Original Article

Adverse drug reactions of Intermittent chemotherapy compared to daily regimen in Sudanese patients with pulmonary Tuberculosis

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Abstract

Back ground: The World Health Organization (WHO) declared Tuberculosis a global health emergency in 1993 as it remains a major cause of mortality in developing countries. The World Health Organization's Directly Observed Treatment Short course (DOTs) strategy achieve 87% success rate in the areas where it is implemented, usually with five drugs, lasts for 6months. Till 1998 Sudan was classified as one of the slowly moving countries in implementation of the DOTS strategy and making no progress against tuberculosis.

Objective: A prospective comparative, randomized clinical trial, hospital based study carried out at Kosti Teaching Hospital using directly observed treatment short course (DOTS), to assess the adverse drug reactions of intermittent chemotherapy compared to the currently adopted short course therapy.

Methodology: Patients with smear positive new cases of tuberculosis were enrolled and randomized in to two groups, intermittent treatment group (A) and daily regimen group (B) .The raw data were introduced into SPSS program, the data comparison was carried out by Pearson Chi square and pair independent sample student T-test. The level of significance ($P<0.05$).

Results: A total of 275 were studied, significant initial (pre-interventional) elevated means of aspartate aminotransferase (AST) was detected in the two groups and significantly in the intermittent regimen after two and four months, but the decrease was significant only after two months in the daily group.

Conclusion: Liver injury following antituberculous treatment was minimal and the adverse drug reactions were tolerable concerning the majority of the patients completing the course of the treatment.

Keywords: DOTS, INH, acetylators.

The World Health Organization (WHO) declared Tuberculosis a global health emergency in 1993[1] as it remains a major cause of mortality in developing countries[2]. The World Health Organization's Directly Observed Treatment Short course (DOTs) strategy achieve 87% success rate in the areas where it is implemented, usually with five drugs, lasts for 6months. Till 1998 Sudan was classified as one of the slowly moving countries in implementation of the DOTS strategy and making no progress against tuberculosis[3]. In 2002, DOTS was declared all over the country by Sudan National Tuberculosis Programme Progress Report 2005[4].

Concerning the pharmacokinetics of INH, it is rapidly absorbed from gastrointestinal tract, highly diffuses to body tissues and body fluids, metabolized through acetylation, which depends on genetic variations either rapid acetylators or fast acetylators[5]. As far as can be ascertained a study addressing the adverse drug reactions has not been conducted in Sudan, therefore, assessment of the safety of antituberculous drugs is and highly needed .

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Material and Methods:

This is a prospective comparative, randomized clinical trial, hospital based study was carried out in Kosti Teaching Hospital.

Set up: Kosti Teaching hospital is the major referral hospital of the White Nile State which is inhabited by different ethnic groups, 15 tuberculosis centers were initiated in the state by the local tuberculosis control program.

New smear positive pulmonary tuberculosis patients who attended the department of chest at Kosti Teaching Hospital during March 2006 to March 2008 were enrolled in this study.

The inclusion criteria were as follows:

1. Adult > 15 years old.
2. Three samples sputum smear positive pulmonary case.
3. Absence of associated debilitating diseases or advanced disseminated cases.

According to Eldahian[6], the minimum sample size was calculated as 226 patients, but 275 patients were introduced then randomized using lottery into two groups:

1. Group (A) the intermittent regimen group (128 patients) these patients were treated using Ethambutol (20mg/kg), Rifampicin (10mg\kg)\ Isoniazid (6mg/kg) and Pyrazinamide (25mg/kg) for two months as an initial phase then were given the minimum intermittent dosage of rifampicin 900mg (30mg/kg)\ isoniazid 450mg (15mg/kg) twice weekly (about 12 tablets\week) for four additional months.
2. Group (B), the short course daily regimen group (147 patients) were treated using streptomycin (15mg), rifampicin (10mg/kg)\ isoniazid (6mg/kg) and pyrazinamide (25mg/kg) for two months as an initial phase then rifampicin (10mg/kg)\ isoniazid (6mg/kg) once daily (about 21 tablets\ week) for four additional months.

Liver functions were assessed by spectrophotometrical assay of Alanine Amino-transferase (ALT) and Aspartate Amino-transferase (AST) enzymes according to Monica 2000[7] initially after two and four months.

Statistical analysis:

The raw data were introduced into SPSS program for the performance of 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 significant was taken at ($P<0.05$).

Ethical consideration:

A written consent from the local health authority was taken and each patient was informed and consented. Patients who do not agreed were excluded keeping their right of receiving free drugs, sputum investigation, chest physician consultancy and food supplies.

Results:

A total of 275 patients were included in this study. Out of them males comprise 55%. Their mean age was illustrated in Fig 1 and the levels of ALT before and after treatment for the two groups were dipicted in tables 1 and 2. Considering the educational level, it was found that about 59% of the entered patients were illiterate.

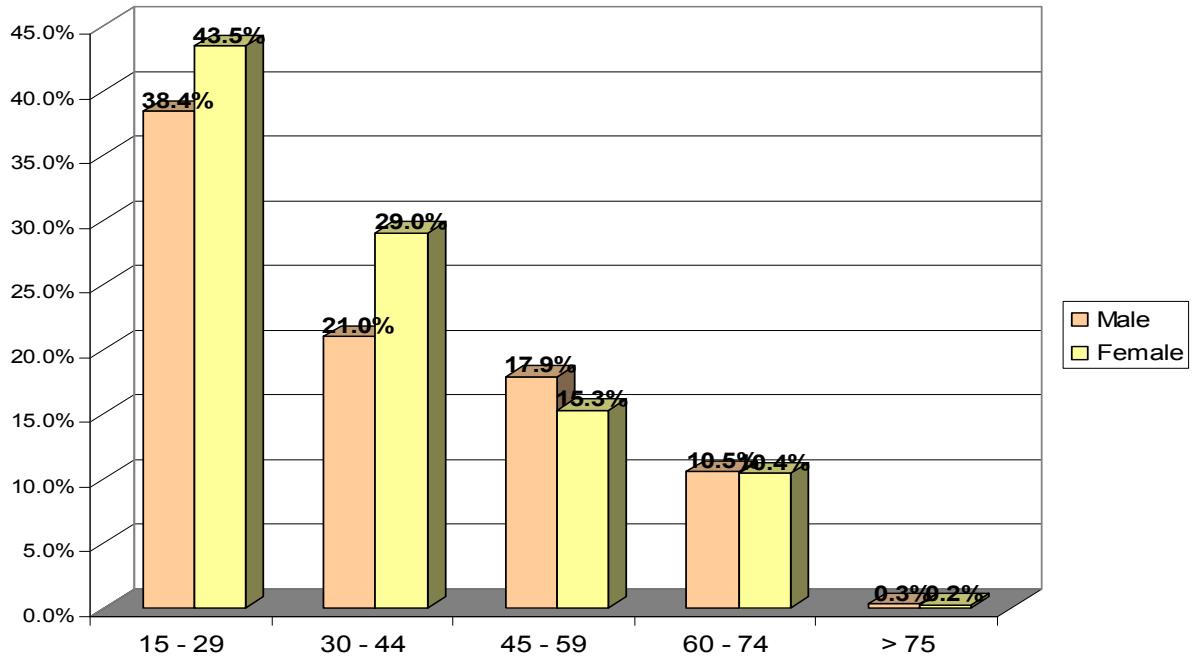
Treatment discontinuation due to Rifampicin induced jaundice and hypersensitivity was deselected in 0.7% (one patient) in group B, the patient was excluded although she recovered after rifampicin was stopped.

Drug- induced jaundice occurred in one (4%) of the patients in group A and 3% in group B. Flu like syndrome was not identified.

Discussion:

A descriptive and comparative designs were used, (275 patients) were enrolled in the study where 55 % of them were males and 45% were females, The male to female ration is not comparable to other studies stated by Mohammed and coworker 2007 in South Africa 56% females, 44% males respectively[8] and nearly similar to the results obtained by Muhan and coworker 2007 in Pakistan 54 males and 46 females[9].

In general the Sudan National Tuberculosis Program stated that the number of the infected males and females is nearly equal[10].



P-value = 0.723

Figure (1): Age and sex distribution of the study population (group A and B) N = 275 patients

Table (1) The percentage of elevated ALT among tuberculous patients (N = 138)

ALT		GROUP				Total		Pearson Chi-Square	
		Group A		Group B					
		No	%	No	%	No	%	Value	P-Value
initial ALT (pretreatment)	Normal	56	78.9%	58	86.6%	114	82.6%	1.420	0.233
	Elevated	15	21.1%	9	13.4%	24	17.4%		
ALT after 2 months	Normal	57	80.3%	58	86.6%	115	83.3%	0.981	0.322
	Elevated	14	19.7%	9	13.4%	23	16.7%		
ALT after 4months	Normal	62	87.3%	60	89.6%	122	88.4%	0.167	0.683
	Elevated	9	12.7%	7	10.4%	16	11.6%		

Normal value > 35 units \ liter

Table (2): The percentage of elevated AST among tuberculous patients (N = 138)

AST		GROUP				Total		Pearson Chi-Square	
		Group A		Group B				Value	P-Value
		No	%	No	%	No	%		
Initial AST (pretreatment)	Normal	33	46.5%	41	61.2%	74	53.6%	3.001	0.083
	Elevated	38	53.5%	26	38.8%	64	46.4%		
AST after 2 months	Normal	51	71.8%	47	70.1%	98	71.0%	0.047	0.828
	Elevated	20	28.2%	20	29.9%	40	29.0%		
AST after 4 months	Normal	60	84.5%	49	73.1%	109	79.0%	2.686	0.101
	Elevated	11	15.5%	18	26.9%	29	21.0%		

Considering the educational level, it was found that about 59 % of the entered patients were illiterate, which is higher than the percentage mentioned by Sudan National Tuberculosis Program 27.3% were illiterate in Khartoum state[10],Generally it is known that the tuberculous infection rate is inversely proportional to the educational level (figure 3.2). Treatment discontinuation due to hepatitis as a result of rifampicin hypersensitivity was detected in 0 .7 % (one patient) in group B, the patient was excluded although she was recovered after rifampicin was stopped.

Drug-induced jaundice occurred in 1, 4% of the patients in group A and 3% in group but, these patients recovered after stopping the treatment for a week then treatment continued without any problem.

Flu like syndrome was not identified which usually limits the use of Rifampicin dependent intermittent regimen and many investigators describe the syndrome. In India according to Rajinder Singh Bedi and coworkers, Flu like Syndrome due to ethambutol, the flu syndrome has usually associated with intermittent (rarely daily) use of Rifampicin, though a case of Ethambutol-induced[11]. Flu like syndrome was identified, and three cases of flu like symptoms due to Isoniazid were found in 1989. The findings are also different from the fact stated by James and coworker that flu like is a common adverse drug reaction of rifampicin dependent regimen[12], also different from Gerald K. Mc Evoy and coworker 1988 who mentioned that Flu like syndrome was been associated with the use of twice a week intermittent rifampicin and identified in 1% of the patients[13].

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