101.85±13.634		0.610
Temp. (°C)	37.04±0.134		37.06±0.168		37.02±0.087		0.162
RR (breaths/min)	25.71±4.537		26.41±4.771		25.03±4.261		0.224
WBCs×10^9/L	9.83±1.620		9.95±1.618		9.71±1.639		0.553
CRP (mg/L)	18.4±10.058		16.59±10.014		20.15±9.937		0.156
PCT (ng/mL)	0.34±0.131		0.32±0.132		0.36±0.129		0.171
GCS	9.11±1.134		9.06±1.162		9.15±1.121		0.754

MAP: Mean arterial pressure, HR: Heart rate, RR: Respiratory rate, Temp: Surface body temperature, GCS: Glasgow Coma Scale. *p value is significant when p≤0.05. Data are expressed as number, % or mean ±S.D.

Table 2: The measured outcomes of all enrolled patients

	Overall (n=65)		Probiotic group (n=32)		Control group (n=33)		p value
	No.	%	No.	%	No.	%	
Incidence of VAP	12	18.46	5	15.63	7	21.21	0.751
Pseudomonas	4	33.33	2	40.0	2	28.57	0.554
Streptococci	2	16.67	0	0	2	28.57	
Klebsiella	3	25.0	2	40.0	1	14.29	
Acinetobacter	2	16.67	1	20.0	1	14.29	
MRSA	1	8.33	0	0	1	14.29	
Duration of MV (days)	9.46±3.845		11.60±4.775		9.10±3.642		0.182
ICU LOS (days)	12.91±3.838		14.60±4.775		12.63±3.681		0.296
ICU mortality	23	35.38	11	34.38	12	36.36	1.000

MRSA: Methicillin-resistant *Staphylococcus aureus*. *p value is significant when p≤0.05. VAP: Ventilator-associated pneumonia, ICU: Intensive care unit. Data are expressed as number, % or mean ±S.D.

one study showed that there was a strong justification for the use of probiotics in trauma patients[11].

In all included studies, different compositions of probiotics were tested. For example, a synbiotics formulation which contains *Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *Lactobacillus paracasei* sp., and *Lactobacillus plantarum* was associated with similar incidence of VAP (9%) when compared to placebo (13%) [15]. While, another contain only *Lactobacillus rhamnosus* was associated with lower incidence (19%) versus placebo (40%) [16].

To the best of our knowledge, this was the first RCT to investigate the role of probiotics in multiple trauma patients after the previously mentioned two reviews. We think that there are many confounding factors incorporated in these conflicting results other than mixed populations included, different formulations of prebiotics, probiotics, and synbiotics, no standard content in these products was used, different preventive strategies and bundles for VAP and lack of evidence supporting the use of these formulations in nasogastric and orogastric tubes. All these limitations can be applied to our study besides its small sample size.

CONCLUSION

From the results of this study, routine use of early probiotics in mechanically ventilated multiple trauma patients was not associated with lower incidence of VAP, duration of MV, or ICU mortality. After controlling confounding factors, further larger multicentric studies are required to verify these results.

AUTHORS' CONTRIBUTIONS

All authors had equal contribution.

CONFLICTS OF INTEREST

The authors declare that there are no any conflicts of interest.

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