



The Combination of Salbutamol Nebulizer and Oral Procaterol to the Indonesian Children with Pneumonia

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Abstract

This study aimed to examine the effectiveness of combining salbutamol nebulizer and oral procaterol compared to only oral procaterol on the respiratory rate, temperature (fever), spasm, cough frequency, thoracic retraction, and length of stay (LOS) among young children with pneumonia. This prospective cohort study included 48 consecutive sampling subjects with pneumonia in Indonesia. The subjects were classified based on the type of therapy they received: intervention group used the combination of salbutamol nebulizer and oral procaterol therapy (n=24 subjects) and the control group received oral procaterol only (n=24). The result showed that the combination therapy salbutamol nebulizer and oral procaterol was more effective than the administration of oral procaterol only with the rate of clinical change. Combination therapy nebulized salbutamol and oral procaterol significantly respiratory rate ($p=0.006$) and temperature (fever) ($p=0.002$) compared to the only oral procaterol. The combination had clinical change in reducing spasm, cough frequency, thoracic retraction, and length of stay (LOS) however there are was no significant effect of this combination in reducing spasm ($p=0.348$), cough frequency ($p=0.964$), thoracic retraction ($p=0.666$), and length of stay (LOS) ($p=0.192$) compared to the only oral procaterol among the Indonesian children with pneumonia.

Keywords: Children, Cough, Length of stay, Pneumonia, Procaterol, Salbutamol nebulizer.

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1. Introduction

The mortality rate of children due to pneumonia is estimated to be 1.1 million/year which is higher in children under five years

[1]. The death rate caused by pneumonia in 2013 reached 940.000 (15% of all under- five years death) [2]. In 2013 in Indonesia around 14% of child deaths were caused by pneumonia [3]. Pneumonia can be caused by bacteria, viruses, fungi and protozoa [4]. The community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) caused by *Streptococcus pneumonia* and *Haemophilus influenza B* (Hib) with symptoms such as pneumatic cough, fever, rapid breathing, and crepitation [5]. In general upper or lower

airway obstruction in children with pneumonia is due to increased secretion production as one of the manifestations of inflammation of the airways [6]. Risk factors that cause an increase in the incidence and severity of the disease include prematurity, low socio-economic status, exposure to passive cigarette smoke, living in childcare, and having a history of pneumonia [7]. Nebulizer is a safe supportive therapy that works directly on the bronchi and bronchioles using a bronchodilator agent as a drug that dilates the bronchi and bronchioles which are narrowed so that air flow increases in the lungs [8]. Research in Pakistan that administered budesonide nebulizer in neonatal care because the ventilator causes pneumonia can reduce ventilation time, length of stay (LOS), improve lung diffusion function, reduce infant mortality without affecting future child growth [9].

This researcher was aimed to conducting a study the effectiveness of the combination the nebulizer salbutamol and oral procaterol in comparison with only oral procaterol in paediatric pneumonia in reducing respiratory rate and clinical symptoms namely temperature (fever), cough, spasms, thoracic retraction and length of stay (LOS). This study is expected to be put into consideration in the treatment of paediatric pneumonia and description effectivity of combination of salbutamol nebulizer and oral procaterol.

2. Materials and Methods

2.1. Drugs

The drugs used in this study were salbutamol nebulizer (Velutin® contain

salbutamol 2.5 mg, Novell Pharmaceutical Laboratories) and oral procaterol (Ataroc® contains procaterol hydrochloride 25 mcg/tablet, Novell Pharmaceutical Laboratories). Both of these drugs are selective beta-2-adrenoreceptor agonists that are indicated for treating obstructive airway diseases in pediatric patients with pneumonia. The initial dose of Velutin® is 2.5 mg, can be repeated up to 4 times a day and given through a nebulizer. Ataroc® tablets can be given to children aged >6 years at a dose of 25 mg per day, while children aged <6 years can be given at a dose of 1.125 mcg per day or 0.2-0.25 mg/kg every 12 hours.

2.2. Preparation of Drugs

Patients were administrated salbutamol solution for nebulization dosage 1.25-2.5 mg every 8 hours, not exceed 10mg/24 hours and oral procaterol dosage 10-25µg every 12 hours. Oral procaterol were administrated in the morning and before bed during treated in hospitalization.

2.3. Experimental Design

This research is an observational study with a prospective cohort design of consecutive sampling during the period between September and November 2018 in the private hospital, Bantul, Yogyakarta province, Indonesia. This study was divided into two groups, namely the intervention group (given salbutamol nebulizer and oral procaterol)

(n=24) and the control group (given oral procaterol only) (n=24) ([Figure 1](#)).

Inclusion criteria were male or female paediatric patients of 0 and 18 years old, diagnosed pneumonia with positive examination and no obvious abnormalities from chest X-ray also received combination salbutamol nebulizer and oral procaterol therapy, and signed informed consent form.

Exclusion criteria were unable to comply with protocol, refuse to be a participant in this study, having history of allergic or intolerance to β_2 agonist receptors, and having respiratory disease, cardiovascular disorders, and immunodeficiency.

2.4. Measured Parameters

After administration of salbutamol nebulizer and procaterol, respondents in both study groups were monitored clinical outcomes to determine the effectiveness of therapy. Clinical outcomes are respiratory rate, temperature (fever), cough frequency, spasms, and thoracic restriction. The thoracic retraction included paroxysmal cough and pertussis, rhonchi, wheezing, malaise, myalgia (in children), abdominal pain, spasms, and fever [10]. Monitoring of clinical outcomes is carried out while the patient is hospitalized.

In addition to clinical outcomes, this study will also calculate the length of stay (LOS) to determine the effectiveness of the combination of salbutamol nebulizer and oral procaterol compared to single therapy with oral

procaterol on the length of stay of pneumonia patients in pediatric wards.

2.5. Statistical Analysis

The data was analyzed using frequencies, Chi-square, Fishers (if the Chi-square requirements (table 2x2) are not fulfilled), and Mann-Whitney tests. The difference was considered significant if $p < 0.05$ with the confidence level of 95%. This study was approved by the Ethics Committee of the Faculty of Medicine, the Islamic University of Indonesia.

3. Results and Discussion

3.1. Characteristics of Child Pneumonia Subjects

The results of this study showed that pneumonia in boys (56.2%) was higher than in girls (43.8%) ($p=0.771$) ([Table 1](#)). Research in Sumatera Selatan, Indonesia conducted that in boys had 1.1 times the risk compared to the girls but in statistically no significant relationship with the incidence of pneumonia as indicated by the value OR 1.1 (95% CI: 0.7-1.6) [11]. According of the *British thoracic society* (BTS), most pneumonia occurs in boys, unknowing with certainty of the mechanism or causes [12]. The prevalence of pneumonia in this study with the highest incidence rate was found in children aged >12-36 months (toddler) (39.6%) and the highest was found >144-216 months (teen) (2.1%) ($p=0.686$) ([Table 1](#)). Children under 4 years old who tend to increase activity and the immune system is still vulnerable so that they

are easily infected with respiratory diseases. Young age children and geriatric are also more susceptible to severe pneumonia [13].

Pneumonia with clinical symptoms of fever (41.7%) was less than children with no fever (58.3%), spasms (29.2%) and no spasms (70.8%) ($p=0.525$). The frequency of coughing in pediatric patients includes coughing with frequent intensity (85.4%), sometimes coughing (8.3%), and very often coughing (63%) ($p=0.062$), thoracic retraction (43.7%), and no retraction (56.3%) ($p=0.001$) (Table 1).

3.2. Effectivity of therapy

The clinical symptoms of pneumonia depend on the critical age of infection and the types of microorganism (bacteria, viruses, fungi and protozoa). The clinical features are usually characterized by fever, shivering, increasing temperature of 40°C , cough with mucoid or purulent phlegm sometimes with blood, spasms and chest pain [4].

The comparative analysis of the effectiveness between the intervention group (36.67°C) and the control group (36.83°C) with a significant value of $p=0.187$ to temperature (fever) with the clinical changes in the intervention group (3.02%) showed that statistically the intervention group was more effective in reducing fever than the control groups ($p=0.001$). The assessment of the antibiotic effectiveness used in both of groups is Cephalosporin generation III and there were significant differences between the two groups on changes in reducing temperature (Table 2). Research in Pakistan shows the average

temperature of young children with pneumonia that is $>37.8^{\circ}\text{C}$ (176 subject, 68%) [14].

Based on Fig. 2 there are no significant differences between the two groups analysed by Chi-square and Fisher's ($p>0.050$). The analysis of survival temperature curve with Kaplan Meier shows that both of groups have clinical improvement on the third day, in the intervention group (blue curve) the escalation of clinical estimation of fever was more (98%) and in the control group (green curve) (80%) and 50% subject has an escalation of clinical of fever on the day four (Figure 3).

In conditions of spasm the value of respiration rate velocity above normal values differs based on age groups, namely the normal value of the baby respiratory rate up to the age of 6 weeks: 30-60 times/minute, >6 weeks-6 months: 25-40 times/minute, >6 months-3 years: 20-30 times/minute, >3 years-6 years: 18-25 times/minute, >6 years - 10 years: 15-20 times/minute [15].

Based on Fig. 4 comparisons spasm subjects pneumonia each day showed that there was no significant difference ($p>0.050$) between the intervention 28.5 times/minute and control 27 times/minute groups with the respiratory rate, based on the clinical change in intervention groups (29%) greater than the control (16%) ($p=0.006$) had a significant difference (Table 2), in Fig. 5 the analysis of survival spasm curve with Kaplan Meier shows that the chances of survival of the intervention groups 95% were greater than controls 90% the fourth day.

The result of the control group showed that before the intervention, the status was very

severe (12.5%) and after hospitalization, the coughing status decreased coughed (58.3%) on the fourth day. Before the intervention, the cough status changed from often (87.5%) to sometimes (43.6%) on the fourth day ([Figure 6](#)). This study showed that the intervention group was more effective in reducing the frequency of coughing. Statistically, there were significant differences between two groups ($p > 0.050$) (Table 2). Kaplan Meier's survival analysis of coughing conditions with Likert score showed that the intervention group had a better chance of survival than the control group because coughing recovered faster (79%) than that in the control group (77%) ([Figure 7](#)).

Thoracic retraction on the first day was significantly different in both of groups ($p = 0.001$), than the second to sixth days. However, on the fifth day, there was a decrease in thoracic retraction in both groups with a value ($p > 0.050$) ([Figure 8](#)). The Kaplan Meier curve showed on the fourth day that intervention groups had a better chance of survival more than the control group because the thoracic retraction incidence in the intervention group recovered the survival rate of (98%) above the control group (92%) ([Figure 9](#)).

The analysis results show that the length of stay (LOS) in intervention group was 77 hours (4.29 days) and in the control 78 hours (4.46 days). Statistically, there were no significant differences in both groups in a term of hours ($p = 0.262$) and in days ($p = 0.192$) ([Table 3](#)).

Onset of action β_2 agonist is more rapid than other bronchodilator, the drug bind to β_2 -receptors in the airway smooth muscle and activate adenylate cyclase which increases cAMP, resulting in bronchodilation, β_2 -agonists also enhance ciliary movement and excretion of airway secreta and increase airway clearance, therefore β_2 agonist can relax the airway smooth muscle in a few minutes after the drug reached the airways [16].

In regular use of inhalation β_2 -agonists over the long time can decrease bronchodilating effect, unlike oral in long term use rarely decrease bronchodilating effect and the characterized simple to just swallow tablets or into powder with dose as needed for patients with decreased lung function, children and elderly patients with difficulties in inhaling drugs compared to inhalants which require special devices and techniques [17], but oral formulations are systemic and should not be used in patients with hyperthyroidism, underlying cardiovascular disease, hypertension or diabetes [18].

The report from New Zealand in 1980 has revealed between increased deaths and used of short-acting β_2 -agonists and it was followed by many other reports suggesting relationship between increased deaths and increased use of short-acting β_2 -agonists across the world. To overcome this issue, long-acting inhaled β_2 -agonists were developed. A new oral β_2 -agonists should be a once-a-day formulation with a longer duration of action for 12 to 24 hours rather than the current 8–10 hours and have much fewer cardiovascular side effects,

and others such as tremor and headache to be used as a controller because it does not aggravate airway hypersensitivity as short-acting β_2 -agonists do like procaterol have high selectivity for β_2 -receptors and longer duration of action [19].

In this study, combination is required between short acting β_2 -agonists and long acting β_2 -agonists to lower the risk of death due to decrease bronchodilating effect in long term use. The significant clinical change of the status respiratory rate hyper-responsiveness improved after co-administration of oral procaterol and salbutamol nebulizer.

4. Conclusion

The use of salbutamol nebulizer and oral procaterol (long acting β_2 agonist) in combination with salbutamol nebulizer (short acting β_2 agonist) might improve pneumonia symptoms better than oral procaterol (long acting β_2 agonist) alone.

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Tables:**Table 1.** Characteristic among children with pneumonia (*Statistical analysis: a.Chi-square. b.Fisher. c.Mann Whitney*).

Characteristics	Control (n=24)	Intervention (n=24)	Amount (n.%)	p
• Gender, n (%)				
- Male	13 (54.2)	14 (58.3)	27 (56.2)	0.771 ^a
- Female	11 (45.8)	10 (41.7)	21 (43.8)	
Amount, n (%)	24 (100)	24 (100)	48 (100)	
• Age ($\bar{X} \pm SD$)	29.42±35.68	23.21±17.34	26.31±27.93	0.967 ^c
- 0-12 months (<i>Baby</i>), n (%)	8 (33.3)	9 (37.5)	17 (35.4)	
- >12-36 months (<i>Toddler</i>)	10 (41.7)	9 (37.5)	19 (39.6)	
- >36-60 months (<i>Pre-schooler</i>)	2 (8.3)	5 (20.8)	7 (14.6)	
- >60-144 months (<i>Gradeschooler</i>)	3 (12.5)	1 (4.2)	4 (8.3)	
- >144-216 months (<i>Teen</i>)	1 (4.2)	0 (0)	1 (2.1)	
Amount, n (%)	24 (100)	24 (100)	48 (100)	0.686 ^c
• Vital Sign ($\bar{X} \pm SD$)				
- Temperature (⁰ C)	37.42±0.654	37.38±0.576	37.40±0.610	0.907 ^c
- Respiration Rate (x/minute)	31.63±6.800	40.17±12.461	35.90±10.828	0.001 ^c
• Clinical Symptoms, n (%)				
- Fever				
Yes	10 (41.7)	10 (41.7)	20 (41.7)	0.745 ^a
No	14 (58.3)	14 (58.3)	28 (58.3)	
Amount, n (%)	24 (100)	24 (100)	48 (100)	
- Spasm				
Yes	6 (25)	8 (33.3)	14 (29.2)	0.525 ^a
No	18 (75)	16 (66.7)	34 (70.8)	
Amount, n (%)	24 (100)	24 (100)	48 (100)	
- Coughing				
Sometimes Coughing (++)	1 (4.2)	3 (12.5)	4 (8.3)	0.062 ^c
Often Coughing (+++)	20 (83.3)	21 (87.5)	41 (85.4)	
Severe Coughing (++++)	3 (12.5)	0 (0)	3 (6.3)	
Amount, n (%)	24 (100)	24 (100)	48 (100)	
- Retraction				
Yes	5 (20.8)	16 (66.7)	21 (43.7)	0.001 ^a
No	19 (79.2)	8 (33.3)	27 (56.3)	
Amount, n (%)	24 (100)	24 (100)	48 (100)	

Table 2. Effectiveness of therapy salbutamol nebulizer and oral procaterol on clinical symptoms in children with pneumonia (Statistical analysis: a.Chi-square. b.Fisher's. c.Mann Whitney).

Clinical Symptoms	Control (n=24. %)	Intervention (n=24. %)	Amount (n.%)	<i>p</i>
• Fever				
- Yes	24 (100)	24 (100)	48 (100)	0,352
- No	0 (0)	0 (0)	0 (0)	
Amount (n.%)	24 (100)	24 (100)	48 (100)	
• Spasm				
- Yes	20 (83.3)	23 (95.8)	43 (89.6)	0.348 ^b
- No	4 (16.7)	1 (4.2)	5 (10.4)	
Amount (n.%)	24 (100)	24 (100)	48 (100)	
• Coughing				
- Sometimes Coughing (++)	8 (33.3)	6 (25)	14 (29.2)	0.964 ^c
- Once times Coughing (+)	10 (41.7)	14 (58.3)	24 (50)	
- No Coughing (-)	6 (25)	4 (16.7)	10 (20.8)	
Amount (n.%)	24 (100)	24 (100)	48 (100)	
• Retraction				
- Yes	4 (16.7)	2 (8.3)	6 (12.5)	0.666 ^b
- No	20 (83.3)	22 (91.7)	42 (87.5)	
Amount (n.%)	24 (100)	24 (100)	48 (100)	
Vital Sign	$(\bar{X} \pm SD)$			<i>p</i>
	Control (n=24)	Intervention (n=24)		
• Temperature				
- Pre-test	37.42±0.654	37.38±0.576		0.002 ^a
- Post-test	36.83±0.381	36.67±0.482		
- Changes	3.04±1.85	3.50±2.126		
- Changes (%)	3.02	3.58		
• Respiratory Rate				
- Pre-test	31.63±6.800	40.17±12.461		0.006 ^c
- Post-test	27.00±2.414	28.54±4.011		
- Changes	15.58±15.95	29.33±16.92		
- Changes (%)	16	29		

Table 3. Effectiveness of therapy salbutamol nebulizer dan oral procaterol against length of stay (LOS) among children subjects with pneumonia (Statistical analysis: Mann Whitney).

Statistical	$\bar{X} \pm SD$ (minimum-maximum value)		<i>p</i>
	Control n=24 (%)	Intervention n=24 (%)	
Days :	4.46±0.658 (4-6)	4.29±0.955 (3-6)	0.192
Hours :	78.00±16.971 (60-95)	77.00±19.029 (57-97)	0.262

Figures:

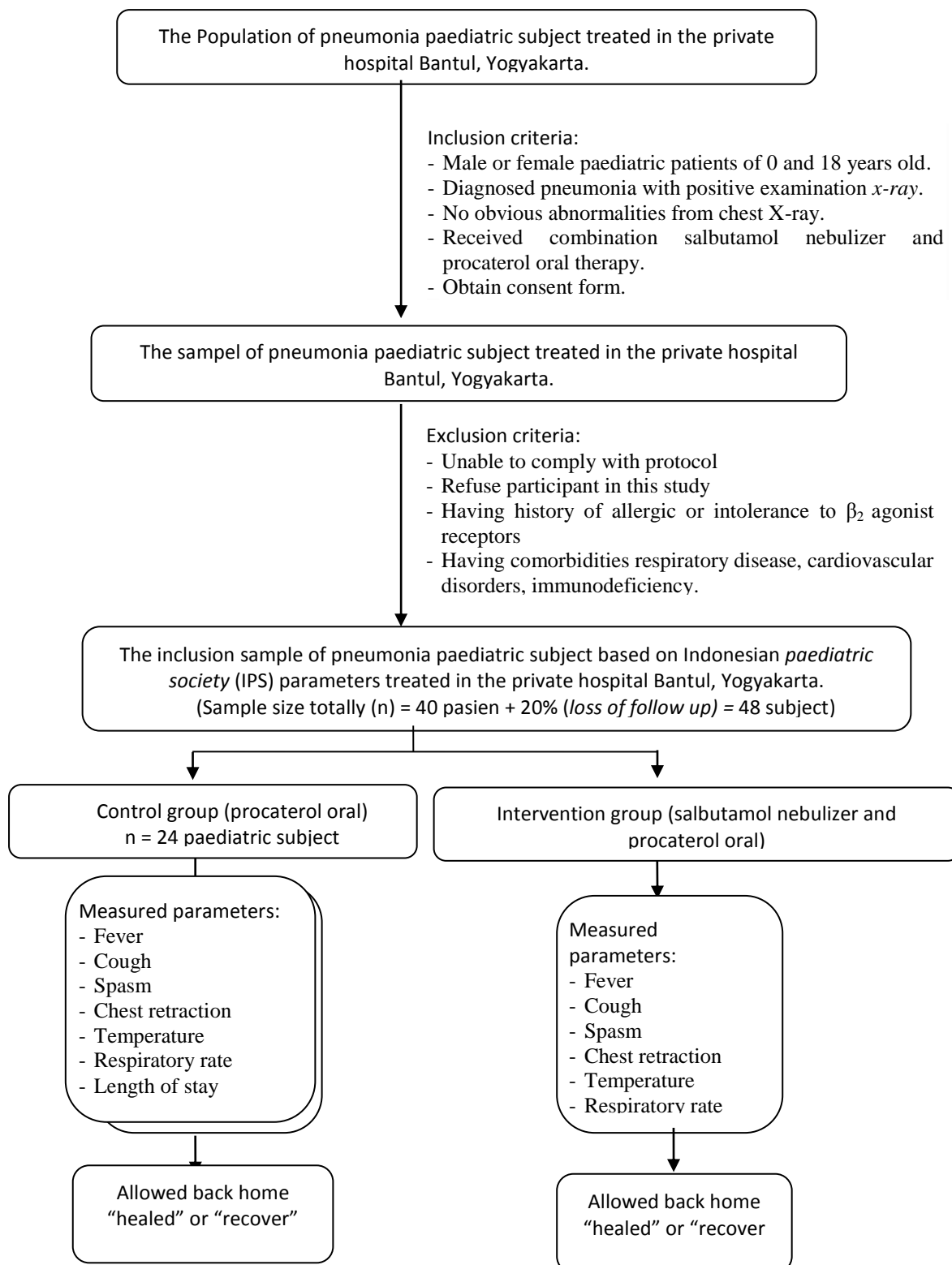


Figure 1. Protocol design study.

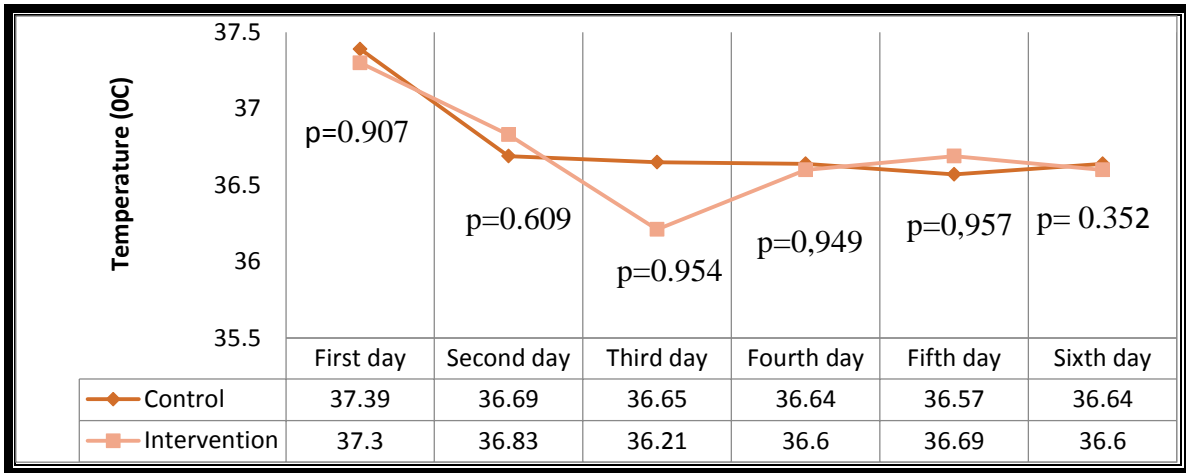


Figure 2. Temperature decline among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procatamol.

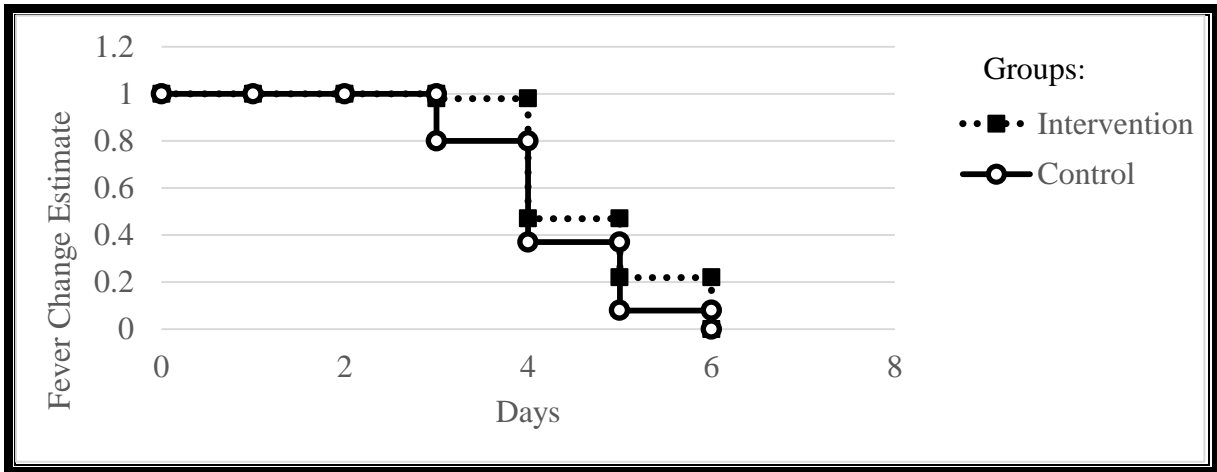


Figure 3. Survival curve fever among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procatamol.

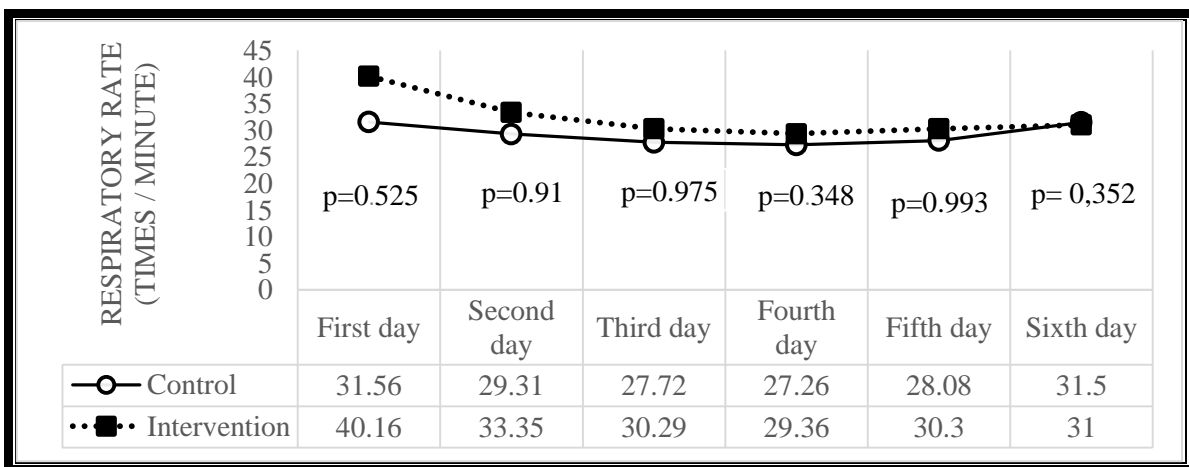


Figure 4. Respiratory rate decline among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procatamol.

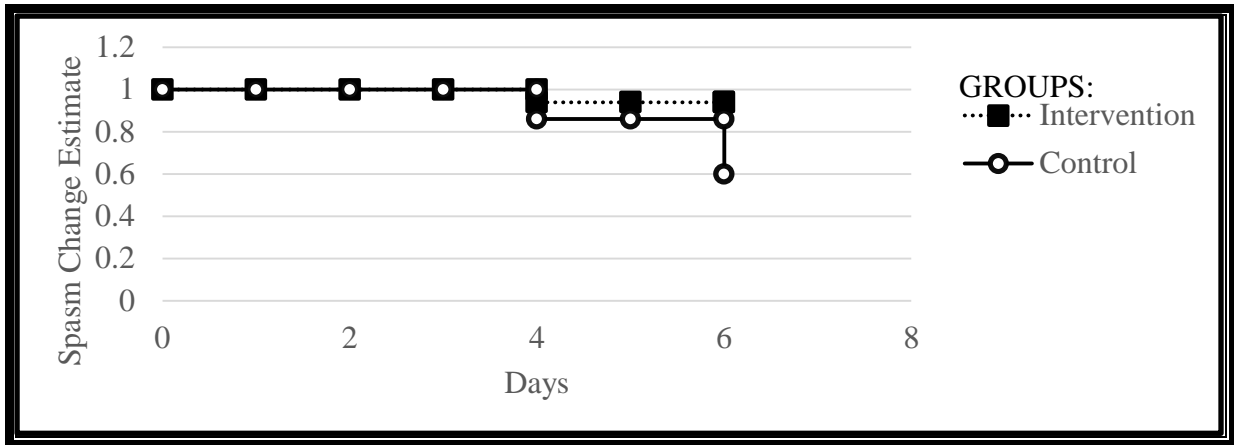


Figure 5. Survival curve spasm among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procaterol.

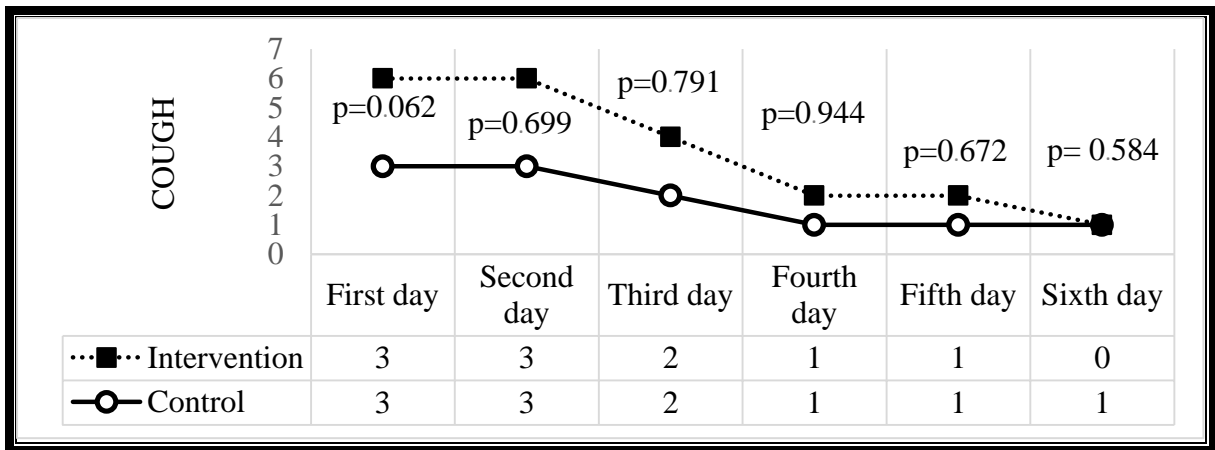


Figure 6. Cough decline among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procaterol.

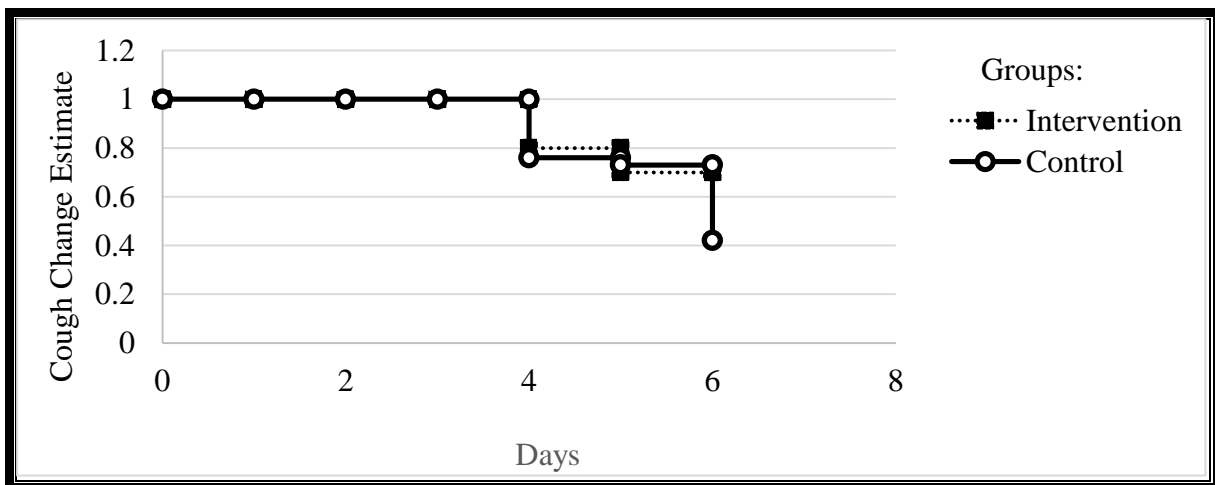


Figure 7. Survival curve coughing among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procaterol.

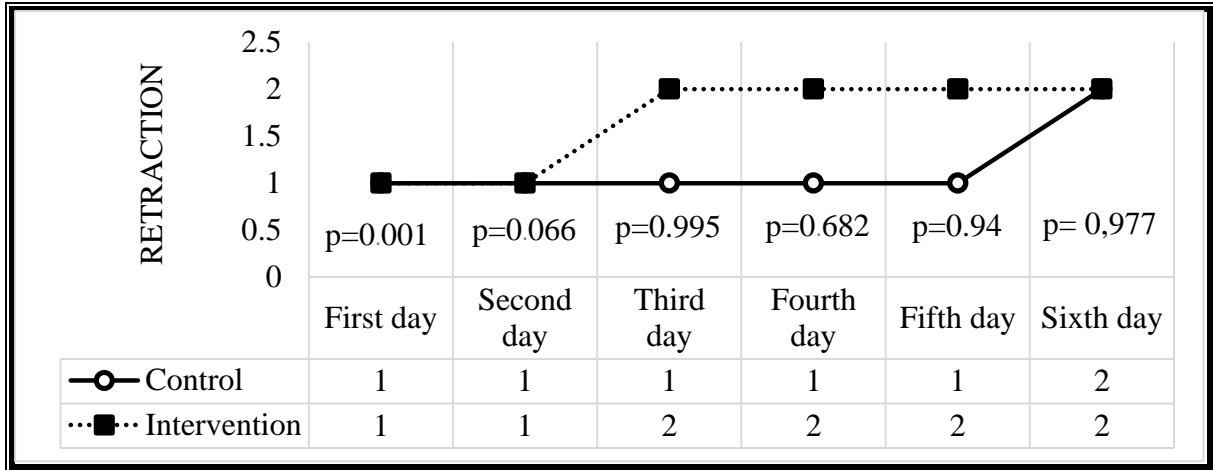


Figure 8. Retraction decline among young children subjects with pneumonia after given therapy salbutamol nebulizer and oral procaterol.

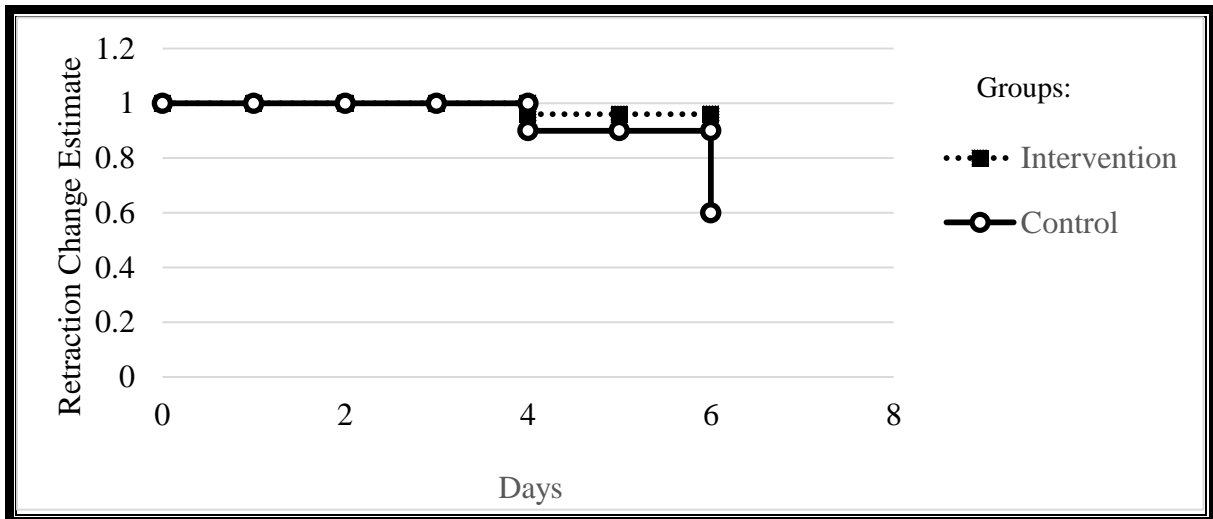


Figure 9. Survival curve retraction among young children subjects with pneumonia after given therapy salbutamol nebulizer dan oral procaterol.

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