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The effectiveness of probiotic as adjuvant therapy of severe pneumonia in children below 5 years-old at Sanglah General Hospital, Bali, Indonesia

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ABSTRACT

Background: Pneumonia is a respiratory disease that can cause a lot of morbidity and mortality. Factors that associated with severe pneumonia in children include toddler age, malnutrition, male sex, exclusive breastfeeding, incomplete immunization. This study aims to evaluate the probiotic effectiveness as adjuvant therapy in childhood pneumonia compared to placebo.

Methods: This is a randomized, double-blind controlled trial among 54 children with severe pneumonia aged 2 months-5 years who received standard therapy and probiotics compared to standard therapy and placebo from August 2017 to July 2019. Both groups were evaluated for treatment outcomes after receiving 5 days of adjuvant therapy at Sanglah General Hospital, Bali, Indonesia which divided into Group I (n=27) (standard therapy and probiotics) and Group II (n=27) (standard therapy and placebo). Variables assessed in this study include the characteristic of subjects, length of stay, duration of fever, shortness of breath, retractions, rales, C-reactive protein (CRP), probiotics, and history of breastfeeding. Data were analyzed by SPSS version 20 for Windows.

Results: Both groups were shown predominantly in male gender (66.67% and 59.26%), exclusive breastfeeding (88.89% and 77.78%), no malnutrition status (81.48% and 77.78%), and having complete immunization history (81.48% and 88.89%) in Group I and II, respectively. There was no statistically significant difference on the length of stay, length of fever, duration of the breath, length of subcostal retraction and decrease in CRP levels on both groups ($p>0.05$). Meanwhile, there was a statistical difference in rales duration ($p=0.037$). Multivariate analysis using Ancova found probiotics were able to reduce the duration of rales significantly by 5.87 hours ($p=0.022$; 95% CI: -10.89 – (-0.86)).

Conclusion: This study concluded that adjuvant therapy with probiotics significantly reduced rales duration in children with severe pneumonia.

Keywords: Severe Pneumonia, Children, Probiotic, Effectiveness

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INTRODUCTION

Pneumonia is inflammation of the lung parenchyma. Most of these are caused by a microorganism (viruses/bacteria) and a small portion related to other things (aspirations, radiation).[1] According to the National Health Survey in 2001, 27.6% of infant deaths and 22.8% of toddler deaths in Indonesia were caused by respiratory system diseases, especially pneumonia.[2]

Various factors influence pneumonia outcomes in children under five years in developing countries, including age, gender, history of breastfeeding, nutritional status, air pollution, the presence of comorbidities (congenital heart disease, immunodeficiency) and adjuvant therapy like probiotics.[3,4]

Probiotics are defined as living microorganisms which are given in sufficient quantities can provide health benefits to the host.[5,6] Probiotics are widely developed, such as *Lactobacillus* or *Bifidobacterium* species and non-pathogenic *Escherichia coli* which are known to have health benefits.[5] *Lactobacillus reuteri* and *L. rhamnosus* GG have a mechanism in the airway by modulating the allergic-immunological system and against infectious agents.[6]

A Randomized Clinical Trial (RCT) by Bayer-Mulsid TB et al. about probiotic containing *Lactobacillus, Bifidobacterium* and *Streptococcus* that have given to patients with severe pneumonia aged 6-24 months, has a significantly shorter length of stay in patients given probiotics than the control group ($P<0.007$), duration of shortness of breath based on age ($P<0.001$), chest wall retractions disappear ($P<0.001$), and duration of rales faster in the probiotic group than controls ($P<0.001$).[7]

A similar literature study by Esposito S which evaluating the role of several probiotics such as *Lactobacillus acidophilus, Bifidobacterium longum,* and *Streptococcus thermophilus* in patients with

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severe pneumonia aged 2 months-5 years with results improvement of rhonchi and subcostal retractions found statistically significant in probiotic compared placebo.[8]

Becina PGA in 2014 presented different results using the probiotic *Lactobacillus casei, L. rhamnosus, L. acidophilus, L. bulgaricus, Streptococcus thermophilus, Bifidobacterium breve, B. infantis, Fructooligosaccharide* (FOS) in patients with moderate pneumonia aged 2 months-4 years found no statistically significant difference in the length of stay, improvement shortness of breath, fever, retraction in the group given probiotics compared placebo.[9]

However, unfortunately in those studies were not mentioned the inflammatory response after administration of probiotics, which were assessed from improvements in complete blood count (CBC) and C-reactive protein (CRP) as a marker of infection. Chalmers JD et al. used CRP levels as predictors of the severity in pneumonia with sensitivity test 97.6%, specificity test 33.9%, positive predictive value 10.5%, negative predictive value 99.4%.[10] Pramana KP and Subanada IB received an average CRP level in the very severe pneumonia group of 42.6 (SD 41.7) mg/L.[1]

Based on the mentioned above, this study aims to determine the effectiveness of probiotics in children with severe pneumonia seen from clinical improvement as well as markers of infection such as CRP, at Sanglah General Hospital, Bali, Indonesia.

METHODS

An experimental study with Double-Blind Randomized Controlled Trial (RCT) was conducted in this study in Departement of Child Health, Faculty of Medicine, Udayana University/ Sanglah Hospital, Denpasar in August 2017 until July 2019. The target population was all children aged 2 months-5 years who diagnosed severe pneumonia according to the WHO revised criteria. We use consecutive sampling to select the samples. Inclusion criteria were patients aged 2 months-5 years, and their parents were willing to participate in this study and have signed the informed consent. Exclusion criteria were patients used immunosuppressant drugs, immunodeficiency states, pneumonia with comorbidities, and underwent probiotic therapy at least 2 weeks before being treated.

During the study period, 328 patients with severe pneumonia were found, 58 patients did not meet the inclusion criteria, 216 subjects were excluded and 270 patients met the inclusion criteria, 54 patients became the study subjects. From a total of 216 patients that excluded, 56 patients with HIV, 85 patients had congenital heart disease, 38 patients with cerebral palsy and 37 patients with respiratory failure. The selected subjects were 54 patients and then randomized allocation into groups that received additional probiotic or placebo therapy each as many as 27 patients. During the study, there were no subjects who experienced drop-outs, so at the end of the study, there were 27 subjects analyzed by each group.

Estimates of the magnitude of subjects were determined by the hypothesis test formula for the mean difference, with significance level, α=0.05; desired confidence interval (CI) of 95%, and power of 80%, obtained a sample size of 27 patients for each group. In selected subjects, a random allocation with permitted block 4 will be performed to determine the intervention group or placebo.

The standard therapy for severe pneumonia was antibiotic intravenous ampicillin 50 mg/kgBW/ time every 6 hours and gentamicin 7.5 mg/kgBW/ time every 24 hours. The Group I as the intervention group was subjects who received probiotics (*L. acidophilus, B. longum, Streptococcus thermophilus* each 1x107 cfu/gr) in the form of granules in the package, given 2 times a day for 5 days, with an interval of 3 hours after standard antibiotic administration. The Group II was the combination of standard therapy and placebo which packaged to resemble a probiotic containing *Saccharum lactis*. Nutritional status according to the WHO 2006 growth curve, based on Waterlow, classified as malnutrition if nutritional status < 90% and not malnutrition if > 90%. Clinical outcomes of the patients were evaluated every 12 hours include the length of stay, duration of fever, shortness of breath, subcostal retraction, and duration of rales. The CRP examination was carried out by the Clinical Pathology Laboratory of Sanglah Hospital Denpasar, which was evaluated when diagnosed and after 3 days of probiotic/placebo. Drop out if the subject has not taken probiotic/placebo for 1×24 hours, or has a discharge or moved to the hospital at the request of the parents or died.

Data were analyzed using a computer with the SPSS 20.0 software. Univariate analysis was used to describe the basic characteristics of the subject, including the median, minimum-maximum, and frequency distribution. The normality test used the Shapiro-Wilk test, and the variance similarity test used the Levene test. Bivariate analysis was done using the Mann-Whitney test, and multivariate analysis was using Ancova analysis. The level of significance is determined based on P<0.05.

RESULTS

Age, sex, exclusive breastfeeding, nutritional status, and immunization status were obtained equally in the two groups. Most of the respondents were male gender (66.67% and 59.26%), underwent exclusive breastfeeding (88.89% and 77.78%), no malnutrition status (81.48% and 77.78%), and having complete immunization history (81.48% and 88.89%) in both Group I and II, respectively, as shown in Table 1.

Table 1 Baseline characteristic of respondents

Characteristics	Group I (N = 27)	Group II (N = 27)
Age, month, median (min-max)	18 (6-50)	18 (6-48)
Sex, n (%)		
Male	18 (66.67)	16 (59.26)
Female	9 (33.33)	11 (40.74)
Exclusive breastfeeding, n (%)		
Yes	24 (88.89)	21 (77.78)
No	3 (11.11)	6 (22.22)
Malnutrition, n (%)		
Yes	5 (18.52)	6 (22.22)
No	22 (81.48)	21 (77.78)
Complete immunization, n (%)		
Yes	22 (81.48)	24 (88.89)
No	5 (18.52)	3 (11.11)

Table 2 Bivariate analysis of several variables into the Group I compared to Group II

Variables	Group I (N=27)	Group II (N=27)	p
Length of stay (hour), median (min-max)	132 (132-144)	132 (132-144)	0.538
Duration (hour), median (min-max)			
Fever	36 (24-60)	48 (24-60)	0.231
Shortness of breath	84 (72-96)	84 (72-108)	0.070
Retraction	84 (72-108)	96 (84-108)	0.068
Rales	72 (60-96)	84 (72-108)	0.037*
C-Reactive Protein (CRP) (mg/L), median (min-max)			
After Diagnosis	31.24 (19.86-45.57)	29.88 (20.17-47.07)	0.401
Third Day	2.78 (1.24-4.45)	3.82 (2.80-5.10)	
Decrease of CRP (mg/L), median (min-max)	27.94 (17.90-43.45)	25.39 (16.68-42.17)	0.137

*Mann-Whitney: statistically significant if p-value less than 0.05; CRP: C-Reactive Protein

Tabel 3 The multivariate analysis by Ancova between variables that expected to affect duration of rales

Variables	B	CI 95%	P
Exclusive breastfeeding	-0.90	-7.63 – 5.81	0.780
Probiotic	-5.87	-10.89 – (-0.86)	0.022*

*Analysis of Covariate (Ancova): statistically significant if p-value less than 0.05; CI: Confidence Interval.

The median C-Reactive Protein (CRP) concentration when patients were diagnosed with severe pneumonia has no statistically significant difference in the Group I (31.24 (19.86-45.57) mg/L) compared to Group II (29.88 (20.17-47.07) mg/L), respectively (P=0.401). However, median CRP after administration of the third day of probiotic adjunctive therapy resulted in 2.78 mg/L (1.24-4.45), while 3.82 mg/L (2.80-5.10) in the placebo group. The decrease of CRP concentration was also not statistically significant between Group I (27.94 (17.90-43.45) mg/L) and Group II (25.39 (16.68-42.17) mg/L) (p=0.137) (Table 2). However, in the bivariate analysis, we found that the duration of rales has a statistically significant difference between both groups (P=0.037) (Table 2).

The multivariate analysis (Ancova) was conducted to find out the variables that affected the duration of rales. Table 3 shows that the probiotic variable taking from history of exclusive breastfeeding has a statistically significant effect in reducing rales duration of 5.87 hours (p=0.022; 95% CI: -10.89 - (-0.86)).

DISCUSSIONS

Pneumonia mostly occurs in children under the age of 5 years, malnutrition, boy, non-exclusive breastfeeding, incomplete immunization.[11] In this study, the median age was 18 months (minimum 6 months and maximum 50 months), malnutrition 20%, boy 59%, non-exclusive breastfeeding 16% and incomplete immunization 15%.

The use of broad-spectrum antibiotics can affect the balance of commensal bacterial microflora in the digestive tract. A previous study recommended that the administration of probiotics no later than 3 hours after antibiotics.[12] In this study, probiotics were given 3 hours after intravenous antibiotics to avoid the effects of antibiotics on the probiotics.

A systematic review based on RCT by Araujo GV et al. related to the use of probiotics compared to placebo in children with respiratory infections obtained there are three significant RCT that has disease symptom reduction (P<0.05).[13] A study by Leyer GJ et al. about probiotics were divided into two groups: single (*L. acidophilus*) and combination (*L. acidophilus* and *B. animalis*).[14] They revealed a reduction of fever 53.0% and 72.7%, cough 41.4% and 62.1%, and rhinorrhea 28.2% and 58.8%, respectively, when compared to placebo group.[14] Study by Skovbjerg S et al. using probiotic spray (*S. sanguinis, L. rhamnosus*), in children

with respiratory infections.[15] They got 36.8% of patients was improved compared to only 5.8% of patients in the placebo group. A study by Kumpu M et al. revealed that disease duration was significantly shorter in the probiotic group (*L. rhamnosus GG*) compared to the placebo group (P<0.001).[16] Although studies by Leyer GJ et al. and Skovbjerg S et al. were showing a statistically significant decrease in symptoms, these studies have a wide confidence interval.[14,15] Both of them used a different definition of respiratory tract infections in their studies.

In our study, there were no statistically significant differences in outcomes for a length of stay, duration of fever, duration of shortness of breath, duration of retraction and CRP. However, there was a statistically significant difference in the duration of the rales between the intervention (Group I) and placebo (Group II) group. A clinical difference of 12 hours (0.5 day) to 24 hours (1 day) may provide benefits in terms of hospital services, patient comfort and hospitalization costs, especially patients without health insurance coverage.

A study by Becina PGA has similar results to our study, and their RCT study found no statistically significant findings related to the use of probiotics (*L. casei, L. rhamnosus, Streptococcus thermophilus, B. breve, L. acidophilus, B. infantis, L. bulgaricus,* each 109 cfu/gr, FOS) as adjunctive therapy in pneumonia to improved the outcomes.[9]

In contrast, our results differ from other RCT, perhaps due to differences in the type and duration of probiotics and also the operational definition of pneumonia variable outcomes that used. An RCT by Bayer-Muslid TB and Gathcheco FN in severe pneumonia of children aged 6-24 months who received standard therapy and *OMX Ohhira®* probiotic compared to controls found in the intervention group was statistically significantly shorter in the duration of the length of stay (P<0.007), duration of shortness of breath (P<0.001), and retraction of subcostal disappear faster (P<0.001).[7]

The release of proinflammatory cytokines such as IL-1, IL-6, and TNF-α corresponded to the lung parenchyma damage that occurs so that it will correlate with the severity of pneumonia. The liver synthesizes C-reactive protein (CRP) in response to tissue damage.[10] IL-6 is considered as the primary mediator of CRP production, besides IL-1, TNF-α, TGF-α, and IL-8.10 CRP is the protein that reacts most quickly, susceptible, easily measured, has fast response time, short half-life, and its catabolism is not influenced by the type of inflammation.[1]

In systematic review and meta-analysis by Mazidi M et al., the administration of probiotics indicates a significant decrease in CRP levels.[17] This result was supported by Asemi Z et al. that probiotics were significantly able to reduce CRP compared to placebo.[18] Several mechanisms were thought to explain the effects of probiotics on reducing CRP, including Short-Chain Fatty Acid (SCFA) produced from probiotics in the large intestine that could reduce CRP synthesis in the liver. The decrease in CRP may also due to reduced expression of IL-6.[17] Different results from our study found no significant differences in CRP in the probiotic or placebo groups. Agrawal S et al. also suggested that the administration of Bifidobacterium breve did not significantly reduce CRP compared to placebo.[19]

In multivariate analysis, probiotics were obtained from exclusive breastfeeding affecting the improvement in rales duration 5.8 hours faster in children with severe pneumonia who received probiotics compared to placebo. Rales or crackles on auscultation are considered significant findings that indicate pneumonia. Rales are a series of additional sounds during the inspiration phase that indicate the presence of secretions in the alveoli due to the immune process against infection/inflammation. The specificity of rales to diagnose pneumonia was 71% (95% CI: 62-81) based on the previous study.[20] The Bayer-Muslid TB and Gathcheco study of severe pneumonia in children aged 6-24 months who received standard therapy and *OMX Ohhira®* probiotic compared to controls revealed that rales disappeared faster in the probiotic group compared to controls.[7] The protective mechanism produced by probiotics through increased regulation of NK cells and activation of respiratory mucous macrophages.[6]

In this study, no adverse events were obtained during the administration of probiotics or placebo. In systematic review based on RCT by Araujo GV et al. and Wang Y et al. found that probiotics have a safety profile because the majority of RCT found no adverse events.[4,13] Mild adverse events, such as decreased appetite, regurgitation, dry skin, mild abdominal pain, diarrhoea, nausea, rashes and constipation. This study has several limitations due to did not examine faecal cultures before and after the administration of probiotics to find out an increase or decrease number of probiotic colonies. In this study, temperature measurements were carried out upon arrival at the hospital; a history of obtaining prior antibiotics was not traced. From these limitations, further study should gain complete data and larger sample sizes to determine the effectiveness of using probiotics as adjunctive therapy for pneumonia.

CONCLUSION

The duration of rales for children aged 2 months-5 years with severe pneumonia who received standard therapy and probiotics was shorter than those who received standard therapy and placebo.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this study.

ETHICAL CONSIDERATION

This study was performed under the supervision of Respirology division, Department of Child Health Medical Faculty of Udayana University/ Sanglah Hospital Denpasar and approved by ethical clearance 2139/UN.14.2/KEP/2017 from the ethics committee of Faculty of Medicine, Udayana University/Sanglah Hospital Denpasar, Bali

AUTHOR CONTRIBUTIONS

All of the authors are equally contribute to the study from the conceptual framework, data gathering, data analysis, until interpreting the results through publication.

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