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Original Article

Randomized controlled trial of *Phyllanthus niruri Linn* extract

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ABSTRACT

Background Clinical benefits of antiviral treatment in children experience varicella without complications, remains controversial. *Phyllanthus niruri Linn* extract as a natural medicine is used to increase cellular and humoral immunity.

Objective To determine the efficacy and safety of *Phyllanthus niruri Linn* extract in the treatment of varicella in children compared to placebo.

Methods This was a double-blind randomized controlled trial on children ages 2-14 years who experienced varicella without complications. Subjects were randomly assigned to receive either *Phyllanthus niruri Linn* extract syrup (5 mg/5ml, 3 times daily) or placebo. Efficacy was measured by calculating the number of papules and crusts after taking the extract for 4 days of administration. A five-day monitoring sheet to record daily follow up and adverse effects of the subjects were given to their parents.

Results Efficacy of *Phyllanthus niruri Linn* measurement based on no more new papules occurred at the five-day monitor was detected in 46 subject (51.1%) of the *Phyllantus niruri Linn* group compared to the placebo group (P=0.723). Meanwhile, the difference of efficacy based on time of crusts disappear in *Phyllanthus niruri Linn* and placebo group were 22 subjects (43.1%) and 15 subject (30.0%), respectively (P=0.053). This finding proved have clinical benefit (NNT=7.6).

Conclusion There was no significant difference between the efficacy of *Phyllanthus niruri Linn* and placebo in terms of the prevention appearing new papules and crusts. However, clinically *Phyllanthus niruri Linn* accelerates appearing and aborting crust compared to placebo **[Pediatr Indones 2006;46:77-81].**

Keywords: *varicella, varicella-zoster virus, papule, crust, phyllantus niruri*

Varicella, known as chicken pox, is highly contagious. In the tropics it is reported as a benign disease in childhood yet not in adults. The disease caused by the herpes virus named varicella-zoster virus which also causes herpes zoster (shingles).[1] Hospital data showed that varicella mostly affect 5-13 year old children.[2]

Healthy (immunocompetent) children have received symptomatic treatment only for varicella without complications. In such children, the clinical benefits derived from antiviral treatment remains controversial. Questions have arisen as to the economic advisability of using an antiviral agent to treat a generally benign disease. Other objections are the inconvenience of taking four doses a day and the possibility that resistant strains of the virus will develop.[3,4]

The course of illness of viral disease significantly correlated to immune status. Thus, efforts have been done to increase human immunity by immunostimulant

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agents which work as adjuvant to conventional treatment.[5]

Phyllanthus niruri Linn extract as a natural medicine could be used to increase the non-specific and specific immunity in host. An in-vitro study on mice proved that oral administration of the extract increased the productivity of specific antibodies and in increases either macrophage activity or T-lymphocyte proliferation. A part of this T-lymphocyte will differentiate to T-helper-1 which has an important role in cellular immune response. This extract might also induce TNF-a secretion from activated macrophages.[6]

The extract of *Phyllanthus niruri Linn* is an Indonesian herbal medicine which lacks advanced study to establish its virtue in health services.[7] We studied it in the management of varicella in children.

Methods

This study was double-blind randomized controlled trial conducted at the Outpatient Clinic, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta and from December 1, 2002 to July 31, 2004. Prior to this study, approval was obtained from the Ethical Committee of Medical School, University of Indonesia. The subjects were children who experienced varicella without complications, acquired papules for less than two days, range in aged from 2-14 years, and never received varicella vaccination before being enrolled to this study. Informed consent was obtained from parents. Exclusion criteria were those with immunodeficiency diseases, had taken corticosteroid or immunosuppressant agents, had severe malnutrition, and had taken antiviral medication for the last two weeks.

Subjects who met the inclusion criteria were randomly divided into two groups by simple randomized sampling. The study group received *Phyllanthus niruri Linn* extract syrup and the placebo group received placebo syrup. Both preparations were packed and labeled to appear the same. A commercially available *Phyllanthus niruri Linn* extract (Stimuno®) was used in this study. The dosage for the *Phyllanthus niruri Linn* extract syrup according to pharmaceutical recommendations was 25 mg 3x5 ml for 5 days. Other medications could be given unless indicated in exclusion criteria. At the first visit, physical examination and laboratory tests for renal and liver functions were performed. A diary was given to the parents to record daily symptoms and signs of the disease, side effects, and the other medications which were administered. Subjects were followed-up on the second visit after taking the extract for four days where physical, laboratory examination, and diary collecting was performed. Efficacy of *Phyllanthus niruri Linn* extract was measured by examining papules and crusts. Statistical analysis was performed by chi-square test.

Results

One hundred and one subjects were enrolled. Fifty one patients in the study group were given *Phyllanthus niruri Linn* orally and fifty patients were given placebo. The subject's characteristics are shown on **Table 1**.

Clinical assessment at the first visit was performed by using the scoring system shown on **Table 2**. There was no difference in clinical manifestations between the two groups. At the second visit which was detected by no new papules, appearance of crusts more than 50%, and parts of them almost aborted. Appearance crusts and parts of them aborted did not differ significantly between groups (**Table 3**). These parameters were also monitored by the patient's diary. **Figure 1** shows that the number of patients with crusts in the study group was higher than that of the placebo group, although the difference was not statistically significant (P=0.63).

TABLE 1. SUBJECT'S CHARACTERISTICS

Characteristics	Study group (n=51)	Placebo group (n=50)
Sex		
Male	30	23
Female	21	27
Age (mean±SD; years)	7.0±2.7	7.6±3.1
Body weight (mean±SD; kg)	24.0±7.9	25.7±9.7

During the five-day observation period, no increase in diuresis was found in the subjects. The side effects were monitored by examined the transaminase, ureum, and creatinin serum concentration. Liver and renal function tests were normal.

TABLE 2. CLINICAL MANIFESTATIONS AT THE FIRST VISIT

Signs and symptoms		Group* A (n=51)	Group* B (n=50)
Fever (°C)	< 37.5	14	18
	37.5-38.5	36	31
	> 38.5	1	1
Pruritus	No itch	3	2
	Mildly itchy, not disturbing daily activities	47	48
	Moderately up to severely itchy, disturbing daily activities	1	0
Papul	No new papules	0	1
	Up to 20 new papules	42	43
	More than 20 new papules	9	6
Vesicle	No vesicle observed	2	0
	Up to 20 vesicles	36	39
	More than 20 vesicles	13	11
Crusts	No crust or only a few crust	43	42
	Many crusts	2	4
	Numerous crusts, most may almost disappear	6	4

* A: Study group B: placebo group

TABLE 3. CLINICAL MANIFESTATIONS AT THE SECOND VISIT

Signs and symptoms		Group A (n=51)	Group B (n=50)	P
Fever	Body temperature (<37.5°C)	51	50	
Pruritus	No itch	20	19	0.900
	Mildly itchy, not disturbing daily activities	31	31	
Papule	No new papule	46	44	0.723
	Up to 20 new papules	5	6	
Vesicle	No vesicle	11	4	0.160
	Up to 20 vesicles	32	37	
	More than 20 vesicles	8	9	
Crust	No crust or only a few crusts	8	3	0.053
	Many crusts	21	32	
	Numerous crusts, most may almost disappear	22	15	

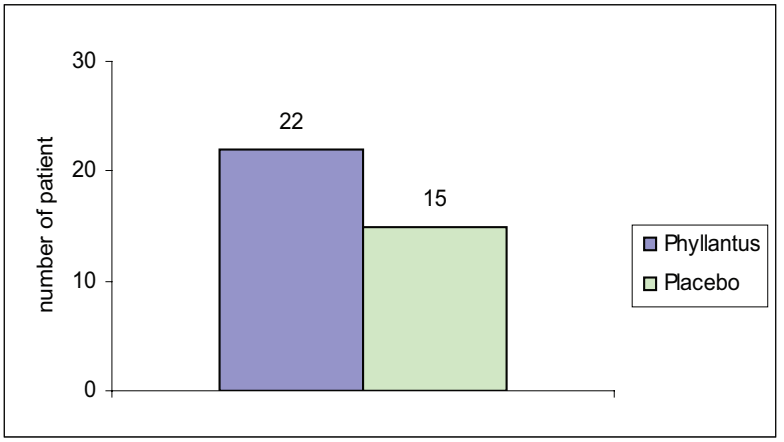

FIGURE 1. DISAPPEARANCE OF CRUSTS IN A FIVE-DAY FOLLOW-UP ON *PHYLLANTUS NIRURI LINN* EXTRACT ADMINISTRATION.

Discussion

According to epidemiological studies on varicella in Indonesia, the highest incidence was children ages 5-9 years.[2] Our study findings were similar to that of other studies mentioned above where the mean age of the study group was 7 years and in the placebo group was 7.6 years. Ooi *et al*[8] found that varicella occurs more prevalent in boys than in girls with ratio of 1.4:1, this is not quite different than that found in our study which had a ratio of 1.1:1.

Clinical manifestations detected at the first visit consisted of mild fever concomitant with skin lesions, such as papules, vesicles, and mild pruritus. During that time, crusts had not appeared yet. The healing process of varicella was marked by normal body temperature, decreasing number of papules, and detection of crusts in most parts of the body; as a sign that the disease was not contagious anymore.[1] It showed that after four days of *Phyllanthus niruri Linn* extract administration, crusts appeared more than 50% and a most were almost aborted in 43.1% and 30.0% of the patients in the study group cmpared to the placebo group, respectively. Data from diary reported that in day-3 of follow-up, subjects in the study group have more crusts compared to that of the placebo group.

As shown in this study, we could not prove whether there was a significant difference between the two groups, although clinical observations showed that *Phyllanthus niruri Linn* extract benefited more progress for crusts and aborting of them. Kurniati[9] reported that subjects who receive *Phyllanthus niruri Linn* extract in combination with acyclovir for herpes zoster without complication obtained better recovery in skin lesions compared to the placebo group which received acyclovir alone.[9] The skin lesion improvement manifested as erythema, edema, and vesicles ($P<0.01$). Subjects in the study group had better clinically progress than that of the placebo group, in proportion of 90.2% and 88%, respectively; although there was no statistically significance.

We observed that the duration of fever in children with varicella appears simultaneously along with skin lesions. This was quite different in adolesence and adults where fever appears withih one to two days before the skin lesions manifest.[10] Furthermore, this study found that fever in both groups disappeared at the second visit at day two of taking *Phyllanthus niruri Linn* extract. However, in both groups subjects still have mild pruritus at the second visit. Contrary to our study, Kurniati[9] reported that *Phyllanthus niruri Linn* extract could reduce clinical symptoms in adult patients with uncomplicated herpes zoster.

The administration of *Phyllanthus niruri Linn* extract in clinical use has been proven to be safe. No subjects complained of increase in diuresis, this data was also supported by other studies.[9,11] Munasir[11] reported *Phyllanthus niruri Linn* extract was used as well in treating children with acute respiratory disease without antipiretic or antibiotic therapy; subjects had no complaints during follow-ups after administration. Kurniati[9] found 60 herpes zoster subjects with mild diuresis which occured in 21.4% of the study group compared to 27.6% in the placebo group. Meanwhile, there were no other side effects, such as disturbance of liver and kidney functions observed. Therefore, *Phyllanthus niruri Linn* extract is safe enough to be consumed by children with varicella. We suggest that *Phyllantus niruri Linn* extract can be given during early stages of the illness to children with varicella to enhance recovery of and shorten the course of illness.

In conclusion, there was no significant difference between the efficacy of *Phyllanthus niruri Linn* and placebo in terms of the prevention appearing new papules and crusts. However, *Phyllanthus niruri Linn* accelerates the appearance and abortions of crust compaired to placebo.

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