

Full Length Research Paper

Intermittent chemotherapy compared to the daily regimen in Sudanese patients with pulmonary tuberculosis

Mutasim Siddig Mohammed Salih^{1*}, Idris Babiker Eltayeb, Abullahi Mahgoub Zaki, Badr Eldein H Idris, Abdelmoneim Ismail Awad, Alaa Eldein Hassan Ahmed and Hassan M. Mohi Eldein

¹Department of Pharmacology , Faculty of Medicine, University of Al Imam Al Mahdi,

²Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, P.O. Box 1996, Khartoum, Sudan.

³Department of chest - Faculty of Medicine- Omderman Islamic University,

⁴Department of Radiology, Dean Faculty of Medicine, University of Al Imam Al Mahdi,

⁵Department of Pharmacy Practice, Faculty of Pharmacy, Kuwait University P.O. box 24923 SAFAT 13110 Kuwait.

⁶Department of Medicine, Faculty of P Medicine, University of Khartoum- Sudan.

⁷Department of Medicine, Kosti Teaching Hospital, Coordinator of TB control Program, The white Nile State, Sudan.

*Corresponding author. E-mail: mutasimq@yahoo.com.

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A prospective comparative, randomized clinical trial, hospital based study, carried out at Kosti teaching hospital using directly observed treatment short course (DOTS), to evaluate the efficacy of intermittent chemotherapy compared to the currently adopted daily short course therapy. A total of 275 smear positive new cases of Tuberculosis were enrolled and randomized in to two groups 2006-2008, intermittent Group A and daily short course regimen group (B). The raw data were introduced into SPSS program, data comparison was carried out by Pearson Chi square and pair independent sample student T-test. The level of significance was ($P<0.05$). By the end of the fourth, fifth and the sixth month, there was no patient with positive sputum in the two groups. By the end of the second month, there was a significant decrease in the means of ESR after 6 month compared to the initial results ($P<0.05$). The twice weekly 6 month intermittent regime was as effective as the daily regimen, complete conversion in the two groups occurred after the end of third month. No relapse case was detected in the two groups and death rate was comparable in the two regimens.

INTRODUCTION

World Health Organization (WHO) declared tuberculosis as a global health emergency in 1993 (De Souza, 2006). In Pakistan, the disease is one of the major illnesses responsible for increase in the morbidity and mortality (Muhan and Darak, 2007). Tuberculosis remains a major global public health problem , in Tanzania and in Timor leste (Stevenson et al., 2007; Kibiki et al., 2007; Martins et al., 2007).

In Japan , the intermittent regimen has a great advantage to induce Directly Observed Therapy (DOTS) (Wada M et al., 2006). In 50 poverty countries, the registered new smear positive cases increased year by year (Liu, 2007).

Till 1998 Sudan was classified as one of the slowly moving countries in implementation of the DOTS strategy and making no progress against TB (Wise,

1983). According to Sudan National Tuberculosis Programme progress report 2005, it was planned to fulfill the WHO targets (70% case detection and 85% cure rate) by the year 2004 to 2005.

WHO has been propagating the use of intermittent supervised treatment for all cases including children (Singh, 2006). And to investigate whether administration of high dosage of rifampicin (R) (20 mg/kg) will increase the bactericidal activity and the speed of sterilization or not (Diacon, 2007).

Intermittent regimens markedly reduce the manpower required for observed therapy and clinical studies are needed to formulate new regimens against the ever-increasing threat of multi - drug resistant TB (Brausch and Bass, 1993).

Further studies are required to establish the equivalence of fully intermittent, with the short course (Mwandumba, 2001). According to Elkheir (2005), the intermittent regimens may be more suitable in the Sudan but no clinical trial addressing the efficacy of intermittent chemotherapy was conducted in Sudan, therefore, such study is justifiable and , putting in mind the increasing incidence rate of TB in the Area of study.

This study aimed to evaluate the efficacy of intermittent TB chemotherapy compared to the daily short course regimen in regards to: microscopical examination, Erythrocyte Sedimentation rate (ESR) progress and relapse rate.

MATERIALS AND METHODS

Study area

Kosti province is inhabited by different Ethnic groups and it constitutes more than 40% of the population of the State (702000 out of 2000000). This study was conducted in Kosti teaching hospital at a distance of 312 Kilometers south of Khartoum which the major referral hospital of the White Nile State. Other 15 T.B centers were initiated in the state by the Local TB control programme. The field of the study was prepared by frequent visits, to initiate good relations with the working staff, which allowed and ensured a maximum fruitful co-operation. IT is possible in routine?

Patients

The incidence or prevalence of tuberculosis in the study area, depending on the proper records available in TB programme in the White Nile State, sample size was calculated as follows:

- The average of smear positive tuberculous patient attending chest department at Kosti teaching hospital for the last 5 years (2001 to 2005) was calculated (550

patient), the minimum sample size to be admitted for this study was 226 patient, but 275 patients were introduced to the study (Eldahian, 2002).

- New smear positive (three samples) were taken from Adult > 15 years old without associated debilitating diseases or advanced disseminated cases of pulmonary Tuberculosis with sputum smear positive, Who attended to department of chest at Kosti Teaching hospital during March 2006 to March 2008 were enrolled in this study. A written consent from the local health authority was already taken and each patient was informed and consented. Each patient gain benefits of free investigations, antitubercular drugs and food supplies was assured

Clinical procedures

Chest specialist, physicians and other doctors at the private sector were informed that such a study will be conducted at Kosti Teaching Hospital and they were requested to send the targeted tuberculous patients to the investigator immediately after diagnosis.

Laboratory procedures

Sputum smear and Erythrocyte Segmentation Rate (ESR) were examined according to (Monica Cheesbrough 2000).

Management of patients

The patients were randomized using lottery into two groups

In Group A, the intermittent regimen group patients were treated using ethambutol (20 mg/kg); rifampicin (10 mg/kg); isoniazid (6 mg/kg) and pyrazinamide (25 mg/kg) for 60 days as an initial phase then were given the minimum intermittent dosage of rifampicin 900 mg (30 mg/kg)\ isoniazid 450 mg (15 mg/kg) twice weekly (about 12 tablets\ week) for four additional months 128 patients were enrolled. The drugs are manufactured by Svesra company India).

In Group B, the short course daily regimen group patients were treated using streptomycin (15 mg, Svesra India), rifampicin (10 mg/kg) \ isoniazid (6 mg/kg) and pyrazinamide (25 mg/kg) for two months as an initial phase then rifampicin (10 mg/kg)\ isoniazid (6 mg/kg) once daily (about 21 tablets\ week) for 120 additional days, 147 patients were enrolled.

Sputum smear to evaluate the efficacy and relapse rate of chemotherapy in regards to: Microbiological examination. Directly Observed Therapy (DOT) and closed supervision was applied. Patients were given instructions to come to Kosti teaching hospital regularly in

Table 1. Sex distribution and education among the study group at the beginning, N = 275 patients (P - Value = 0.053).

Variable	Percentage
Males	55
Females	45
Illiterate	59
Khalwa	7
Primary	24
Secondary	8
University	2

Table 2. Treatment outcome in group A and B; N = 275 patients.

Variable	Intermittent regimen	Daily short course regimen	
Cured	55.5%	45.5%	
Defaulted	40.6%	51%	
Absconded	2.3%	1.4%	
Transferred	0.8%	1.4%	
Died	0.8%	0.7%	
Relapse	0%	0%	
ESR	110.3 to 36	105 to 35.6	(Means, P-value 0) N= 128
Weight	48.6 to 53 Kg	50 to 55.5 Kg	(Means, P-value 0) N=147

two weeks interval; patients who did not adhere to the regimen were considered as defaults and excluded. The patients were visited frequently in the villages and community leaders were involved to help in encouraging patients to adhere to treatment and follow up of relapse. Patients who completed the course of treatment 71 in group A and 67 in Group B were requested to come regularly at the end of the third, sixth, twelfth and eighth month providing two samples of sputum that were investigated also patient satisfaction form was filled for each patient.

Data analysis

The raw data were introduced into SPSS program for the performance the descriptive and comparative analysis. The data comparison was carried out by Pearson Chi square and pair independent sample student T-test. The level of significance was ($P < 0.05$).

RESULTS

A descriptive and comparative designs were used, (275 patients) were enrolled in the study where 55% of them were males and 45% were females. Considering the educational level, it was found that about 59% of the entered patients were illiterate, 7% Khalwa level, 24%

Primary school, 8% secondary school and 2% were at the University level P-Value (0.053).

The twice weekly 6 month intermittent is effective as the daily regimen more preferred by the vast majority of patients exposed to this regimen and less expensive than the daily 6 month regimen.

Complete conversion of sputum from positive to negative by the end of the first month occurred in Group B, while in 2.8% in Group A it was still positive and by the end of the second month the sputum was completely converted to negative in Group A while in 3% of Group B it was still positive.

Complete conversion in the two groups occurred after the end of third month. No relapse case detected in the two groups and death rate was comparable in the two regimens.

Decrease in the means of ESR after 6 month compared to the initial results in the two groups from 110.3 to 36 in Group A and 105.6 to 35.6 in Group B.

Weight gain was detected in the two groups, which is confirmed by the increase in the means of weights from 48.6 to 53 kg in Group A and 50.6 to 55.3 kg in Group B (Tables 1 and 2; Figure 1).

DISCUSSION

As randomized clinical trial addressing the intermittent chemotherapy has not been conducted yet in the Sudan,

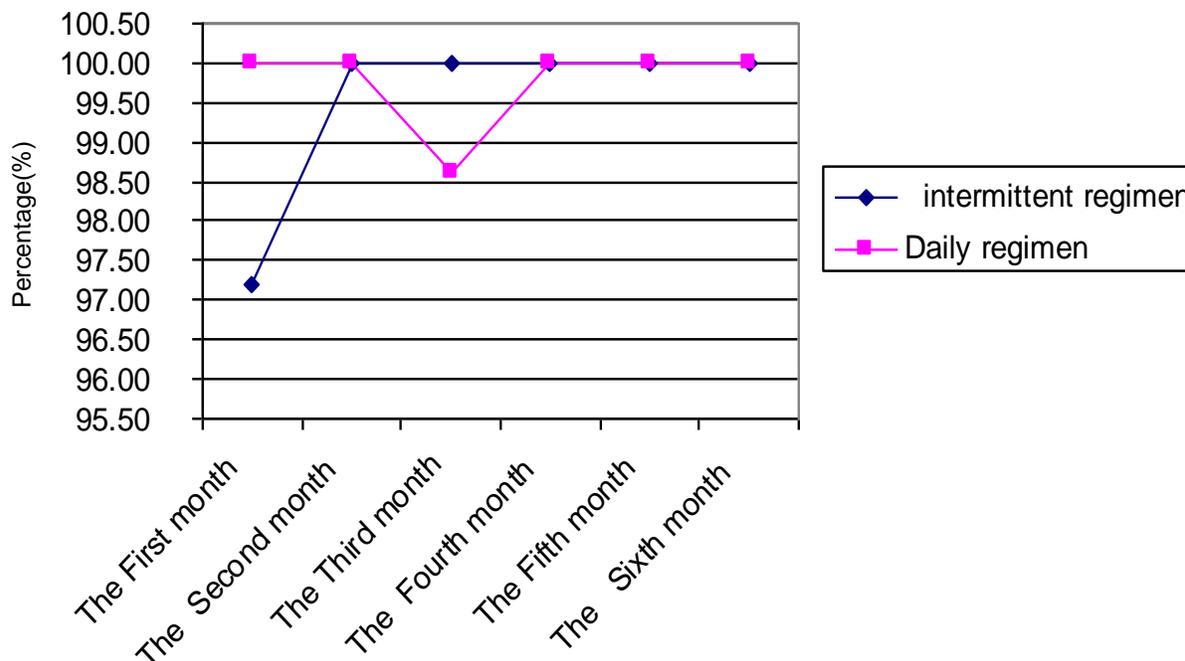


Figure 1. Percentage of sputum conversion from positive to negative during the course of treatment, N = 138 patients.

according to Elkheir (2005), the intermittent regimens may be more suitable in Sudan, therefore, a study to assess the efficacy of the intermittent chemotherapy and the adverse drug reactions of the antituberculous drugs is justifiable and highly needed, Putting in mind the increasing incidence rate of TB in the Sudan generally and specially in the White Nile area.

A comparative study was conducted. Complete conversion from positive to negative by the end of the first month occurred in all patients of group B, while (2 cases) in group remained positive after the end of the first month, however, 97.2% of the patients converted to negative, it was observed that (2 cases) by the end of the second month in Group B remained positive, unfortunately one of these two cases defaulted the treatment. This can be explained either by false negative by the end of the first month or emergence of new positive strains, whatever the cause, one of these patients defaulted and the other converted to smear negative by the end of the third month and remained negative through her follow up. By the end of the fourth, fifth and the sixth month, no patient with positive sputum in the two groups, the differences were insignificant.

Default rate was lower in Group A, it was found that (71 out of 128 patients) 55.5% of the patients were cured, while only (67 out of 147 patients) 46.5% of Group B cured, (P-value 0.097) it is known that patients adherence is inversely proportional to many factors one of them is the dosing frequency, the difference was statistically nonsignificant, it was found that default rate was higher than that in South Africa stated by (Wilkinson,

1994).

Concerning the relapse rate, it was assessed by clinicobacteriological (sputum for alcohol acid fast bacilli) measurement, after 6, 12 and 18 months, fortunately no relapse case i.e. sputum positive was detected in the two groups, which is different from the findings of previous study conducted in Indonesia by (Suryinto and Coworker, 2008) who found that the relapse rate was 10.1%.

One of the philosophies of giving short course chemotherapy were to minimize the defaulter rate, moreover intermittent regimen was formulated and advised to induce acceptability and adherence of the patients to their prescribed regimen, although the enrolled patients gain free medicines, laboratory investigations, X-Ray, proper follow up and medical consultancy in addition to food supplies, the defaulter rate was still high, this may be explained by the influence of well-being sensation after starting the treatment or due to Economic factor because most of the patients were coming from rural areas. Significant decrease in the percentage of patients with initial tree figures ESR in the two groups.

Significant weight gain was detected in the two groups, which is confirmed by the increase in the means of weights, patient adherence and regular food supply may assist in weight gain (Table 2).

Conclusion

The twice weekly 6 month intermittent is effective as the

daily regimen, more preferred by the vast majority of patients exposed to this regimen and less expensive than the daily 6 month regimen. Complete conversion of Sputum from positive to negative in the two groups occurred after the end of third month. No relapse case detected in the two groups and death rate was comparable in the two regimens. Ultimately the intermittent regimen reduced about 43% of the cost of drugs consumed in the continuation phase of TB treatment compared to the daily regimen approximately (12 tablets\week) VS (21 tablets \week) successively.

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