CSCanada
Advances in Natural Science
Vol. 5, No. 2, 2012, pp. 76-80
DOI:10.3968/j.ans.1715787020120502.1846

ISSN 1715-7862 [PRINT]
ISSN 1715-7870 [ONLINE]
www.cscanada.net
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Comparative Double Blind Clinical Trial Study of Side Effects of *Areca catechu* L., TTHF, and Mebendazole, in Treatment of Human Mixed Worm Infection

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Supported by Division of Research Dissemination and Facilitation, Mahasarakham University, Thailand.

Received 11 March 2012; accepted 26 June 2012

Abstract

This study was carried out in Mahasarakham Primary Healthcare Centre, Mahasarakham province in the area of Northeastern of Thailand. The experiment was carried on with 200 samples with randomized control trial clinical study in order to examine the side effects of ***Areca catechu* Linn.**, TTHF and Mebendazole after the treatment of antihelmintic activity of mixed worms infection in human. The 3 experimental groups consisted of 50 patients in each group and 50 patients for control group testing with placebo with inclusion and exclusion criteria which were screened by parasitologist of mixed worm infection symptoms samples. The investigation of side effects were investigated after treating the first dose of ***Areca catechu* Linn**, **TTHF** and **Mebendazole** which were confirmed by the physician and the pharmacist. The side effects data were collected before and after the treatment with ***Areca catechu* Linn**. and with **placebo**. The result showed that Areca catechu Linn. had 20% of diarrhea and 20% of nausea, 20% of diarrhea in **Mebendazole** and 0% in ***TTHF***.

The suggestion of this study should increase the number of samples of worm infected patients and also the numbers of locations in Thailand in order to obtain various kinds of helminthes.

Key words: TTHF (Thai Traditional Herbal Formula); Mebendazole; *Areca catechu* Linn.; Side effects; Antihelmintic activity

Buavaroon Srichaikul, Weerasak Seubsoh, Supachai Samappito, Gordon Bakker (2012). Comparative Double Blind Clinical Trial Study of Side Effects of *Areca catechu* L., TTHF, and Mebendazole, in Treatment of Human Mixed Worm Infection. *Advances in Natural Science*, *5*(2), 76-80. Available from URL: http://www.cscanada.net/index.php/ans/article/view/j.ans.1715787020120502.1846 DOI: http://dx.doi.org/10.3968/j.ans.1715787020120502.1846

INTRODUCTION

In tropical countries such as Thailand we have a high incidence rate of human parasitic infection which can be very harmful to humans. The initial stage of parasitic infection such as Nematode, tapeworm, hook worm do not have sudden severe harmful effects to the human body. The symptoms will develop gradually and slowly which can destroy the internal organs. Some parasites can withdraw blood from human intestines or other internal cell wall organs and also nutrients from human bodies. The patients will slowly lose their weight and turn pale. The patients will also possess a lack of cognitive thinking and less intellect.

Over 32 countries face the problems of clean food consumption and clean drinking tap water management supplied to the main population. There are over 12 million people who suffer from helminthes infection.

WHO (World Health Organization) has considered the parasitic problem as one of the major health communicable disease issues in the world. In Thailand the Ministry of Health has launched the project in order to decrease the incidence of food borne diseases especially parasitic diseases which occurred in people who have less exposed to sanitation of food and water intake. Normally these patients will contact the parasites through food intake, water intake and skin transmission. One cause is the style of Thai Northeastern food preparation which is involved undercooked foods. The villagers like to consume raw food from fish, pork, beef which promote

worm diseases. Another reason is the polluted local drinking water that the people consume on a daily basis from the river which was not clean and was contaminated with bacteria, worms and viruses. WHO is responsible for the record of 133 million of infected worm diseases patients throughout the world. The indication showed that the numbers of infected patients were under the age below 5 years mostly. Since 2006-2011 the incident rate of parasitic human diseases was decreased gradually from 1,051,447 to 800,000 patients.

The worms which were discovered in Thailand were multi cellular and one structure. Helminthes live in human body and also in animal body. They work as possible parasitic condition consuming the nutrients and blood from the body. There are many species of parasites which live in soil, weed, water in the fresh of terrestrial, in aquatic and in amphibians etc. Helminthes can transmit through oral skin absorption and even through placenta movement from mother to baby. Helminthes are tapeworm, Strongyloides, liver flukes, lung flukes and some may be travel through skin such as Trichunoris.

The patients who was infected may show the symptoms as more food intakes, weight loss, diarrhea, irritable colon, Bloating, body pain, blurred vision. The patients should go to see the physician in order to have stool examination test for Worm Eggs per Gram of fecae by any method such as Kato Katz method or Ether-Formalin sedimentation test method. Some patients have shown the severe symptoms which cause paralysis or death. Types, size, volumes and location of helminthes and also the duration of infection are important for indicating the severity of infection. Some patients exhibit signs of Jaundice, Liver Cirrhosis and result in liver carcinoma.

The side effect of antihelminthic medicines may cause stomachache, diarrhea, and irritable colon. Some also cause nausea, vomitting. The research team had introduced **Thai Traditional Herbal Formula medicine (TTHF)** in the treatment of helminthes and compared the efficacy and side effects among **Mebendazole (500 mg**) and ***Areca catechu Linn***.

Thai Traditional Herbal Formula medicine consists of 7 herbals which are ***Terminalia chebula*** (Retz) (SamaoThai), ***Terminalia Citrina*** (Roxb.) (Samao Ted) (Arjun), ***Curcuma zedoaria*** (Berg) Rosco. (Kamin Aoi), ***Terminalia Citriva*** (Gaertn). ***Roxb. Flem*** (Samao Ngu), ***Cuttle Bone*** (Tricosan) (Lintalay), ***purified water,*** Croton tiglium Lin. (Purging croton), Diospyros mollis (Griff.) (Ebony tree). Dosage of TTHF is orally, 3-6 capsules daily before breakfast (500 mg), continue for 3 days. Each of 7 medicinal herbs and purified water is mixed as dry powder in equal portions and was filled into capsules.

Mebendazole 500 mg is the drug of choice in treatment of helminthes infection in this research and considered as modern medicine. Dosage form is chewable tablet, 500 mg, and taken as once daily for 3 days continuously.

***Areca catechu* Linn.** was prepared for herbal medicine in the treatment of mixed antihelminthes infection. Dosage was 60-90 mg in dried powder capsules and taken by mixing with syrup water as once daily for 3 days continuously. All medicine were tested to meet the standardization quality with free from bacterial or foreign contamination, free from steroidal substance and free from pesticide from the Department of Oriental Medicine, Rungsit University, Thailand.

MATERIAL AND METHOD

This research was proceeded during September, 2011 at Primary Health Care Center Mahasarakham Hospital, Mahasarakham, Thailand. The 200 samples were screened purposively relevance to the inclusion and exclusion criteria of 16-65 years old with both genders males and females(not pregnant), non-medicated with any of antihelminthic drugs, non-medicated with any of antibiotic, phenytoin, carbamazepine, no complication of gastrointestinal symptoms, no hepatitis or liver diseases. The collected samples were divided for 50 patients in each group for 4 groups as follows: Placebo control group, treated with Mebendazole experimental group, treated with Thai Traditional Herbal Formula (TTHF) experimental group and treated with Areca catechu Lin. experimental group.

The screening method used in this experiment was Ether Formalin Stool Sedimentation Examination which could be used to identify and quantify the EPG (numbers of eggs per gram of feces of infected patient). The study was randomized control trial in the comparative study of the efficacy and side effects. The efficacy and side effects were compared with the % reduction of EPG in each group with treated with Mebendazole, Areca catechu and TTHF medicine.

Preparation of Thai Traditional Herbal Formula (TTHF)

TTHF was prepared from 7 herbs as listed from the above. Firstly we extracted Terminalia chebula (Retz) by boiling the immature fruits of Terminalia chebula (Retz) with portable water and dried it with the Spraying Technique in order to obtain dry powder. Then we repeated the same process of extraction with Terminalia citrina and Terminalia citriva to obtain the purified dry powder of them. Then we took the underground stem of Curcuma zedroaria and grated it. The grated Curcuma zedroaria was blended in very fine powder. The cuttle bone was triturated as fine powder. We also took the seed of Croton triglium and was triturated as fine powder. We took the fresh fruits of Diospyros mollis and sliced them to very thin pieces and triturated as the fine powder, then mixed it with coconut milk and dried with Spray Drying Technique. Each of them was weighed equally and mixed together with the amount of 72 mg in each prepared

dried herbal powder and were filled in 500 mg aseptic capsules by using encapsulation method. All herbs were collected with uncontaminated of bacteria, heavy metals, viruses, and free of pesticides with adequate cleansing methods. They were passed through Gamma-rays for aseptic purposes. The process for preparation and purified of all sample capsules were also tested for quality control at the Faculty of Oriental Medicine, Rungsit University, Thailand to assure quality, safety in production. Therefore the products were free from any toxicity. TTHF (500 mg) contained 7 plant species as mentioned above used for antihelmintic formulae in this experiment.

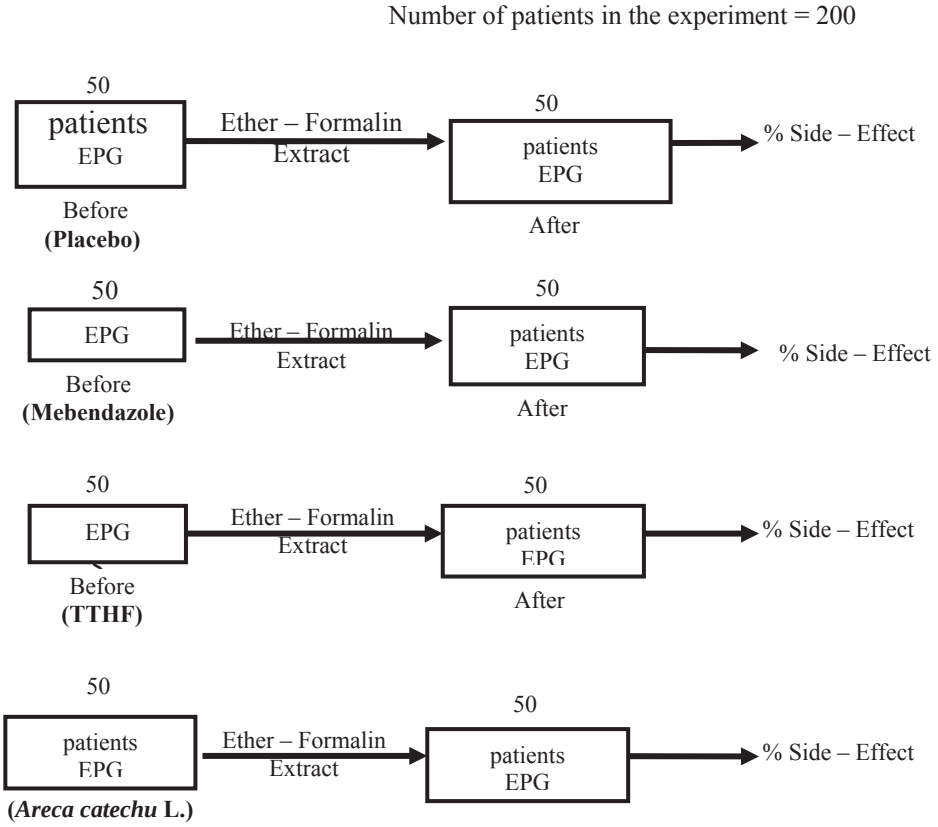
Areca catechu Linn.

Preparations

In this experiment we used ***Areca catechu* Linn**. (**Betel Nut**) seeds in order to prepare antihelminthic medicines. We have chosen the brownish white color derived from thin sliced pieces of the nuts which have a high qualitative content of Arecoline as one of the active ingredients in antihelmintic action of Areca catechu Linn. The betel nut seeds were weighed between 60-90mg, and then triturated as a very fine powder. The powder was mixed with the syrup water for oral administration. The dosage suggested was taken in syrup once daily for 3 days before breakfast.

Mebendazole 500 mg is the drug of choice in treatment of helminthes infection in this research and considered as modern medicine. Dosage form is chewable tablet, 500 mg, and taken as once daily for 3 days continuously.

Conceptual Research Framework



RESULT

The result of the experiment after treating 200 patients with Placebo, Mebendazole, *Areca catechu* L. and TTHF showed that the side-effects of Mebendazole had 20% of diarrhea while *Areca catechu* L. had 20% of diarrhea and 20 % of Stomach discomfort and nausea. These were not found any side-effect in treatment with TTHF.

CONCLUSION AND SUGGESTIONS

This study was carried out 3 days dosages and the % EPG Reduction was collected after the 4th day of the experiments in each group of samples. There may be some variations in the results after the first dosage given of each vermicidal medicine. Because some patients may have parasites presented in different locations of

the human bodies such as blood stream, lung, liver, etc. Therefore the efficacy would be different in different species of helminthes. The extensive study should be recommended in various dosages and repeated dosages of 7 days, 14 days and 20 days should be measured the end result of % side effects .The result would be more reliable which was suggested to increase the size of samples and other forms of dosage preparation. The suggestion also aimed to investigate future research of more other types of helminthes for comparative efficacy study and also the side effects. In this study the side effects showed rather high in the percentage of diarrhea and nausea in *Areca catechu* and much higher than Mebendazole and Thai Traditional Herbal Formulae

ACKNOWLEDGEMENT

This research study was supported for funding by Division of Research Dissemination and Facilitation, Mahasarakham University, Thailand. The research team would like to express our special thank to Assist. Prof. Dr. Supachai Samappito, Prof. Dr.Preecha Prathepa, Sunthorn Dejchai and also to Assoc. Prof. Dr. Surapote Wongyai in preparation of Thai Traditional Herbal Formula, Faculty of Oriental Medicine, Rungsit University., Thailand.

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TABLES

Table 1
Comparative in % Side Effects Among Mebendazole, Tthf and *Areca Catechu*
(Analyse with Wilcoxon Signed Ranks Test)

Name of	Numbers of patients	Mean	Z	-value
Before	50	463.40	-2.023	.031
After	50	65.80		

Table 2
Numbers of Eggs Per Grams of Feces Before and After Treated with Thai Traditional Formulae
(Analyse with Wilcoxon Signed Ranks Test)

TTHF	Number of patients	Mean	Z	p-value
Before	50	383.00	-2.023	.031
After	50	25.00		

Table 3
Numbers of Eggs Worm Before and After Treated with *Areca Catechu*
(Analyse with Wilcoxon Signed Ranks Test)

Areca catechu	Numbers of Patients	Mean	Z	p-value
Before	50	427.20	-2.023	.031
After	50	136.80		

Table 4
Anti Helmintic efficacy Among Mebendazole, TTHF and Areca Catechu
(Analyse with Wilcoxon Signed Ranks Test)

Drug Name	% Efficacy
Mebendazole	87.50
TTHF	93.69
Areca catechu	68.12

Table 5
Comparison in Efficacy Among Mebendazole, TTHF, *Areca catechu*
(Analyse with Kruskal-Wallis Test)

	Num. of patients	Mean Rank	X^2	p-value	95% CI
Mebendazole	50	8	12.50	.000	.000
TTHF	50	13			-0.181
Areca catechu	50	3			

FIGURES

Figure 1
Terminalia chebula (Retz) (SamaoThai)
URL http://www.mpbd.info/plants/terminalia-chebula.php

Figure 2
Curcuma zedoaria (Berg) Rosco. (Kamin Aoi)
URL http://blog.naver.com

Figure 3
Croton tiglium Lin. (Purging croton)
URL http://www.payer.de/amarakosa/amara206.htm

Figure 4
Diospyros mollis (Griff.) (Ebony tree)
URL http://www.biogang.net/biodiversity_view.php?menu=biodiversity&uid=898&id=3524

Figure 5
Mebendazole
URL http://www.stanford.edu/class/humbio103/ParaSites2006/Enterobius/