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ORIGINAL ARTICLE

A DOUBLE – BLINDED, RANDOMIZED, CONTROLLED TRIAL OF THE EFFICACY OF MULTIPLE STRAIN PROBIOTICS AS ADJUNCT THERAPY FOR PATIENTS 2 MONTHS – 4 YEARS WITH MODERATE RISK COMMUNITY ACQUIRED PNEUMONIA**

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Objective: The purpose of the study was to determine the efficacy of probiotics as adjunct therapy for patients (2 months – 4 years old) with moderate risk community acquired pneumonia.

Methods: The study population consisted of 77 children, 2 months – 4 years old with Moderate Risk Community Acquired Pneumonia (PCAP guidelines), with no Hib vaccination, no previous intake of antimicrobials, no contraindications to feed within the first 24 hours upon admission and with informed consent. Participants were randomized to the probiotics group, given Ampicillin (100 mkd), supplemented with probiotics (1 sachet for 7 days) while the control group was given Ampicillin and a placebo. Patients with co – morbidities (i.e. cardiac problems, malnutrition etc.), and those with previous intake of antimicrobials were excluded. Both groups were compared based on the following: cardiac rate, respiratory rate, temperature, presence or absence of chest retractions and length of hospital stay. The physicians and patients were blinded as to which group they belonged to.

Results: For subjects ≤1 year old in the probiotics group, cardiac rates normalized at day 2. In the placebo group, fluctuating cardiac rates were noted although this difference was statistically significant. Among >1 year olds, normal cardiac rate was reached on days 4 and 5 in the probiotics group and this was not reached in the placebo group. The respiratory rate normalized in both groups starting day 1 for those ≤ 1 year old. Respiratory rates in the probiotics group were also noted to be lower than the placebo group. Among >1 year old, normal respiratory rate was reached on day 2 for both groups. The respiratory rates of the probiotics group were lower than the placebo group but this was not statistically significant. The temperature decline between the two groups was not significantly different. Presence of chest retractions was lower in the probiotics group as compared to the placebo group by day 4. Both groups had an average length of hospital stay of 3 days.

Conclusion: The results of the study suggest that probiotics may possibly be helpful as an adjunctive therapy for patients, 2 months to 4 years old, with moderate risk community acquired pneumonia.

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KEYWORDS:

Community Acquired Pneumonia, Multistrain Probiotics, Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Lactobacillus acidophilus,

INTRODUCTION

Pneumonia is one of the, if not the most common illness that we pediatricians encounter everyday. According to the Philippine Health Statistics of the Department of Health, pneumonia is still the number one cause of morbidity in our country, with 690,566 reported cases (2005). In addition, pneumonia is also the number one leading cause of mortality in children, specifically ages 1 – 4, with 2,118 cases per 100,000 population in the most recent identification of the ten leading causes of child mortality (2009).[1,2] This illness has been a bane in our society despite proper diagnosis and advances in modalities of treatment. Hence, pursuing avenues for adjunct therapy is greatly needed in order to decrease the prevalence of this killer disease.

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (FAO/WHO, 2002) [3]. Investigations in the probiotics field during the past decades have evolved from bacteria isolated from fermented products to those of intestinal origin[4]. Hence, the possible benefits have been documented on previous studies, both internationally and locally, which centered mainly on diseases of the gastrointestinal tract[5,6,7]. Throughout the years, the mechanisms on how probiotics confer their beneficial effects have been hypothesized and looked further into. Immunomodulation is one avenue being continuously pursued. Through enhancement of specific and nonspecific immune response, inhibition of pathogenic growth and translocation, thus leading to reduction of infection from common pathogens[3], probiotics can be used as adjunct therapy for many diseases and not only to those confined in our gut. Hence, the aim of this study is to determine the efficacy of multistrain probiotics as adjunct therapy in patients with moderate risk community acquired pneumonia admitted in a Tertiary Government Hospital.

METHODS

A double – blind, randomized controlled trial was conducted in children with Moderate Risk Community Acquired Pneumonia, admitted the National Children's Hospital. Patients 2 months to 4 years old with Moderate Risk Community Acquired Pneumonia, based on the PCAP guidelines, with no Hib vaccination, no previous intake of antimicrobials, who had no contraindications to feed within the first 24 hours upon admission and with informed consent were included in the study. Patients with other co – morbidities such as cardiac problems, other pulmonary diseases and gastroenteritis, those who are malnourished based on the Z score and those with previous intake of antimicrobials were excluded.

Parents of children who fulfil the inclusion/exclusion criteria were informed of the study and invited to participate. The details of the study were discussed by the study physician (or the resident on duty/resident in charge) and all questions were entertained and answered. Once all inquiries were fulfilled, the parents were asked to sign the written informed consent for study participation. Randomization was achieved via toss coin Then, the patients were allocated to two possible groups: the experimental group, administered Ampicillin at 100 mkd, which is the drug of choice for this age group based on the PCAP Guidelines, supplemented with multistrain probiotics, at a dose of 1 sachet for 7 days; or the control group administered the same antimicrobial and given a placebo at the same dose. The probiotics and placebo came in indentical sachets, the identities of which were unknown to the study physician as well as the participants. Upon inclusion to the study, baseline clinico – demographic data were gathered. Parents or

guardians were advised to give the probiotics at a constant time prior to lunch. Outcome parameters (cardiac rate, respiratory rate, temperature, presence or absence of subcostal or intercostal retractions and length of hospital stay) were then monitored by the study physician (resident in charge) during the morning rounds until the patients were discharged.

The probiotics used was Protexin Restore which contains Per 1 billion CFU/sachet of *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus*, fructooligosaccharide (FOS) and is manufactured by Prebiotech Advanced Pharma.

The research proposal was reviewed an approved by the Ethics Committee of the National Children's Hospital.

RESULTS

There were 77 subjects who satisfied the eligibility criteria and were randomly assigned to either the Probiotic Group or the Control Group. Table 1 shows the comparison of the different demographic characteristics between the two groups. The results showed that there was no significant difference noted as proven by all p values >0.05. This means that both groups were comparable in terms of the different characteristics. There were more females than males in the Probiotics Group, hence, the proportion of males and females was also comparable. Table 2 shows the comparison of the cardiac rate (CR) at different intervals between the two groups according to age groups. The normal CR for ≤ 1 year old subject is ≤ 120 bpm while ≤ 110 bpm is considered normal for subjects > 1 year old. The

Table 1. *Comparison of Demographic Characteristics Between the Two Groups*

	Probiotic N=37	Placebo N=40	P value
Age **Mean ± SD** **Range**	 1.23±0.82 0.17-3.08	 1.25±0.93 0.17-4.5	0.93
Sex **Female** **Male**	 17 (46%) 20 (54%)	 26 (65%) 14 (35%)	0.09
Weight (kg) **Mean ± SD** **Range**	 8.26±1.91 4.80-13	 74.31±8.95 4.10-15	0.29
Height (cm) **Mean ± SD** **Range**	 74.05±8.48 52-90	 74.31±8.95 56-96	0.90

results showed that there was no statistically significant difference noted as proven by all p values >0.05. However, it can be seen that in the Probiotic Group, a CR of at most 120 was noted starting day 2 for ≤1 year old subjects. However, in Placebo Group, fluctuating cardiac rates were noted. A CR of ≤120 was on seen day 4, but it increased again on day 5 and day 6. Among >1 year old subjects, a CR of at most 110 was reached on days 4 and 5 in the Probiotic Group. This outcome was not reached in Placebo Group.

Table 3 shows the comparison of CR at different intervals between the two groups with no age consideration. The results showed that there was no statistically significant difference noted as proven by all p values >0.05. However, the cardiac rates of subjects in Probiotic Group were noted to be lower than the cardiac rates of subjects in the Placebo Group. In each group, comparing the CR from day 0 until day 7, there were significant decreases noted as shown by all p values <0.01. It can also be seen that there was a faster decline in CR in the Probiotic Group than in the Placebo Group, starting on day 1 of admission. This trend persisted and was also evident during the succeeding hospital days.

Table 2. ***Comparison of Cardiac Rate (bpm) at Different Intervals Between the Two Groups According to Age Group***

Cardiac Rate (bpm)	≤1 y/o			>1 y/o		
	Probiotic	Placebo	P value	Probiotic	Placebo	P value
Day 0	137.05 ± 11.75	138.46 ± 11.40	0.70 (NS)	131.22 ± 14.99	132.33 ± 13.22	0.81 (NS)
Day 1	128.52 ± 12.14	130.59 ± 15.84	0.64 (NS)	122.28 ± 9.70	123.72 ± 14.94	0.73 (NS)
Day 2	120.07 ± 12.15	124.40 ± 11.64	0.30 (NS)	114.00 ± 10.78	120.06 ± 13.38	0.14 (NS)
Day 3	120.01 ± 7.75	121.80 ± 7.57	0.97 (NS)	113.50 ± 10.10	116.50 ± 14.60	0.58 (NS)
Day 4	117.38 ± 9.44	119.38 ± 12.24	0.72 (NS)	105.00 ± 13.23	118.00 ± 9.25	0.12 (NS)
Day 5	113.00 ± 15.72	122.67 ± 2.52	0.35 (NS)	100.00 ± 0.00	116.25 ± 5.06	0.06 (NS)
Day 6	120.00 ± 0.00	125.50 ± 0.70	0.29 (NS)	118.00 ± 0.00	123.00 ± 7.81	0.64 (NS)
Day 7	116.00 ± 0.00	---	---	113.00 ± 0.00	121.00 ± 15.56	0.19 (NS)

Table 3. ***Comparison of Cardiac Rate (bpm) at Different Intervals Between the Two Groups***

Hospital Day	Group A (n=37)	Group B (n=40)	P value
0	134.22 ± 13.56	135.70 ± 12.48	0.62 (NS)
1	125.48 ± 11.32	127.50 ± 15.64	0.52 (NS)
2	117.38 ± 11.82	122.51 ± 12.46	0.07 (NS)
3	(n=25) 117.76 ± 9.7 1	(n=25) 119.68 ± 10.98	0.52 (NS)
4	(n=11) 114.00 ± 11.44	(n=14) 118.78 ± 10.68	0.29 (NS)
5	(n=4) 109.75 ± 14.38	(n=7) 119.00 ± 5.16	0.14 (NS)
6	(n=2) 119.00 ± 1.41	(n=5) 124.00 ± 5.70	0.29 (NS)
7	(n=2) 114.50 ± 2.12	(n=2) 121.00 ± 15.56	0.62 (NS)
	<0.01 (S)	**<0.01 (S)**	

Table 4 shows the comparison of respiratory rate (RR) at different intervals between the two groups according to age groups. The normal RR for ≤ 1 year old subject is ≤ 50 cpm while ≤ 40 bpm is considered normal for subjects > 1 year old. The results showed that there was no statistically significant difference noted as proven by all p values >0.05. Although it can be seen that a RR of at most 50 was achieved by subjects in both groups starting day 1 for those ≤ 1 year old, the RR in the Probiotic Group was noted to be lower than that of the Placebo Group. Among >1 year old subjects, a RR of ≤ 40 was reached on day 2 for both groups. However, it can be noted that the RR of subjects in the Probiotic Group were lower than the RR of subjects in the Placebo Group.

Table 4. ***Comparison of Respiratory Rate (cpm) at Different Intervals Between the Two Groups According to Age Group***

RR (cpm)	≤1 y/o			>1 y/o		
	Group A	Group B	P value	Group A	Group B	P value
Day 0	60.16 ± 9.62	60.82 ± 5.27	0.94 (NS)	55.39 ± 10.15	57.17 ± 9.66	0.59 (NS)
Day 1	42.58 ± 11.20	45.18 ± 9.37	0.42 (NS)	43.06 ± 9.51	42.00 ± 9.67	0.74 (NS)
Day 2	38.52 ± 10.50	37.73 ± 8.82	0.79 (NS)	34.11 ± 6.90	34.12 ± 10.72	0.99 (NS)
Day 3	38.92 ± 8.77	37.07 ± 5.87	0.51 (NS)	29.50 ± 3.82	32.90 ± 6.04	0.24 (NS)
Day 4	33.62 ± 7.46	33.50 ± 4.20	0.96 (NS)	29.67 ± 4.73	35.50 ± 10.91	0.42 (NS)
Day 5	30.67 ± 9.60	35.67 ± 6.42	0.50 (NS)	28.00 ± 0.00	34.75 ± 14.29	0.46 (NS)
Day 6	36.00 ± 0.00	35.00 ± 7.07	0.82 (NS)	27.00 ± 0.00	30.33 ± 10.12	0.65 (NS)
Day 7	30.00 ± 0.00	---	---	27.00 ± 0.00	28.50 ± 9.19	0.60 (NS)

Table 5. ***Comparison of Respiratory Rate (cpm) at Different Intervals Between the Two Groups***

Hospital Day	Group A (n=37) Mean ± SD	Group B (n=40) Mean ± SD	P value
0	57.32 ± 9.93	59.18 ± 7.68	0.36 (NS)
1	42.81 ± 10.27	43.75 ± 9.52	0.63 (NS)
2	36.38 ± 9.09	36.15 ± 9.73	0.92 (NS)
3	(n=25) 34.40 ± 8.26	(n=25) 35.40 ± 7.42	0.65 (NS)
4	(n=11) 32.55 ± 6.84	(n=14) 34.36 ± 7.51	0.54 (NS)
5	(n=4) 30.00 ± 7.96	(n=7) 35.14 ± 10.78	0.43 (NS)
6	(n=2) 31.50 ± 6.36	(n=5) 32.20 ± 8.38	0.92 (NS)
7	(n=2) 28.50 ± 2.12	(n=2) 28.50 ± 9.19	1.00 (NS)
P value	**<0.01 (S)**	**<0.01 (S)**	

Table 5 shows the comparison of RR at different intervals between the two groups with no age consideration. The results showed that there was no statistically significant difference noted as proven by all p values >0.05. However, the respiratory rates of subjects in the Probiotic Group were noted to be lower than the respiratory rates of subjects in the Placebo Group . In each group, comparing the RR from day 0 until day 7, were significant decreases noted as shown by all p values <0.01. It can also be seen that the RR decreased faster in the Probiotic Group than in the Placebo Group , starting on day 3 of admission. This decline was also noted during the succeeding hospital days until day 6, when the RR was comparable for both groups.

Table 6 shows the comparison of temperature at different intervals between the two groups. The results showed the subjects became afebrile starting day 2 for both groups. There was no statistically significant difference noted as proven by all p values >0.05. In each group, comparing the temperature from day 0 until day 7, there were decreases noted as shown by all p values <0.01.

Table 6. *Comparison of Temperature (C^0) at Different Intervals Between the Two Groups*

Hospital Day	Group A (n=37) Mean ± SD	Group B (n=40)	P value
0	37.79 ± 0.86	37.86 ± 0.91	0.72 (NS)
1	37.05 ± 0.56	37.02± 0.56	0.79 (NS)
2	36.83 ± 0.33	36.89 ± 0.37	0.45 (NS)
3	(n=25) 36.93 ± 0.42	(n=25) 36.72 ± 0.32	0.05 (S)
4	(n=11) 36.53 ± 0.30	(n=14) 36.64 ± 0.32	0.36 (NS)
5	(n=4) 36.68 ± 0.56	(n=7) 36.38 ± 0.40	0.34 (NS)
6	(n=2) 36.75 ± 0.35	(n=5) 36.70 ± 0.41	0.89 (NS)
7	(n=2) 36.50 ± 0.56	(n=2) 36.55 ± 0.35	0.92 (NS)
P value	**<0.01 (S)**	**<0.01 (S)**	

Table 7 shows the comparison of the proportion of subjects with chest retractions at different intervals between the two groups. The results showed that there was no statistically significant difference noted as proven by all p values >0.05. However, it can be seen that on day 1, presence of chest retractions was lower in the Probiotics Group (48.6%) as compared to the Placebo Group (55%). By day 4, no subjects belonging in the Probiotics Group had chest retractions. This was not the case for th Placebo Group wherein one subject was observed to have chest retractions until day 6. In each group, comparing the proportion of subjects with chest retractions from day 0 until day 7, there were significant decreases noted as shown by all p values <0.01.

Table 7. *Comparison of the Proportion of Subjects with Chest Retractions at Different Intervals Between the Two Groups*

Chest Retractions	Group A (n=37)	Group B (n=40)	P value
Day 0	37 (100%)	40 (100%)	1.00 (NS)
Day 1	18 (48.6%)	22 (55.0%)	0.58 (NS)
Day 2	6 (16.2%)	6 (16.2%)	0.88 (NS)
Day 3	6 (16.2%)	6 (16.2%)	0.88 (NS)
Day 4	0	1 (2.6%)	1.00 (NS)
Day 5	0	1 (2.6%)	1.00 (NS)
Day 6	0	1 (2.6%)	1.00 (NS)
Day 7	0	0	1.00 (NS)

The mean duration of hospital stay was 3.2+1.26 days in the Probiotics Group, with a range of 2-7 days. This was not statistically significant from the Placebo Group which had a mean duration of 3.3+1.51 days and range of 2-7 days.

DISCUSSION

Pneumonia is defined as an inflammation of the parenchyma of the lungs, mostly caused by microorganisms. The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including mucocillary clearance, the properties of normal secretions, Immunoglobulin A (IgA), and clearing of the airway by coughing. Immunologic defense mechanisms of the lungs that limit invasion of by pathogenic organisms include macrophages that are present in the

alveoli and bronchioles, secretory IgA and other immunoglobulins [8].

During the past decade, microbiologists, immunologists and gastronenterologists have actively studied the mechanism by which probiotics improve mucosal defenses[9]. Probiotic cultures have been shown in a variety of test systems to stimulate certain cellular and antibody functions of the immune system. Animal and some human studies have shown an effect of yogurt or lactic acid bacteria on enhancing levels of certain immuno – reactive cells (e.g. macrophages, lymphocytes) or factors (e.g. cytokines, immunoglobulins, interferon) (4). It has been discovered that colonizing bacteria that interact with the gastrointestinal mucosa can communicate with underlying epithelial and mucosal lymphoid elements and that such interaction stimulates host defenses in the gut. However, it was not until recently that investigators began to understand the so – called bacterial epithelial cross talk at the cellular level. With the discovery of toll – like receptors (TLRs) on eukaryotic, epithelial, endothelial and lymphoid cells, which could interact with molecular patterns on both pathogens and commensal bacteria, a molecular and cellular basis for communication could be appreciated. With this interaction, a series of signalling molecules is activated in the cell to release the transcription factor nuclear factor into the nucleus, which in turn transcribes inflammatory cytokines, specifically IL – 8 and IL – 6, that provide basis for an acute innate inflammatory response to an invading pathogen. The appreciation of microbial patterns that interact with pattern – recognition receptors on eukaryotic cells has been the basis for understanding of bacterial – epithelial cross talk and its role in both innate and adaptive mucosal immunity[9]. Probiotic modulation of host immunity is a very promising area for research since supportive data is emerging, such as those carried out in humans showing that probiotic microorganisms can enhance the host's defenses by induction of mucus production or macrophage activation by lactobacilli signalling, stimulation of IgA and neutrophils at the site of probiotic action [10] which can be beneficial in the treatment of many diseases outside the gastrointestinal tract.

Studies done both locally and internationally have shown that multistrain probiotics have indeed advantageous effects in other systems, specifically disease which are respiratory in nature. Multistrain probiotics were used as adjunct treatment of neonatal pneumonia in a tertiary government hospital in both studies. The results showed that a statistically significant difference in rapid breathing, with subjects in the treatment group had shorter duration of rapid breathing as well as early feeding tolerance and shortened hospital stay when compared to the control group. This also led to a significant reduction in neonatal sepsis in the experimental group 1[1,12].

In this study, there were more females admitted and enrolled, however this was not statistically significant. The age, weight and height were all not contributory. Similar to the aforementioned studies[11,12], beneficial effects were also observed in the Probiotics group as compared to the Placebo group. The cardiac rates normalized faster for the Probiotics group as compared to the Placebo among $\leq$ 1 year and >1 year old subjects. In addition, the cardiac rates of subjects in the Probiotics group were noted to be lower. Another parameter considered was the respiratory rate. Although it can be seen that the respiratory rate reached normal levels in both groups starting on similar days for both ≤ 1 year

and >1 year old subjects, it can be noted that the respiratory rates of subjects in the Probiotics group were lower as compared to the Placebo group. One parameter which showed some beneficial effect was the proportion of subjects with chest retractions at different intervals between the two groups. It can be seen that on day 1, presence of chest retractions was considerably lower in the Probiotics group (48.6%) as compared to the Placebo (55%). By day 4, no subjects belonging in the Probiotics group had chest retractions as compared to the Placebo group wherein one subject had persistent chest retractions until day 6. Lastly, both groups had an average length of hospital stay of approximately 3 days.

CONCLUSION

The results of the study suggest that multistrain probiotics may be helpful as an adjunct therapy for patients, two months to four years old, with moderate risk community acquired pneumonia in the improvement of their clinical picture and hospital stay. Multistrain probiotics together with IV antibiotics in patients admitted appeared to induce a more rapid decrease to normal in terms of cardiac rates and respiratory rates, as well as decrease in patients with chest retractions although this was not statistically significantly different from the placebo group.

LIMITATIONS AND RECOMMENDATIONS

The data may turn out to be significant if this study had a large sample size. Moreover, the study is only limited to those who have not receive any oral antibiotic at home, either self – medicated or prescribed by a physician, as well as those with no co – morbidities. In line with this, pneumonia seems to occur frequently in patients with other co – morbidities such as those with congenital heart diseases and malnutrition because of the status of their immune system. Further studies therefore are needed to investigate the ability and efficacy of multistrain probiotics as an adjunct therapy in these cases.

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