Randomized Controlled Study of Probiotics Containing *Lactobacillus casei* (Shirota strain) for Prevention of Ventilator-Associated Pneumonia

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Objective: *To evaluate the efficacy of probiotics, Lactobacillus casei (Shirota strain), in reducing the incidence of ventilator-associated pneumonia (VAP) in medical patients who received mechanical ventilation at Siriraj Hospital.*
Material and Method: *A prospective, randomized, open-label controlled trial was conducted in 150 adult hospitalized patients in medical wards who were expected to receive mechanical ventilation for 72 hours or longer. The patients were randomized to the probiotics group or the control group. All patients received regular care for mechanical ventilation. The patients in the probiotics group received 80 ml of Lactobacillus casei (Shirota strain) for oral care after having standard oral care once daily and additional 80 ml of the aforementioned fermented dairy product was given via enteral feeding once daily. The primary outcomes were incidence of VAP and incidence rate of VAP episodes per 1,000 ventilator-days. The secondary outcomes were length of hospital stay, mortality at day 28 and 90, incidence of diarrhea, and presence of resistant bacteria in oropharyngeal and rectal swab samples taken from the patients at baseline, day 7 and day 28 after enrollment.*
Results: *The baseline characteristics of the patients in the probiotics group (75) and the control group (75) were not significantly different. The patients in the probiotics group were less likely to develop VAP compared with the control group (24% vs. 29.3%, p = 0.46), respectively. The incidence rates of VAP in the probiotics and control groups were 22.64 and 30.22 episodes per 1,000 ventilator-days, respectively (p = 0.37). A trend of lower prevalence of some resistant bacteria cultured from oropharyngeal swabs in the probiotics group than that in the control group was observed. Overall 28- and 90-day mortality and length of hospital stay of the patients in both groups were not significantly different.*
Conclusion: *Administration of probiotics containing Lactobacillus casei (Shirota strain) has a tendency to reduce the incidence of VAP and colonization with resistant bacteria in oropharyngeal cavity without significant effects on mortality and length of hospital stay.*

Keywords: *Probiotics, Lactobacillus casei (Shirota strain), Prevention, Ventilator-Associated Pneumonia*

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Ventilator-associated pneumonia (VAP) remains a common hazardous complication in mechanically ventilated patients resulting in prolongation of hospital stay and increased mortality[1]. Endogenous flora in the oral cavity and upper airway of the patients play an important role in the development of VAP, and abnormal colonization and translocation of potential pathogenic microorganisms in the oral cavity and upper airway are believed to be the main pathogenesis of VAP. Micro-aspiration of oropharyngeal secretions contaminated with endogenous flora around the endotracheal tube cuff is the major route for microbial invasion. The stomach and sinuses are postulated as the potential reservoir of certain bacteria colonizing the oropharynx[2]. Several approaches for prevention of VAP have been proposed[3,4]. Selective digestive decontamination (SDD) and selective oropharyngeal decontamination were found to be effective preventive measures against VAP[5-8]. However, the administration of antibiotics may have collateral damage on the patients and healthcare system due to antibiotic resistance[9]. Probiotics are live microorganisms that confer a beneficial health effect to the host when administered in adequate amounts[3,10]. Many probiotics are available such as *Lactobacillus*, *Bifidobacterium*, *Streptococcus* species, and *Saccharomyces*. There are many conditions

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for which probiotics are often used including prevention of antibiotic-associated diarrhea, traveler's diarrhea, cow milk-induced food allergy in children, and relapsing *Clostridium difficile*-induced colitis[11]. Previous studies suggested that probiotics may reduce incidence of VAP, attributed mortality, length of stay, and hospital cost. Meta-analysis of randomized controlled trials demonstrated a significant decrease in the incidence of VAP in the probiotics group[12]. However, the effect of probiotics on VAP prevention has been controversial since the available high-quality RCTs were limited and yielded inconsistent results[13-20]. The reasons for inconclusive results on efficacy of probiotics for prevention of VAP could be the differences in using the varied diagnostic criteria of VAP, different types, amounts and durations of probiotics[13-20].

An in vitro study showed that fermented milk product containing *Lactobacillus casei* (Shirota strain) (LcS) exerted inhibitory activity against multi-drug resistant (MDR) bacteria including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) resulting in eradication of such organisms at 24 hour[21]. A study on viability of LcS in Thai healthy subjects regularly taking milk product containing LcS $8x10^9$ CFU for 1 week confirmed the survival of LcS in their gastrointestinal tracts[22]. Daily consumption of LcS is found to reduce the incidence of upper respiratory tract infections and is also safe in the critically ill patients[23,24].

The objective of this study was to evaluate efficacy of the probiotics containing *Lactobacillus casei* (Shirota strain) in preventing VAP in mechanically-ventilated medical patients in a tertiary-care facility.

Material and Method

The study was approved by the Siriraj Institutional Review Board and all enrolled patients or their legal representatives signed the informed consents to participate the study. The study design was a prospective, randomized, open-label controlled trial at Siriraj Hospital, a 2,300-bed tertiary care university hospital in Bangkok, from May 2011 to August 2013. The study subjects were adult hospitalized medical patients who were expected to receive mechanical ventilation at least 72 hours and had no VAP at enrollment.

The eligible patients were randomized to the probiotics group and the control group. All patients received oral care with 2% chlorhexidine solution four times per day as standard care as well as VAP-preventive measures according to the hospital protocol. The patients in the probiotics group received 80 ml of commercially-available fermented dairy product containing $8x10^9$ colony-forming units (cfu) of *Lactobacillus casei* (Shirota strain) (Yakult®) for oral care after the standard oral care once daily. An additional 80 ml of the aforementioned fermented dairy product was given via enteral feeding once daily for 28 days or when their endotracheal tubes were removed. Probiotics was discontinued when diarrhea related to probiotics occurred. The patients in the control group did not receive any additional products. The samples taken from oropharynx and rectum of each patient were collected at day 0 (baseline), 7, and 28 for bacterial cultures. The target organisms were ESBL-producing *Klebsiella pneumoniae*, ESBL-producing *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and MRSA. The patients were followed-up to day 90 after enrollment.

The primary outcomes were incidence of VAP and incidence rate of VAP episodes per 1,000 ventilator-days. A diagnosis of VAP was made if the patient had a new, persistent, or progressive infiltrate visible on a chest radiograph in combination with at least 3 of the following 4 criteria: 1) body temperature greater than 38°C or less than 35.5°C, 2) leukocytosis (>10,000 leukocytes/mm^3) or leukopenia (<3,000 leukocytes/mm^3), 3) purulent tracheal aspirate, and 4) a semi-quantitative culture of tracheal aspirate samples that was positive for pathogenic bacteria[3]. The secondary outcomes were length of hospital stay, mortality at day 28 and 90, incidence of diarrhea, and presence of resistant bacteria in oropharyngeal and rectal swab samples on day 0, 7 and 28.

A sample size of 75 patients per group was estimated based on the assumptions that probiotics could reduce the rate of VAP from 21 to 7 episodes per 1,000 ventilator-days with 5% type I error (1-sided) and 80% power. Continuous variables with normal and non-normal distributions were compared, using the independent t-test, and the Mann-Whitney U test, respectively. Categorical variables were compared using the Chi-square test or the Fisher's exact test, when appropriate. Poisson regression was used to compare the incidence rate of VAP episodes per 1,000 ventilator-days. For all tests performed, a two-tailed p-value <0.05 was considered as denoting statistical significance. The statistical software SPSS, version 21.0 was employed for all the analyses performed.

Results

The total number of subjects was 150. Seventy-five patients were in the control group and 75 patients in the probiotics group. The demographic and baseline characteristics of the patients in both groups are shown in Table 1. Most of the patients were elderly females with co-morbidities and severe health problems leading to mechanical ventilation. The baseline characteristics of the patients in both groups were not significantly different.

Primary outcomes

The patients in the probiotics group were less likely to develop VAP compared with those in the control group (24% vs. 29.3%, $p = 0.46$). The incidence rate of VAP in the probiotics group was lower than that in the control group (22.64 vs. 30.22 episodes per 1,000 ventilator-days, $p = 0.37$) as shown in Table 2. *A. baumannii* was the most common cause of VAP in both groups.

Secondary outcomes

Length of hospital stay and mortality at day 28 and 90 are shown in Table 3. The length of hospital stay and ICU stay did not differ significantly between the probiotics group and the control group. The mortality of the patients in the probiotics group and the control group were 24% vs. 22.7% ($p = 0.85$) at day 28, and 33.3% vs. 34.7% ($p = 0.86$) at day 90, respectively. Overall incidence of diarrhea was 22% (19 vs. 14 episodes, $p = 0.32$, in the probiotics and the control groups, respectively). One of them in the probiotics group was considered to be probiotics-related. No hyperglycemic episode was observed. No

Table 1. Demographics and baseline characteristics of 150 study patients

Characteristic	Control group (n = 75)	Probiotics group (n = 75)	*p*-value
Age (years), mean ± SD (range)	68.95±18.45 (20-97)	73.09±13.16 (30-94)	0.12
Gender: female	43 (57.3)	45 (60.0)	0.74
Co-morbidity	70 (93.3)	69 (92.0)	0.75
DM	41 (54.7)	37 (49.3)	0.51
HT	53 (70.7)	53 (70.7)	1.00
Cardiovascular disease	18 (24.0)	14 (18.7)	0.43
Chronic kidney disease	23 (30.7)	16 (21.3)	0.19
Chronic lung disease	15 (20.0)	25 (33.3)	0.10
CNS disease	3 (4.0)	3 (4.0)	1.00
Indication for endotracheal intubation			
Oxygenation failure	35 (46.7)	40 (53.3)	0.41
Airway protection	27 (36.0)	24 (32.0)	0.61
Ventilatory failure	14 (18.7)	13 (17.3)	0.83
Secretion obstruction	10 (13.3)	8 (10.7)	0.62
Upper airway obstruction	2 (2.7)	2 (2.7)	1.00
Duration of mechanical ventilation (days), median (range)	7 (1-98)	7 (1-109)	0.37
Risk factor for VAP			
Nasogastric tube	74 (98.7)	73 (97.3)	1.00
Acid reduction agent use	69 (92.0)	67 (89.3)	0.58
Prior pulmonary infection	30 (40.0)	32 (42.7)	0.74
Prior antibiotic use	27 (36.0)	32 (42.7)	0.40
Invasive medical device	17 (22.7)	11 (14.7)	0.21
Aerosol therapy	16 (21.3)	23 (30.7)	0.19
Corticosteroid use	7 (9.3)	9 (12.0)	0.60
Reintubation	6 (8.0)	10 (13.3)	0.29
APACHE II score, mean ± SD (range)	19.88±6.89 (5-35)	19.41±7.04 (5-42)	0.68
Glasgow coma score, mean ± SD	10.09±3.7	10.43±4.05	0.60

VAP = ventilator-associated pneumonia; APACHE = Acute Physiology and Chronic Health Evaluation; DM = diabetes mellitus; HT = hypertension; CNS = central nervous system
Data are No. (%) of patients, unless otherwise indicated

Table 2. Primary outcomes

Outcome	Probiotics group (n = 75)	Control group (n = 75)	*p*-value
No. of patients who developed VAP (%)	18 (24.0)	22 (29.3)	0.46
Mean VAP episodes per 1,000 ventilator-days	22.64	30.22	0.37
Isolated etiologic organism of VAP, n			
Acinetobacter baumannii	8	6	0.26
Enterobacteriaceae	3	3	1.00
Pseudomonas aeruginosa	2	3	1.00
Stenotrophomonas maltophilia	2	3	1.00
MRSA	0	1	1.00
Polymicrobial VAP	5	7	0.78

MRSA = methicillin-resistant *Staphylococcus aureus*

Table 3. Secondary outcomes

Outcome	Probiotics group (n = 75)	Control group (n = 75)	*p*-value
Length of hospital stay (days), median (range)	20 (2-106)	19 (3-171)	0.79
Length of ICU stay (days), median (range)	30.5 (4-98)	19 (5-30)	0.46
Mortality at day 28	18 (24.0%)	17 (22.7%)	0.85
Mortality at day 90	25 (33.3%)	26 (34.7%)	0.86
Diarrhea	19 (25.3%)	14 (18.7%)	0.32

obvious complications attributed to the probiotics were noted during the study period. There was no evidence of *Lactobacillus* bacteremia in the study patients. The microbiological data of oropharyngeal and rectal swabs are shown in Table 4. The rates of recovering resistant bacteria from oropharyngeal and rectal swabs seemed to be increased at day 7 and day 28 when compared with those of the baseline. A trend of lower prevalence of some resistant bacteria cultured from oropharyngeal swabs in the probiotics group than that in the control group was observed. However, the rates of colonization with resistant bacteria from oropharyngeal and rectal swabs within the same group and between the groups were not significantly different.

Discussion

A meta-analysis of randomized controlled studies revealed that administration of probiotics was associated with lower incidence of VAP, shorter length of intensive care unit stay, and less colonization of the respiratory tract with *Pseudomonas aeruginosa*[12]. However, no differences in mortality, duration of mechanical ventilation, and diarrhea were observed. Another meta-analysis of high-quality randomized controlled studies found that probiotics did not significantly decrease the incidence of VAP[20]. The results of these meta-analyses imply that there should be heterogeneity among the studies on this topic in terms of the study intervention such as the types, doses, routes of administration of probiotics, types of the study population, and diagnostic criteria of VAP.

The present study used *Lactobacillus casei* (Shirota strain) at a dosage of 80 ml ($8x10^9$ cfu of *Lactobacillus casei*) for oral care once daily and 80 ml of the aforementioned probiotics product was given via enteral feeding once daily. The authors found that the incidence rate of VAP in the probiotics tended to be less than that in the control group whereas overall mortality, and oropharyngeal and rectal colonization with MDR bacteria did not differ significantly between the two groups. Several factors could be contributed to observing no differences in the outcomes of the patients in the probiotics group and the control group. A sample size of 75 patients per group was based on the assumption that the incidence rate of VAP in the probiotics group would decrease by 67%, from 21 to 7 episodes per 1,000 ventilator-days, whereas the findings from the present study revealed that such difference was only 27%, from 30.22 to 22.64 episodes per 1,000 ventilator-days. Therefore, a sample size of 75 patients per group is too small to detect a smaller difference of the outcome. The dose of probiotics given via enteral feeding could be too low. More frequent administration might improve the outcome.

Table 4. Comparison of the rates of the organisms cultured from oropharyngeal and rectal swabs between the control group and the probiotics group

Pathogen	Oropharyngeal swab			Rectal swab		
	Control	Probiotics	*p*-value[a]	Control	Probiotics	*p*-value[a]
A. baumannii						
Baseline	n = 75	n = 75	0.62	n = 75	n = 75	0.33
	11 (15%)	8 (11%)		7 (9%)	3 (4%)	
Day 7	n = 53	n = 56	0.31	n = 53	n = 56	0.50
	22 (42%)	17 (30%)		9 (17%)	6 (11%)	
Day 28	n = 5	n = 9	1.00	n = 4	n = 10	1.00
	2 (40%)	3 (33.3%)		0 (0%)	1 (10%)	
ESBL + ve *E. coli* or *Klebsiella* spp.						
Baseline	n = 75	n = 75	0.39	n = 75	n = 75	0.41
	11 (15%)	16 (21%)		40 (53%)	46 (61%)	
Day 7	n = 53	n = 56	0.29	n = 53	n = 56	0.67
	17 (32%)	12 (21%)		31 (58%)	36 (64%)	
Day 28	n = 5	n = 9	0.09	n = 4	n = 10	0.51
	3 (60%)	1 (11%)		4 (100%)	7 (70%)	
P. aeruginosa						
Baseline	n = 75	n = 75	0.17	n = 75	n = 75	1.00
	7 (9%)	3 (2%)		2 (3%)	1 (1%)	
Day 7	n = 53	n = 56	0.70	n = 53	n = 56	0.84
	13 (25%)	11 (20%)		5 (9%)	7 (13%)	
Day 28	n = 5	n = 9	0.58	n = 4	n = 10	1.00
	1 (20%)	4 (44%)		0 (0%)	1 (10%)	
MRSA						
Baseline	n = 75	n = 75	0.62	n = 75	n = 75	1.00
	3 (4%)	1 (1%)		3 (4%)	3 (4%)	
Day 7	n = 53	n = 56	0.09	n = 53	n = 56	0.31
	7 (13%)	2 (4%)		6 (11%)	3 (5%)	
Day 28	n = 5	n = 9		n = 4	n = 10	1.00
	0 (0%)	0 (0%)		0 (0%)	1 (10%)	

ESBL = extended-spectrum β-lactamase

[a] Fisher's exact test or Yates' continuity correction test

Local administration of probiotics into oral cavity might be too low and *Lactobacillus casei* might be inactivated by concurrent use of chlorhexidine for oral care in all study patients, and probiotics once daily might be less frequent. Therefore, a larger study using more frequent doses of probiotics, with no interference from any antiseptics, should be considered to determine if *Lactobacillus casei* (Shirota strain) is effective in preventing VAP.

What is already known on this topic?

Efficacy of probiotics for prevention of VAP is inconclusive.

What this study adds?

Administration of probiotics containing *Lactobacillus casei* (Shirota strain) has a tendency to reduce the incidence of VAP and colonization with resistant bacteria in oropharyngeal cavity without significant effects on mortality and length of hospital stay.

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Potential conflicts of interest

None.

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การศึกษาแบบสุ่มมีกลุ่มควบคุมของการป้องกันปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจด้วย probiotics ที่มี Lactobacillus casei (Shirota strain)

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วัตถุประสงค์: *เพื่อทราบประสิทธิผลของ probiotics ที่มี Lactobacillus casei (Shirota strain) ในการป้องกันปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจ*

วัสดุและวิธีการ: *การศึกษาแบบสุ่มมีกลุ่มควบคุมในผู้ป่วยผู้ใหญ่ 150 ราย ซึ่งได้รับเครื่องช่วยหายใจอย่างน้อย 72 ชั่วโมง ที่หอผู้ป่วยอายุรศาสตร์ ผู้ป่วยทุกรายได้รับการปฏิบัติรักษาตามปกติสำหรับการมีเครื่องช่วยหายใจ ผู้ป่วยได้รับการสุ่มให้อยู่ในกลุ่ม probiotics หรือกลุ่มควบคุม ผู้ป่วยกลุ่ม probiotics ได้รับ probiotics ที่มี Lactobacillus casei (Shirota strain) ปริมาณ 80 มิลลิลิตร เช็ดช่องปากหลังทำความสะอาดตามปกติวันละครั้งและอีก 80 มิลลิลิตร ทางท่อให้อาหารวันละครั้ง ผลลัพธ์หลักคืออุบัติการณ์ของปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจ และอัตราปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจต่อ 1,000 วัน ที่ใช้เครื่องช่วยหายใจ ส่วนผลลัพธ์รองคือระยะเวลาที่อยู่ในโรงพยาบาล อัตราตายที่ 28 และ 90 วัน หลังร่วมโครงการศึกษา อุบัติการณ์ของอุจจาระร่วงและอัตราการพบแบคทีเรียดื้อยาจากตัวอย่างที่เก็บจากช่องปากและทวารหนักเมื่อเริ่มศึกษา วันที่ 7 และวันที่ 28 หลังเริ่มศึกษา*

ผลการศึกษา: *ลักษณะของผู้ป่วยกลุ่ม probiotics (75 ราย) และกลุ่มควบคุม (75 ราย) ไม่แตกต่างกันอย่างมีนัยสำคัญ ผู้ป่วยกลุ่ม probiotics มีแนวโน้มของการเกิดปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจน้อยกว่าผู้ป่วยกลุ่มควบคุม (ร้อยละ 24 และ 29.3, p = 0.46) อัตราการเกิดปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจในผู้ป่วยกลุ่ม probiotics มีแนวโน้มน้อยกว่าผู้ป่วยกลุ่มควบคุม (22.64 และ 30.22 ต่อ 1,000 วัน ของการใช้เครื่องช่วยหายใจ, p = 0.37) ผู้ป่วยกลุ่ม probiotics มีแนวโน้มพบเชื้อดื้อยาจากช่องปากบางชนิดน้อยกว่าผู้ป่วยกลุ่มควบคุม ส่วนอัตราตายที่ 28 วัน และ 90 วัน และระยะเวลาของการอยู่โรงพยาบาลของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญ*

สรุป: *การให้ probiotics ที่มี Lactobacillus casei (Shirota strain) มีแนวโน้มลดอุบัติการณ์ของปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจและอัตราการพบเชื้อดื้อยาบางชนิดในช่องปากโดยไม่มีผลต่ออัตราตาย และระยะเวลาของการอยู่โรงพยาบาล*
