Research Title: Vitamin D Supplementation Effect In Children With Pulmonary Tuberculosis Treatment: Randomized Double Blind Controlled Trial

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Summary of Clinical Trial Protocol

Study Description:
This randomized, double-blind control trial with a cohort design was conducted in Bethesda Hospital West Borneo from December 2020 - May 2021. The inclusion criteria were children between 6 to 18 years old, newly diagnosed with pulmonary tuberculosis with vitamin D insufficiency. Diagnosis of the tuberculosis case was based on The Indonesian Pediatric Tuberculosis Scoring System. It consists of history taking and laboratory findings that support tuberculosis common symptoms such as household contact, prolonged fever more than two weeks, non-remitting cough more than three weeks, and decrease body weight, and lymph node enlargement; laboratory findings include Tuberculin Skin Test (TST) and chest X-ray (CXR). Scoring ranges from 0 to 3 for each variable with a total score of more than six is considered as tuberculosis diagnosis. Patients also collect the sputum for gram staining and Xpert MTB/RIF examination. The isolation of Mycobacterium tuberculosis was not done in this study because of limited resources.

Subject selection was determined based on consecutive sampling, namely the order of patients who came to the clinic until the minimum sample size (84 subjects) met the inclusion criteria. The exclusion criteria are children with a history of liver or kidney abnormalities, immunocompromised, and already received vitamin D supplementation. After obtaining written consent, all subjects had their blood specimens drawn 3cc from the brachial vein to measure alanine transaminase (ALT), alkaline phosphatase (ALP), serum active 25-hydroxyvitamin D using the ELISA method. Vitamin D is categorized as deficiency if serum 25-hydroxyvitamin D is below 20ng/mL, insufficiency between 20–30ng/mL, and normal levels above 30ng/mL. In this study, the 95% confidence level ($Z\alpha = 1.65$ one-sided test) and 80% power test ($Z\beta = 0.84$) were selected. The calculation of the sample size above obtained n = 35 people for each group. The total study subjects were added by 20% of the minimum number of samples to compensate for loss-to-follow-up, so the total sample was 84, consisting of 42 patients in the intervention group and 42 patients in the placebo group.

For each subject, the following data were entered into the study database demographic data (name, age, sex), signs and symptoms (fever, cough), Tuberculin Skin Test (TST), Chest X-Ray, and also GeneXpert for Mycobacterium tuberculosis from gastric lavage or sputum induction, liver function test and 25-hydroxyvitamin D level. All results were recorded in a study database following international standards to protect the privacy and personal information.

Subjects were randomly assigned to receive either a 1000IU vitamin D supplement dose or a placebo with an allocation ratio of one to one. Before starting recruitment, the project manager prepared 84 packs of study preparation - 42 packs of the active study drug and 42 packs of a placebo, then generated a randomization sequence using a computer program assigning the terms active or placebo to numbers 1 to 84. The packs were then assigned a randomized number according to this computer-generated randomization sequence.

At recruitment, study staff enrolled patients consecutively according to the order of arrival of patients from number 1 to 84. Study staff who assigned patients to active drugs or placebo did not know the following assignment in the sequence because they did not have access to the study code. Treatment allocations were hidden from patients and research staff. Those who analyzed the data were not covered for group assignments. Monitoring of subjects medication adherence and daily symptoms conducted by using a checklist table filled out by the patient's parents and confirmed check by the researcher during the patient follow-up schedule to the clinic.

All subjects received antimicrobial treatment for tuberculosis drugs in the form of a fixed-dose combination. Patients were reviewed on 14, 28, 42, and 56 days after starting antimicrobial treatment; body weight and height were measured at each time point. After the intensive phase of antimicrobial treatment, patients were monitored monthly. A repeated vitamin D level by ELISA and liver function test were done six months after starting the antimicrobial treatment.

Clinical Trial Process
a) Administration of intervention (dose regimen, invasive and non-invasive measures, comparison drugs, placebo): Pediatric patients diagnosed with TB and vitamin D insufficiency will be given vitamin D supplementation of 1000IU/day for six months. Giving a placebo in the control group will get one dose of placebo/day for six months. Vitamin D and placebo preparations are prepared in the same colored bottles containing vitamin D or a placebo.

b) Determination of outcome indicators:
After six months of treatment, the patient will have his vitamin D level checked.

c) Interim analysis plan: sputum examination is performed every two weeks during the intensive phase of antituberculosis treatment.

d) Clinical trial termination procedure:
Parents of patients who refuse to be included in this study can stop the administration of vitamin D supplementation by reporting to the doctor in charge of the service during control at the pediatric outpatient clinic at Bethesda Hospital, West Kalimantan. Patients who do not complete treatment for six months (including unexpected events) will be discontinued from participating in the study and explained to parents that TB treatment is continued but not included in the study, and the test drug package will not be continued.

e) Estimated research time required for one subject per one course of action: 5 minutes per action of blood and phlegm examination.

f) Ethical issues (state your opinion on ethical issues in research that may be encountered):
• Respect for someone (respect for human dignity):
Researchers provide information to parents of research to be carried out, including procedures, benefits, risks, volunteering, and data confidentiality. Information is provided so that the subject's parents can determine whether their child can participate in the study or not. Parents are free to make their own decisions. Subjects' parents who voluntarily participated in this study were then asked to express written consent by signing informed consent.

• Beneficence (beneficial) non-maleficence (not harmful):
There is no physical risk to the child who is the subject of the study, but it can cause it to occur. The benefits of this research are not felt directly by the child/parent. However, the willingness to be a subject will be significant to obtain information on routine vitamin D levels in children with tuberculosis. It can be used as input and the essential information to provide vitamin D supplementation in children with tuberculosis. Suppose the examination results reveal a vitamin D deficiency. In that case, the child will receive vitamin D supplementation at no charge to the parents.

• Justice (fairness):
All subjects are treated equally in the study and are given the same opportunity to be included, which is carried out in a fair and balanced manner.

Adverse Event (AE) reporting plan
a. Recording (Things to be reported): symptoms of side effects of antituberculosis treatment such as jaundice, nausea, and vomiting.
b. Analysis and procedure of action: the patient will be examined for liver function. If the liver function increases, antituberculosis drugs will be discontinued.
c. Emergency rescue system: patients who feel there are complaints of nausea, vomiting, and jaundice will go to the Children's Clinic, Bethesda Hospital, West Kalimantan.
d. Discontinuation of subjects in the study due to adverse events: the administration of antituberculosis drugs will be discontinued, and patients will not be included in the study.

INFORMATION (Translated from Bahasa Indonesia)

VITAMIN D SUPPLEMENTATION EFFECT IN CHILDREN WITH PULMONARY TUBERCULOSIS TREATMENT: RANDOMIZED DOUBLE BLIND CONTROLLED TRIAL

I am a pediatrician from Bethesda Hospital, West Kalimantan, who is conducting a study to assess the administration of vitamin D3 supplementation in pediatric tuberculosis patients; I invite you to participate in this study, your participation in this study is voluntary, so you can decide to participate or vice versa.

Research purposes:
Vitamin D is a vital substance needed by a child's body. Vitamin D deficiency in your child can lead to impaired optimal growth and development. This study aims to assess the administration of vitamin D3 supplementation in pediatric TB patients receiving TB treatment.
Why Subject was selected:
Your child was selected to be included in this study because your child is a tuberculosis patient and is receiving treatment at the Children's Polyclinic, Bethesda Hospital, West Borneo.

Procedures/Procedures:
Suppose you agree that your child is included in this study. In that case, your child will have 2 mL of blood taken at the Bethesda Hospital West Kalimantan laboratory to check vitamin D levels. If the vitamin D level is between 21-29 ng/mL, it will be included in the study. Your child will receive medicine in the form of vitamin D or sugar-coated drugs according to the serial number listed. Vitamin D drug in the form of syrup, taken in the morning as much as 2.5 mL once a day. Sputum collection was carried out every two weeks for the first two months of treatment. After your child has undergone six months of tuberculosis treatment, a re-examination of the vitamin D level will be evaluated by taking 2 mL of blood.

Risks and inconveniences:
The risk in this study was only found when your child was taken for blood, namely pain at the blood collection location. Other risks associated with this study were not found in the literature.

Benefits (direct to the subject and general):
The benefit of this research for your child is to determine the level of vitamin D in your child and get vitamin D supplementation. Giving vitamin D supplementation for six months does not have any side effects for your child. Suppose your child's vitamin D level is still low after six months of treatment. In that case, vitamin D supplementation will be given until the vitamin D level is >30 ng/mL.

Data confidentiality:
As long as your child participates in this research, any information and data will be treated confidentially. It is not possible for others to know.

Estimated number of subjects to be included:
The number of children who will be included in this study is 84 children.

Volunteering:
Your child's participation in this research is voluntary with responsibility until the completion of this research.

Subject Participation Period:
Your child's participation in this study is for six months.

Subjects may be excluded/resigned from the study:
You are free to refuse to participate in this research. If you have decided to include your child, you can also resign without causing a change in the quality of doctor's services if you are sick. However, suppose your child does not follow and fulfill the procedures given by the researcher. In that case, your baby's participation in this study will end.

Possible financing from health insurance companies or researchers:
The researcher will bear all costs of this research.

Incentives and compensation:
For your child's participation in this study, incentives will be given in the form of souvenirs as a token of gratitude, and no compensation in any form will be given.

Question:
If there are any questions related to this research to dr. Lianda Tamara, Sp.A at Bethesda Hospital, West Borneo, Mobile Phone. 081223811821

Informed Consent for Parents/Guardian

INFORMED CONSENT
TO PARTICIPATE IN RESEARCH
WITH CHILD SUBJECT
(Translated from Bahasa Indonesia)

I have read or obtained an explanation, am fully aware, understand, and understand the objectives, benefits, and risks that may arise in the research, and have been given the opportunity to ask questions and have been answered satisfactorily, and may withdraw my child/sister at any time. from their participation, then I agree/disagree*) participate in this research, entitled:

"Vitamin D Supplementation Effect In Children With Pulmonary Tuberculosis Treatment: Randomized Double Blind Controlled Trial"

I voluntarily choose my child/sister to participate in this research without any pressure/coercion from anyone. I will be given a copy of the explanation sheet and consent form that I have signed for my file.
I agree:
Yes/No*)

	Date:	Signature or Fingerprints
Child name: Age: Address:		
Parents/Guardian name:		
Principal Investigator:		
Witnesses name:		

*) select the appropriate

Informed Consent for Child
12> – < 18 years old

APPROVAL AFTER EXPLANATION (PSP)
TO PARTICIPATE IN RESEARCH
WITH CHILD SUBJECT
(*ASSENT*)
(Translated from Bahasa Indonesia)

I have read or obtained an explanation, am fully aware, understand, and understand the objectives, benefits and risks that may arise in the research, and have been given the opportunity to ask questions and have been answered satisfactorily, and may at any time withdraw from my participation. I agree/disagree*) participate in this research, entitled:

"Vitamin D Supplementation Effect In Children With Pulmonary Tuberculosis Treatment: Randomized Double Blind Controlled Trial"

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I agree:
Yes No*)

	Date:	Signature or Fingerprints
Child name: Age: Address:		
Parents/Guardian name:		
Principal Investigator:		
Witnesses name:		

*) select the appropriate