Effects of a novel seven-species probiotic against oropharyngeal bacterial infestation in adult trauma intensive care unit patients

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Abstract

Aim: Ventilator-associated pneumonia results from invasion of the lower respiratory tract and lung parenchyma by microorganisms. Our study aimed to investigate the efficacy of a new probiotic combination containing 7 bacterial species against oropharyngeal bacterial infestation in adult trauma intensive care unit patients. Material and Method: One hundred and fifty patients were placed in the two treatment groups by computerized random allocation in a 1:1 ratio and received either probiotics or placebo. Oropharyngeal cultures were taken on the 1st (before the intervention), 4th, and 6th days of admission. Results: The culture results of the 1st, 4th, and 6th days were comparable, and no statistically significant difference was noticed in the two arms of the study. Discussion: Based on the results of our study, administration of probiotics to alter early oropharyngeal cavity infestation with a potentially pathogenic microorganism in adult trauma patients admitted in Intensive Care Unit appears to be non-efficacious, even when a 7- species combination is used.

Keywords

Probiotics; Bacteria; Culture; Trauma; Intensive Care Unit

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Introduction

Nosocomial pneumonia is the second most common hospital-acquired infection and the primary cause of death among these infections [1]. One of the largest researches investigating the prevalence of intensive care unit (ICU) acquired infections is the EPIC study [2]. It was conducted in 1417 ICUs and included 10,038 patients. The prevalence of ICU acquired infections in this study was 21%, and 47% of these patients had nosocomial pneumonia. The underlying disease process, as well as the severity of the disease, can affect the risk of developing a nosocomial infection. Patients with a primary diagnosis of trauma are at an increased risk because of altered immune responses making them more susceptible to developing infection [2-4].

Ventilator-associated pneumonia (VAP) is considered a type of pneumonia that develops 48 hours or longer after application of mechanical ventilation through an endotracheal or tracheostomy tube. It results from invasion of the lower respiratory tract and lung parenchyma by microorganisms. Intubation compromises the integrity of the oropharynx and trachea and allows oral and gastric secretions to enter the lower airways. This complication occurs in 8%-28% of intubated patients in the ICUs and causes 24% to 76% mortality [5-7].

Many factors increase the susceptibility of critically ill patients to VAP including diminished defense mechanisms due to effects of critical illness and medical therapy, alteration of normal host microbial flora by antibiotic therapy, interference with normal clearance mechanisms due to lack of ciliary reflex, and changes in pH of gastric secretions as a result of proton pump inhibitors and H2 blockers administration [8].

Various preventive measurements have been employed to reduce the incidence of VAP among which, use of probiotics is a novel approach. Probiotics are live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host [9]. This approach is based on the theory that because of previously mentioned reasons, during an acute illness the normal gastrointestinal tract flora is replaced by a potentially pathogenic microorganism (PPM). Probiotics can potentially reduce the incidence of VAP through various systemic and local effects including reduced growth of PPM, improved immune function, improved gut mucosal barrier function, and reduced bacterial translocation [10-13].

Although there are some studies on the effects of 1-3 species-based probiotics on reducing the oropharyngeal pathogenic bacteria of mechanically ventilated patients, we evaluated the efficacy of a new probiotic combination containing 7 bacteria applied both in oral cavity and stomach in this setting.

Material and Method

The study was conducted in four academic adult trauma ICUs. The university ethical review board approved the study protocol (ID: CT_P_9341_4681), and it was registered in Iranian Registry of Clinical Trials (IRCT ID: 2014051417691N1). Written informed consent was taken from patients' surrogates. The intensivist supervised the screening process. Patients were eligible for the study if they were at least 18 years old, informed consent could be taken from the patient's surrogate, there was a high likelihood that the patient would remain intubated for the next 4 days. The exclusion criteria included: pregnancy, immunosuppression, previous prosthetic cardiac valve replacement or vascular grafts, cardiac trauma, history of rheumatic fever, endocarditis or congenital cardiac anomalies, traumas to the aerodigestive tract, tracheostomy, pancreatitis, and base of skull fracture.

Patients were divided into two groups by computerized random allocation in a 1:1 ratio. The doctors, nurses, and laboratory personnel were blinded to the group assignments. All patients continued to receive the routine oral care procedures (cleansed with swabs moistened with 1 mg/ml chlorhexidine (CHX) solution) and the same amount of anti-acid treatment (pantoprazole 40 mg daily).

The probiotic we used was lactocare provided as a capsule containing 1010 colony-forming units (cfu) of 7 probiotics in an inulin base. Included probiotics were; Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophiles, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, and Lactobacillus bulgaricus. It was manufactured by the Zist Takhmir Tehran Company, Tehran, Iran. The placebo capsules were made from dried milk powder by the same company in similar capsules.

The probiotics were administered as follows: each capsule (probiotic or placebo) was suspended in 20 cc of distilled water, and sterile gauze was soaked in the suspension and was rubbed in the oropharyngeal cavity by a trained nurse. The process was repeated every 12 hours, one hour before mouthwash and two hours before feeding. The cultures were taken before the daily oral health care and nasogastric feedings on the 1st (before the intervention), 4th, and 6th days of admission. For this, the patient's tongue was restricted with a tongue blade, and a sterile swab was rubbed against the oropharyngeal cavity and behind the uvula. The swab was then placed in a test tube considering sterile measurements and sent to the central lab within half an hour to be cultured on macconkey agar media. Culture results were categorized according to the number of colonies per high power field as follows: rare (<2 colonies), few (2-15 colonies), moderate (15-50 colonies), and many (> 50 colonies). The culture results were then compared between groups at the end of the study.

Statistical Analysis

Descriptive statistics were used to report the results. Also, t-test and its alternative Mann–Whitney U test, and chi-square tests were employed for analysis and comparing the results between two groups.

Results

Five hundred and eighteen patients were admitted in our trauma ICUs during the study period (Feb. 2014 – Sept. 2014), but only 150 were eligible for the study. One hundred and thirty-two cases were excluded because no relative was available during the first 24 hours of ICU admission, and 236 of cases were further omitted according to other exclusion criteria. After randomization, 10 patients from the probiotic group and 1 patient from the placebo group were excluded from the study due to incomplete data or occurrence of exclusion criteria. Finally, there were 65 patients in the probiotic and 74 patients in the placebo arms left "Figure 1".

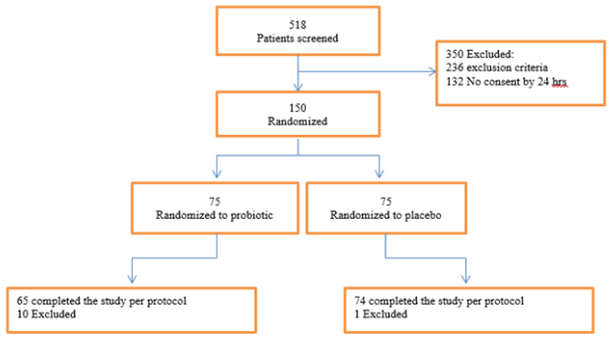


Figure 1. Study participants.

There were no refusals of consent for participation if victims were accompanied by a surrogate.

The demographic characteristics of the two groups and the culture results of the 1st, 4th, and 6th days were comparable, and no statistically significant difference was noticed in the two arms of the study "Table 1 and 2."

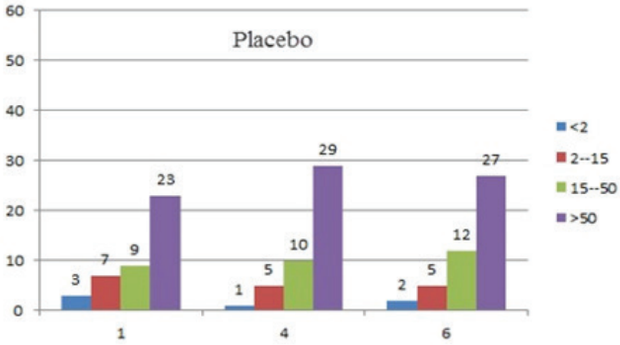
Table 1. Demographic characteristics of the patients in the two groups.

	Probiotic	Placebo	P-value
Number of patients	65	74	
Age, mean±SD	37.90±17.95	39.98±20.04	0.82
Male sex	49	52	0.50

Table 2. Comparison of oropharyngeal culture results between the two groups before (1st day) and after (4th and 6th days) the intervention.

		<2 colonies	2-15 colonies	16-50 colonies	>50 colonies	P-value
Positive 1st day culture	Probiotic	1	2	9	23	0.36
	Placebo	3	7	9	23	
Positive 4th day culture	Probiotic	3	1	10	31	0.29
	Placebo	1	5	10	29	
Positive 6th day culture	Probiotic	1	2	10	35	0.25
	Placebo	2	5	12	27	

Types of bacterial species did not statistically differ significantly between the two groups "Figure 2".



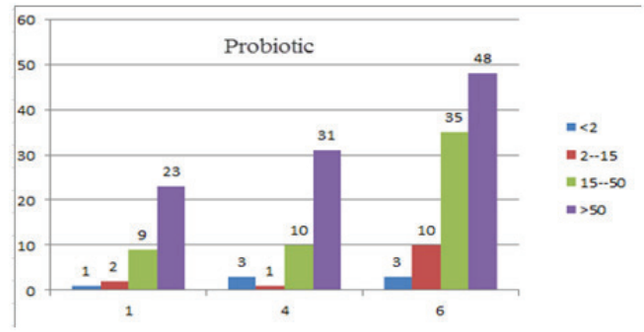


Figure 2. Comparison of bacterial growth in the 1st, 4th, and 6th days between the two groups.

Besides the probiotics had no effects on inhibition of PPM growth when compared by individual species, or as gram-positive and gram-negative groups "Table 3".

Table 3. Types of bacterial species involvement did not differ statistically significant between the two groups.

Bacteria	Probiotic	Placebo	P-value
MSSA	3	5	0.71
Pseudomonas aeruginosa	11	7	0.49
Enterobacteriaceae	4	3	1.00
Acinetobacter	13	12	1.00
Klebsiella	0	4	0.11
Proteus spp.	2	0	0.49
Escherichia coli	3	4	1.00
Citrobacter spp.	2	1	1.00
BHS	0	1	1.00
Serratia spp.	1	0	1.00
Hafnia spp.	0	1	1.00
Pneumococci spp.	0	2	0.49
Candida spp.	0	2	0.49
Normal flora	9	10	0.78
No growth	3	1	0.61
Gram negative bacteria	51	49	0.35
Gram positive bacteria	3	5	0.35

Abbreviations; MSSA: Methicillin Sensitive Staphylococcus Aureus. BHS: Beta Hemolytic Streptococcus.

Discussion

Adult trauma ICU patients are often young with no or minor underlying diseases; however, they are at risk for developing nosocomial infections due to the destruction of natural body barriers, trauma-induced pathophysiologic changes, and intubation in critical medical situations.

VAP is an important cause of increased morbidity, mortality, prolonged ICU stays, and increased health care costs in critically ill patients [14-16]. Early VAP is applied when the disease appears in less than 5 days after the admission and is generally caused by endogenous community-acquired pathogens. Late VAP-responsible pathogens include potentially multidrug-resistant nosocomial organisms residing in oropharyngeal or gastric contents [14, 17]. In the majority of ICUs, Staphylococcus aureus, Pseudomonas aeruginosa, and Acinetobacter baumannii are the most common organisms isolated in VAP; however, causative organisms vary between and within hospitals [18].

In 2008, Rice introduced a coterie of microorganisms that could

escape the effects of antibacterial drugs and had the greatest share of nosocomial infections under the acronym 'ESKAPE' (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species). They termed them as the 'top six bugs' [19]. However, other authors [20, 21] have proposed moving forward the term 'ESKAPE' to a more inclusive acronym termed 'ESCAPE' in order to represent Clostridium difficile (as the new C) and Enterobacteriaceae (as the new final E), encompassing more fully all the current problem pathogens that challenge the efficacious treatment of infectious diseases.

One of the methods applied in providing oral care for the intubated patients in the ICU is the use of CHX. It was proved to reduce the oropharyngeal pathogens and the incidence of VAP in these patients [22, 23]. However, CHX is associated with various side effects ranging from teeth discoloration, irritation of oral mucosa, and burning sensation of the tongue [24, 25] to a more serious adverse effect of allergic reactions in the oropharynx. Moreover, CHX has little effect on gram-negative bacteria [26], and its regular use can result in increased risk for emergence of resistant microorganisms.

A novel approach to decrease the incidence of VAP is the application of probiotics. The World Health Organization's 2001 definition of probiotics is "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" [27]. Use of probiotics does not eradicate the PPM, but it delays the colonization process while the patient is intubated. It also helps boost the patients' immune system and gut mucosal barrier function [28-31].

While all the previous studies had used 1-3 species of bacteria in the form of probiotics, with Lactobacillus as the main species, we decided to use a 7-species combination of probiotics with the concept that the use of a wider range of species can have greater effects on diminishing the colonization of oropharynx with PPM. However, we did not find any benefits in the application of the 7 species probiotic, as it did not alter the rate of PPM growth. This finding is in agreement with a previous study conducted in 2008 with a Lactobacillus based probiotic [32]. Although we used a combination of 7 species, the probiotic was still inefficient [33].

In fact, although not statistically significant, the growth rates were higher towards the end of the study in the probiotic arm (Figure 2). This finding can imply that probiotics might even provide a proper setting for the further growth of PPM and further increase the risk of nosocomial infections.

The results of our study indicate that gram-negative bacteria were more prevalent compared to gram-positive species (92.5% vs. 7.5%) and Acinetobacter was the most common PPM in both groups (24.0 % in the probiotic group and 22.2% in the placebo arm).

However, our study has some limitations; the ICUs this study was conducted in, are mainly trauma-based units and most of the admitted patients are young and without underlying medical diseases. The long list of exclusion criteria also limits our study to a selected group of patients. Hence, further large-scale studies including wider ranges of patients are needed to confirm our findings.

Conclusion

Administration of probiotics to alter early oropharyngeal cavity infestation with PPM in adult trauma patients admitted in ICU appears to be non-efficacious, even when a 7- species combination is used.

Conflict of interest

The authors declare no conflict of interest.

References

1. CDC. Nosocomial infection surveillance, 1984. In: Surveillance summaries. 1986; 35:17–29.
2. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The Prevalence of Nosocomial Infection in Intensive Care Units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA. 1995; 274(8):639-44. https://doi.org/10.1001/jama.1995.03530080055041
3. Appelgren P, Hellstrom I, Weitzberg E, Soderlund V, Bindslev L, Ransjo U. Risk Factors for Nosocomial Intensive Care Infection: A Long-Term Prospective Analysis. Acta Anaesthesiol Scand. 2001; 45:710–19. https://doi.org/10.1034/j.1399-6576.2001.045006710.x
4. Napolitano LM, Faist E, Wichmann MW, Coimbra R. Immune Dysfunction in Trauma. Surg Clin North Am. 1999; 79: 1385–416. https://doi.org/10.1016/S0039-6109(05)70084-0
5. Chastre J, Fagon JY. Ventilator-Associated Pneumonia. Am J Respir Crit Care Med. 2002; 165(7):867-903. https://doi.org/10.1164/ajrccm.165.7.2105078
6. Amin A. Clinical and Economic Consequences of Ventilator-Associated Pneumonia. Clin Infect Dis. 2009; 49(1): S36-43. https://doi.org/10.1086/599814
7. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. VAP Outcomes Scientific Advisory Group. Epidemiology and Outcomes of Ventilator-Associated Pneumonia in a Large US Database. Chest. 2002; 122(6):2115-21. https://doi.org/10.1378/chest.122.6.2115
8. Atul AK, Wendy Zai, Marek M. Ventilator-Associated Pneumonia in the ICU. Crit Care. 2014; 18(2): 208. https://doi.org/10.1186/cc13775
9. Schlundt J. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. FAO / WHO. Retrieved 17 December 2012.
10. Walker WA. Mechanisms of Action of Probiotics. Clin Infect Dis. 2008; 46(2): S87-91; S144-51.
11. Isolauri E, Sütas Y, Kankaanpää P, Arvilommi H, Salminen S. Probiotics: Effects on Immunity. Am J Clin Nutr. 2001; 73(2 Suppl):444S-50S.
12. S Ghosh, D van Heel, R J Playford. Probiotics in Inflammatory Bowel Disease: Is It all Gut Flora Modulation? Gut. 2004; 53(5): 620–2. https://doi.org/10.1136/gut.2003.034249
13. McNaught CE, Woodcock NP, MacFie J, Mitchell CJ. A Prospective Randomized study of the probiotic Lactobacillus Plantarum 299V on Indices of Gut Barrier Function in Elective Surgical Patients. Gut. 2002; 51(6):827-31. https://doi.org/10.1136/gut.51.6.827
14. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and Outcomes of Health-Care-Associated Pneumonia: Results from a Large US Database of Culture-Positive Pneumonia. Chest. 2005; 128(6):3854-62. https://doi.org/10.1378/chest.128.6.3854
15. Kollef MH. What Is Ventilator-Associated Pneumonia and Why Is It Important? Respir Care. 2005; 50(6):714-21.
16. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial Infections in Medical Intensive Care Units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med. 1999; 27(5):887-92. https://doi.org/10.1097/00003246-199905000-00020
17. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the Management of Adults With Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia. Am J Respir Crit Care Med. 2005; 171(4): 388-416. https://doi.org/10.1164/rccm.200405-644ST
18. Restrepo MI, Peterson J, Fernandez JF, Qin Z, Fisher AC, Nicholson SC. Comparison of the Bacterial Etiology of Early-Onset and Late-Onset Ventilator-Associated Pneumonia in Subjects Enrolled in 2 Large Clinical Studies. Respir Care. 2013; 58(7): 1220-5. https://doi.org/10.4187/respcare.02173
19. Rice LB. Federal Funding For The Study of Antimicrobial Resistance in Nosocomial Pathogens: No ESKAPE. J Infect Dis. 2008; 197(8):1079-81. https://doi.org/10.1086/533452
20. Boucher HW1, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB
21. Boucher HW1, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB
22. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clin Infect Dis. 2009; 48: 1-12. https://doi.org/10.1086/595011
23. Peterson LR. Bad Bugs, No Drugs: No ESCAPE Revisited. Clin Infect Dis. 2009; 49: 49. https://doi.org/10.1086/605539
24. Chlebicki MP, Safdar N. Topical Chlorhexidine for Prevention of Ventilator-Associated Pneumonia: A Meta-Analysis. Crit Care Med. 2007; 35(2): 595-602.

https://doi.org/10.1097/01.CCM.0000253395.70708.AC
25. Chan EY, Ruest A, Meade MO, Cook DJ. Oral Decontamination for Prevention of Pneumonia in Mechanically Ventilated Adults: Systematic Review and Meta-Analysis. BMJ. 2007; 334(7599): 889. https://doi.org/10.1136/bmj.39136.528160.BE
26. Cankaya H, Ozen S, Kiroğlu F, Yurttaş V. Effects of Topical Chlorhexidine Applied to The Rabbit Nasal Mucosa. Auris Nasus Larynx. 2003; 30(1): 65-9. https://doi.org/10.1016/S0385-8146(02)00102-5
27. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V. Randomized Controlled Trial and Meta-Analysis of Oral Decontamination with 2% Chlorhexidine Solution for the Prevention Of Ventilator-Associated Pneumonia. Infect Control Hosp Epidemiol. 2008; 29(2): 131-6. https://doi.org/10.1086/526438
28. Spijkervet FK, van Saene HK, Panders AK, Vermey A, van Saene JJ, Mehta DM, et al. Effect of Chlorhexidine Rinsing on the Oropharyngeal Ecology in Patients with Head and Neck Cancer Who Have Irradiation Mucositis. Oral Surg Oral Med Oral Pathol. 1989; 67(2): 154-61. https://doi.org/10.1016/0030-4220(89)90321-6
29. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. FAO / WHO. Retrieved 17 December 2012.
30. Walker WA. Mechanisms of Action of Probiotics. Clin Infect Dis. 2008; 46 Suppl 2: S87-91; S144-51.
31. Isolauri E, Sütas Y, Kankaanpää P, Arvilommi H, Salminen S. Probiotics: Effects on Immunity. Am J Clin Nutr. 2001; 73(2 Suppl): 444S - 50S.
32. S Ghosh, D van Heel, R J Playford. Probiotics in Inflammatory Bowel Disease: Is It All Gut Flora Modulation? Gut. 2004; 53(5): 620–2. https://doi.org/10.1136/gut.2003.034249
33. McNaught CE, Woodcock NP, MacFie J, Mitchell CJ. A Prospective Randomised Study Of The Probiotic Lactobacillus Plantarum 299V on Indices of Gut Barrier Function in Elective Surgical Patients. Gut. 2002; 51(6): 827-31. https://doi.org/10.1136/gut.51.6.827
34. Darvishi M, Ziari K, Mohebbi H, Alizadeh K. Association between iron deficiency anemia and Helicobacter pylori infection among children under six years in Iran. Acta Medica Iranica .2015;53(4): 220-4.
35. Bengt K, Göran M, Bengt J, Anders L. Use of the Probiotic Lactobacillus Plantarum 299 to Reduce Pathogenic Bacteria in the Oropharynx of Intubated Patients: A Randomised Controlled Open Pilot Study. Crit Care. 2008; 12(6): R136. https://doi.org/10.1186/cc7109.

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