PIDSP Journal, 2003 Vol. 7 No. 1

A COMPARATIVE STUDY BETWEEN DAILY SELF-ADMINISTERED AND THRICE WEEKLY DIRECTLY OBSERVED TREATMENT SHORT COURSE (DOTS) REGIMENS FOR THE TREATMENT OF PRIMARY TUBERCULOSIS IN CHILDREN IN SITIO PUTING BATO, NAVOTAS

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ABSTRACT

***Study Objective*: To compare the efficacy and compliance of therapy for tuberculosis in children using daily self-administered treatment (SAT) versus intermittent thrice weekly dosing through the application of Directly Observed Treatment Short Course (DOTS).**

***Design*: Randomized Controlled Pilot Study**

***Setting*: Sitio Puting Bato, Navotas**

***Patients*: Forty-three subjects with newly confirmed primary tuberculosis were randomized into two groups: 22 patients received daily self-administered treatment (SAT) and 21 patients received intermittent treatment (DOTS). Both groups regimens received triple anti-tuberculosis medications consisting of Isoniazid, Rifampicin and Pyrazinamide for the first 2 months and Isoniazid and Rifampicin for the succeeding 4 months. Daily treatment consisted of Isoniazid 5-10 mg/kg/dose; Rifampicin 10-15 mg/kg/dose; and Pyrazinamide 15-25 mg/kg/day. Intermittent treatment (thrice weekly for 6 months) consisted of Isoniazid 20-40 mg/kg/dose; Rifampicin 10-20 mg/kg/dose; and Pyrazinamide 50-70 mg/kg/day.**

***Main Outcome Measures:* Efficacy, compliance and side effects of treatments**

***Results*: At 6 months, the number of children compliant to the treatment was 100% in the daily and 95% in the DOTS group with an average intake of 98% of the prescribed doses taken in the daily versus 96% in the DOTS group. There were no significant differences in weight gain after 6 months (p0.564) and appetite (p0.628). No significant side effects were observed.**

***Conclusion*: We have demonstrated that Directly Observed Treatment Short Course (DOTS) strategy has no statistical significant difference versus the Self Administered Treatment (SAT) regimen with regard to efficacy (improvement of clinical signs and symptoms, and weight gain) and compliance during the 6 months of treatment.**

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3rd Prize PIDSP Research Awards 2003

INTRODUCTION

Tuberculosis is the number one single infectious killer, taking nearly 3 million lives per year. In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a "global emergency". Based on these facts, one person is newly infected with tuberculosis every second. Between 1993-1996, a 13% increase in cases was reported and one-third to one-half of the world's population is infected with TB and 5-10% of these people will develop the disease[1].

In the Philippines, at least 75 Filipinos die everyday from TB. One-third to one-half of the population has TB infection[2]. 200,000-600,000 Filipinos have TB infection and one untreated case of infected TB can infect 15-20 others in one year. Tuberculosis was the second leading cause of death in all DOH retained hospitals[3]. There are about 100,000 children worldwide who may needlessly die from tuberculosis[4].

Diagnosis of TB is difficult in children because physicians tend to confuse TB infection which is asymptomatic, with TB disease which has clinical and/or radiographic signs. What is unique about pediatric TB, especially in the first 5 years of life is that it may develops as an immediate complication of infection[5]. The risk of developing TB disease is 5-15 percent during the first 10 years with 25% risk in children 1 to 5 years of age and 15 percent risk in adolescence[2].

Where tuberculosis is prevalent, detection and treatment of sources, remains the most important preventive measure in the tuberculosis control program. Treatment of adult TB patients have been conscientiously handled by the Department of Health (DOH) through Directly Observed Therapy Short Course (DOTS). But how do we address primary tuberculosis in children in our present setting?

The WHO-recommended strategy for TB control is known as Directly Observed Therapy Short Course (DOTS). DOT is a strategy in which a health worker observes the patient swallow all doses of anti-tuberculosis medications. This strategy allows for standardized, accurate diagnosis and effective treatment for the adult population. However, DOTS

policies for diagnosis and treatment are easily adaptable to a pediatric population. At least 8 studies have shown that short course therapy were also efficacious in children and may provide better compliance[5]. The first local attempt to implement DOTS among children was done in University of Santo Tomas[6]. By improving patient compliance to the full course of therapy, DOTS has been shown to improve cure rates, thereby reducing the development of multi-drug resistant TB.

The aim of chemotherapy is to provide the most effective therapy to prevent treatment failure, drug resistance and relapse. In foreign studies comparing intermittent versus daily treatment during the completion phase, no difference was found. These showed success rates of DOTS regimen for 6 months to be equivalent to those of daily regimen[5]. In another study by Davidson, patients receiving DOTS were more likely to complete treatment earlier that those receiving self-administered treatment (SAT). Even with DOTS, only 52 percent had completed treatment by 8 months[7]. Review of available literature did not reveal any published local prospective controlled trials of patients followed concurrently to support this program.

Encouraging as these projects may be, more efforts of adapting DOTS in the private health sector are needed. The private sector itself can contribute and this would be of great service to the country by easing the burden of the government TB control efforts. Faced with such concern, it is the aim of this study to compare the efficacy and compliance with therapy for tuberculosis in children using daily self administered versus the WHO-recommended DOTS.

GENERAL OBJECTIVE

To compare the efficacy and compliance of therapy for tuberculosis in children using daily self-administered treatment (SAT) versus intermittent thrice weekly dosing through the application of Directly Observed Treatment Short-course (DOTS) in Sitio Puting Bato, Navotas.

SPECIFIC OBJECTIVES

- To compare treatment regimens with intermittent thrice weekly DOTS therapy versus daily self-administered treatment for the management of tuberculosis among pediatric Filipino TB patients in a community setting using the following parameters.
  - Compliance to treatment
  - Clinical response to treatment (seen as improvement of clinical signs and symptoms and weight gain)
- To describe adverse reactions observed or reported for each regimens.
- To identify specific problems and reasons for poor or non-compliance.

METHODOLOGY

INCLUSION CRITERIA

Patients ages 1-9 years old residing in Sitio Puting Bato who sought consultation at the health clinic with clinical symptoms of primary tuberculosis such as the following: failure to thrive of loss of weight; a febrile and/or respiratory illness for > 2 weeks or with failure to respond to antibiotics within 2 weeks; and with exposure to persons with active tuberculosis.

EXCLUSION CRITERIA

- Patients with previous diagnoses of tuberculosis and partial or complete anti-tuberculosis treatment.
- Patients with clinical and physical findings of extra-pulmonary tuberculosis: sinus in the neck; large painless lymph nodes in the neck, axilla or groin; angle deformity of the spine; joint or bone swelling or sinuses; and unexplained abdominal mass or ascites.
- Lack of consent for participation in the study from the child's parents or guardian

STUDY DESIGN

The study was a randomized controlled clinical pilot trial in Sitio Puting Bato, Navotas. The World Health Organization (WHO) criteria was used for the diagnosis of primary tuberculosis which included satisfying at least 3 out of the following:

1. Exposure to persons with active pulmonary tuberculosis
2. A positive Mantoux test
3. Manifests signs and symptoms of TB
   - Cough/wheezing >2 weeks, fever >2 weeks
   - Painless cervical lymphadenopathies
   - Failure to make a quick return to normal health after an infection
   - Failure to respond to appropriate antibiotic therapy
4. Abnormal chest radiograph suggestive of TB
5. Laboratory findings suggestive of TB (histologic,

cytologic, and biochemical).

All children who satisfied the inclusion criteria underwent Mantoux test (PPD) and those who satisfied at least 2 of the first 3 WHO criteria underwent chest x-ray (antero-posterior or postero-anterior and lateral). The fifth criterion was not included as part of the diagnosis. Aside from being technically difficult since the child did not expectorate much, availability of resources limited us from using this 5th criterion.

The standard 5 Tuberculin Unit (TU) was used for purified protein derivative (PPD) as recommended. Administration of a 0.1 ml of tuberculin solution was given intradermally using a gauge 27 needle on the volar aspect of the forearm. The test was done and interpreted using a single caliper by a single designated pediatric resident. The induration was measured transversely to the long axis of the forearm and read within 48-72 hours after administration. A Mantoux test was considered positive if the induration is 8 mm and above.

Chest x-ray with both anteroposterior or posteroanterior and lateral views prior to treatment were done and read by a single radiologist.

Since the rate of adverse reactions to anti-TB drugs among children are low enough, biochemical monitoring usually is not necessary[8,9]. However, monthly assessment for clinical symptoms is warranted[5].

TREATMENT REGIMENS

Patients who satisfied at least 3 of the 4 criteria were randomized using block randomization to one of the 2 groups by a single designated health worker. A written and informed consent was obtained. Group A underwent daily triple anti-tuberculosis medications (Isoniazid, Rifampicin and Pyrazinamide) for the first two months and double anti-tuberculosis (Isoniazid and Rifampicin) for the succeeding four months. Dosages were as follows: Isoniazid (H) at 5-10 mg/kg/day as recommended by the WHO. Medications were given pre-breakfast or 2 hours after meal and were provided every week by an assigned responsible guardian/parent to be given daily.

Group B underwent thrice weekly regimen of triple anti-tuberculosis for the first two months and double anti-tuberculosis for the next 4 months. Dosages were as follows: Isoniazid at 20-40 mg/kg/day. Rifampicin at 10-20 mg/kg/day and Pyrazinamide at 50-70 mg/kg/day as recommended by the WHO. There were administered by the designated health worker in the community and were duly recorded.

MONITORING COMPLIANCE

Compliance to medication intake was defined as receiving 75 percent or more of the prescribed doses as suggested by Chaulet that taking 75 percent or more of an efficacious short course regimen will give a satisfactory outcome in the management of pulmonary tuberculosis[10].

For Group A, the responsible adult in a household with children receiving treatment was required to accomplish a medication sheet sequentially dated and numbered block for each dose (see Appendix 2)

EVALUATION OF RESPONSE TO THERAPY

A detailed clinical assessment of each child was performed which included socio-demographic details, duration of illness, signs and symptoms; a full clinical evaluation including height/length; tuberculin skin testing; and chest radiography.

In both groups, follow-up after initiation of treatment was done monthly by a single designated pediatric resident blinded to the regimen. Children were evaluated based on improvement of clinical signs and symptoms and weight gain recorded on a separate evaluation form based on the study by Mata et al15. Patients were weighed monthly and medications were adjusted accordingly. Appearance of adverse reactions to medications was also recorded.

Data was analyzed using the t-test, p value, chi-square tests, Fischer's Exact Test

RESULTS

There were a total of 90 patients who came for screening form August to November 2001. Of these subjects, 51 (57%) were eligible to enter the study. Of these, 43 patients (84%) followed-up and consented and were randomly assigned to either group A or group B. Table 1 provides the clinical and demographic information on these patients showing no significant differences between the two groups with regards sex, nutritional status and BCG status.

The most common symptoms observed were poor weight gain (100%) followed by painless cervical lymphadenopathies (91%), poor appetite (84%), and cough (77%). There was no significant difference in the PPD reading between the 2 groups (p 0.882).

Nine patients in the daily and eight patients in the

Table 1. Demographic features of children receiving DOTS or Daily Anti-tuberculosis treatment.

VARIABLE	TREATMENT		
	DAILY N=22(%)	DOTS N=21(%)	pVALUE
Sex			0.547
Male	14 (64)	11 (52)	
Female	8 (36)	10 (48)	
Age			0.717
1-3 y/o	8 (36)	9 (43)	
4-6 y/o	11 (50)	6 (28.5)	
7-9 y/o	3 (14)	6 (28.5)	
Ht for Age (Stunting)			0.402
Normal	7 (32)	5 (24)	
Mild	7 (32)	9 (43)	
Moderate	8 (36)	6 (28)	
Severe	0	1 (5)	
Wt for Ht (Wasting)			0.683
Normal	13 (59)	5 (24)	
Mild	7 (32)	9 (43)	
Moderate	1 (4.5)	6 (28)	
Severe	1 (4.5)	1 (5)	
BCG Status			0.323
Positive	20 (91)	21 (100)	
Negative	2 (9)	0	
Household Contacts With PTB			1.00
With exposure	21 (95)	21 (100)	
No exposure	1 (5)	0	

DOTS group satisfied 4 out of 5 WHO criteria. There was an equal distribution in the number of patients satisfying 3 out of 4 WHO criteria.

TREATMENT OUTCOMES

A total of 42 patients completed the treatment on

Table 2: Presenting clinical signs and symptoms and Mantoux test observed between the two groups

VARIABLE	TREATMENT		
	DAILY N=22(%)	DOTS N=21(%)	TOTAL
Clinical symptom			
Cough > 2 wks	19 (86)	14 (67)	33 (77)
On/off wheezing > 2wks	7 (32)	4 (19)	11 (26)
Afternoon fever	5 (23)	8 (38)	13 (30)
Night sweats	13 (59)	11 (52)	24 (56)
Poor appetite	18 (82)	18 (86)	36 (84)
Weight loss	16 (73)	16 (73)	32 (74)
Poor wt gain	22 (100)	21 (100)	43 (100)
Not responsive to appropriate antib.	2 (9)	4 (19)	6 (14)
Painless CLAD	19 (86)	20 (95)	39 (91)
Mantoux Test			
Positive	11 (50)	11 (52)	p value 0.882
Negative	11 (50)	10 (48)	

schedule, with 22 (100%) in the daily and 20 (95%) in the intermittent group (p0.974) shown in Table 4. One patient in the DOTS group stopped the treatment after 3 weeks due to episodes of vomiting. Compliance at

Table 3. Classification of Primary Tuberculosis between Daily and DOTS group.

VARIABLE	TREATMENT	
	DAILY N=22(%)	DOTS N=21(%)
(+) Signs and Symptoms (+) Exposure (+) Mantoux Test (+) CXR findings	9 (41)	8 (38)
(+) Sings and Symptoms (-) Exposure (+) Mantoux Test (+) CXR findings	1 (4.5)	0
(+) Signs and Symptoms (+) Exposure (+) Mantoux Text (-) CXR findings	1 (4.5)	1 (4.5)
(+) Signs and Symptoms (+) Exposure (-) Mantoux Test (+) CXR findings	11 (50)	11 (52)

the end of the treatment ranged from 95-100% for both groups and did not show any significant statistical difference. The mean number of the total medications take comparable in both groups.

Average weight gain did not show any significant difference between the 2 groups from the 1st to the 6th month of therapy.

At the end of six months, 78% (15) in the daily and 79% (15) in the DOTS group showed disappearance

Table 4. Treatment completion and compliance between the daily and DOTS group

Variable	Treatment		
	Daily N=22(%)	DOTS N=21	pValue
Completed the treatment for 6 mos.	22(100)	20(95)	0.974
Did not complete treatment	0	1(5)	
No. of children compliant (%)	22(100)	20(95)	0.974
% prescribed doses taken	98%	96%	

of cough (p0.429).

At the end of the 6-month therapy, improvement in the appetite and in the child's activity were recorded

Table 5. Average monthly weight gain between Daily and DOTS group

Variable (month)	Daily	DOTS(kg)	pValue
1st month	1.05	0.60	0.905
2nd month	0.72	0.54	0.878
3rd month	0.70	0.40	0.702
4th month	0.60	0.50	0.633
5th month	0.90	0.30	0.504
6th month	0.55	0.40	0.654

for both the Daily and the DOTS group although these were not statistically significant.

There were no major side effects observed in either group shown in Table 6 except for one patient in the DOTS group who stopped treatment after 3 weeks due to episodes of vomiting and one patient in the daily group who developed loose bowel movements which spontaneously resolved. Inquiry regarding urine color showed a consistent change of the normal urine color to dark orange.

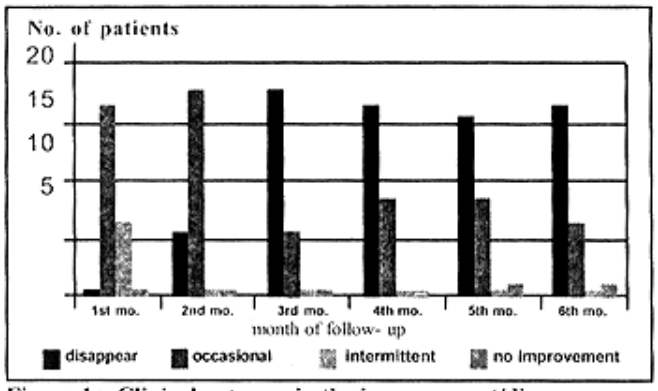

Figure 1a. Clinical outcome in the improvement/disappearance of cough in the Daily group.

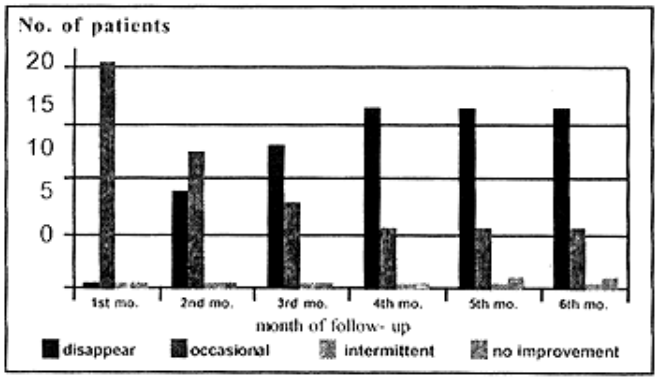

Figure 1b. Clinical outcome in the improvement/disappearance of cough in the DOTS group.

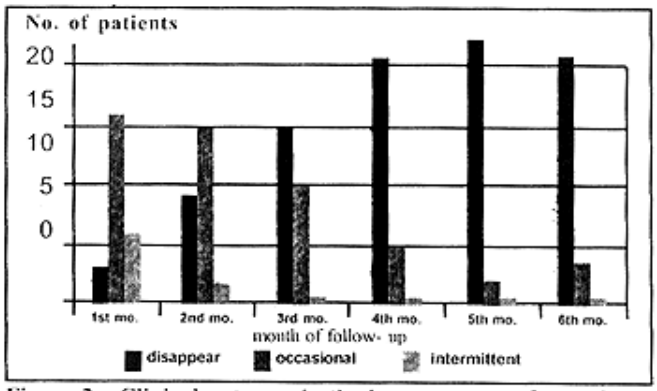

Figure 2a. Clinical outcome in the improvement of appetite in the Daily group.

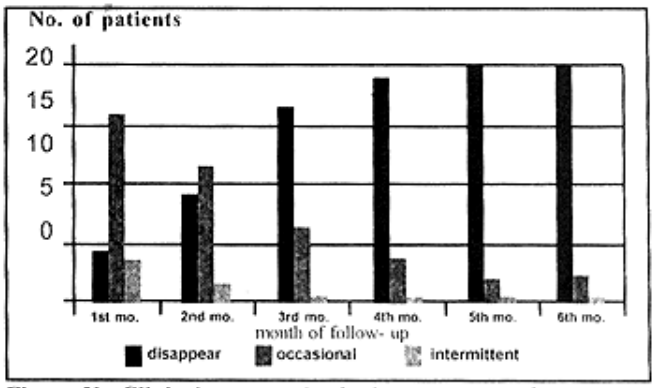

Figure 2b. Clinical outcome in the improvement of appetite in the DOTS group.

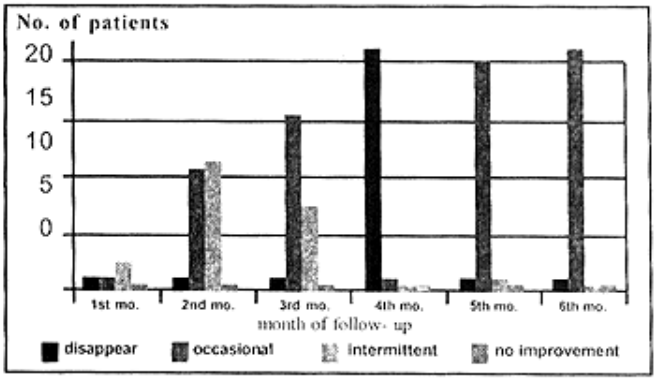

Figure 3a. Clinical outcome in the improvement of activity in the Daily group.

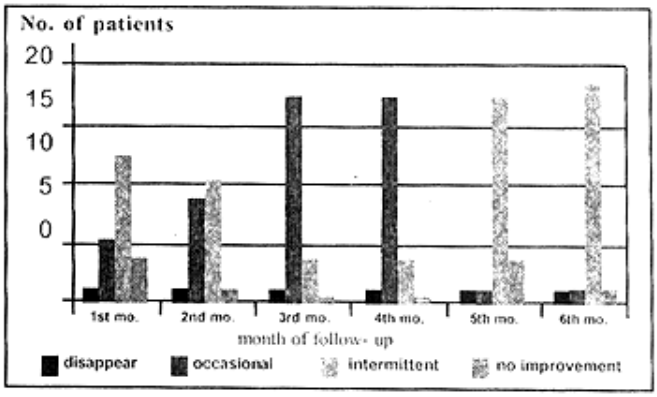

Figure 3b. Clinical outcome in the improvement of activity in the DOTS group.

DISCUSSION

Tuberculosis ranked 5th among the leading causes

Table 6. Side effects observed in the daily or the DOTS group

Variable	Daily N=22(%)	DOTS N=21(%)
Abdominal pain	0	0
Diarrhea	1(4.5)	0
Jaundice	0	0
Rashes	0	0
Vomiting	0	1(4.7)

of mortality[11] and 6th among the leading causes of morbidity[12]. It is estimated that between 2000 and 2020, nearly one billion people will be newly infected; 200 million people will get sick and 35 million people will die from tuberculosis if control is not strengthened. DOTS has progressed worldwide and 55% of the world's population has access to DOT at least in principle[13] with 148 over 210 countries implementing this strategy[11]. It consists of five components: (1) political commitment to sustain TB control; (2) case detection; (3) a standardized short course chemotherapy regimen of 6-8 months with DOT; (4) a reliable supply of high quality drugs; and (5) information system for monitoring and reporting of outcome. Locally, the first attempt to implement DOTS in adults and children was done at U.S.T.

From this study, the most common signs and symptoms observed were poor weight gain (100%); painless cervically lymphadenopathies (91%); poor appetite (84%) and cough (77%) in a survey done by Soriano in 1997, the most commonly seen symptoms of primary TB were failure to return to normal health after an infection and painless cervical and/or other lymphadenopathies[14].

The results of the Mantoux test show that only 50% of the subjects in both groups has positive results that is more than or equal 8mm induration. Ninety-one percent of the subjects in the daily and 100 percent in the DOTS group had BCG vaccination. The first National Consensus (1989) Report of the Committee on BCG and Tuberculin Test has endorsed a minimum of 8 mm induration for indicating TB infection which was also recommended by pediatric pulmonologists until results of newer studies will show otherwise[2]. There have been studies to correlated the influence of BCG vaccination and its effect on the Mantoux test. While a prior BCG vaccination can also lead to a false positive reaction, a number of studies have shown that children and adults from countries of intermediate and high tuberculosis rates like our country had the same prevalence of significant reactions, regardless of the presence or absence of BCG[16]. The US Public Health Service also shared the same view if the patient comes from an endemic country[17]. BCG is just one of the several factors that may influence the PPD reading. False negative reactions may be caused by host factors such as anergy, coexisting viral infections, malnutrition, young age and overwhelming TB which may diminish the induration. According to Starke, 10% of otherwise normal children with culture proven TB disease do not react to tuberculin at the time of presentation, though most become reactive after treatment is initiated[19].

To avoid inter-observer variability, a single radiologist blinded to the study read the chest radiographs with results suggestive of Primary tuberculosis Infection in 98% of the subjects. In general, the radiographic abnormalities in pediatric pulmonary tuberculosis were caused by a combination of parenchymal infiltrate and the mechanical changes (esp. hyperinflation and/or atelectasis) induced by partial or complete airway obstruction due to large intrathoracic lymph nodes[20]. A repeat chest x-ray recommended after completion of the treatment was not done in this study due to limitation of funds.

Success in the treatment of pediatric TB can be assessed mainly in the improvement of clinical signs and symptoms as compared with adult TB patients were labeled as "cured" if there were at least two negative sputum smear examination towards the end of the treatment. In children, direct microscopy of clinical specimens such as sputum and gastric aspirates whenever obtainable may have a low sensitivity (0-20%) for the diagnosis particularly since the bacillary load or density of infection is much lower than in adults[2,21].

The treatment outcome used in this study was the improvement in the clinical symptoms such as cough, appetite, activity and disappearance of fever and weight gain. In all these parameters, there was no significant difference between the daily and DOTS group which means that both regimens were effective at least during the six months of follow-up. Although an adequate balanced diet is difficult to achieve in low-income families, if controlled, could have presented larger weight gains. For those who finished the treatment, there was good compliance (100% in daily and 95% in DOTS) and follow up (100%) for both regimens. The reasons for this can be attributed to parent education regarding the nature of the disease and the consequences of failed therapy prior to enrolment; a dedicated and responsible health worker; and the small catchment. However, eventual relapses among subjects cannot be determined at this point.

There were no significant side effects observed in the study except for one patient (5%) in the DOTS group who stopped the treatment after three weeks due to some episodes of vomiting and one patient (5%) in the daily group who developed diarrhea.

Foreign studies have demonstrated that DOTS strategy was cost-effective compared with daily self administered treatment (SAT). Worthwhile to mention although not included in the objectives, that the average cost per subject for the whole duration of treatment on an out-patient basis for the daily SAT was Php 3,648 versus Php 3,139 for DOTS regimen. Hence, the study showed that DOTS strategy saved five hundred nine pesos (Php 509) per patient which was a considerable amount in this time of economic crisis. However, a full cost effectiveness study should be done locally.

This provided evidence that DOTS is possible even in a pilot urban poor community as long as funding is available and dedicated health workers, caregivers and responsible community leaders are committed to the cause.

CONCLUSION

Directly Observed Treatment Short Course (DOTS) strategy has no statistically significant difference compared with the Self Administered Treatment (SAT) regimen as regards efficacy (improvement of clinical signs and symptoms, and weight gain) and compliance during the 6 months of treatment.

Daily dosing of anti-TB drugs was just as good as thrice weekly dosing in terms of efficiency and compliance provided the guardians/mothers were well oriented and should have a close monitoring.

It is thus recommended in this study (1) to increase the sample size; (2) to have a repeat chest radiograph after completion of the treatment to compare radiologic improvement; (3) to follow up each patient for relapse; and (4) to do a full cost-effectiveness study.

ACKNOWLEDGMENT

This study would not have been possible without the support of the social service, community health program of the Manila Doctors Hospital, Metrobank Foundation Inc. and four drug companies.

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