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A Comparative Study on DOTS and Non-DOTS Therapy in Newly Diagnosed Tuberculosis Patients

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ABSTRACT

Tuberculosis is a major public health problem in India. Regimens of DOTS and Non-DOTS had been administered for controlling and prevention of tuberculosis. A Prospective Observational study was conducted aimed to study the extent and incidence of TB, to compare the safety, effectiveness and patience compliance for a period of 9 months from July 2014-March 2015 in St. Philomena's Hospital, Bangalore, India. Patients who were newly detected with Tuberculosis were enrolled in the study after obtaining informed consent from each patient. During the study period, a total of 59 newly diagnosed tuberculosis patients under CAT regimen-1 of which 28 (47%) were under DOTS and 31 (53%) were enrolled in the study. Comparing both the groups, predominance was higher in males (52%) than females (48%). Lymph nodes were the most predominant among various sites of extra-pulmonary tuberculosis in both the groups. In a total of 18 ADRs, Non-DOTS (77.77%) were showing greater significance of ADRs than DOTS (22.23%). In relation to effectiveness of the therapy, Weight gain of P value was found to be $P<0.05$ which reveals a significant difference whereas in decreased means of ESR levels of $P>0.05$ which shows that there was no significant difference between both the groups. Based on fate of sputum, AFB sputum smear positive patients have shown negative after the completion of the treatment in both the groups. This study reveals that DOTS and non-DOTS were equally effective but with the exception of one defaulter and one death in non-DOTS.

INTRODUCTION

Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. When people with lung TB cough, sneeze or spit, it spreads from person to person via droplets from the throat and lungs of people with active respiratory disease.

About one-quarter of the world's population have been infected by TB bacteria with no symptoms since the host immune system controls the bacteria in which they cannot transmit the disease.[1,2]

In 2019, an estimation of about 10 million people fell ill with TB globally. 5.6 million men, 3.2 million women, 1.2 million children infected and 1.4 million death due to TB worldwide.[3] One fourth of the population in India accounted for global TB burden. In India, an estimation of 2,690,000 infected and more than 440,000 people died due to TB.[4]

Treatment is done based on the clinical presentation and site of disease. Standard short course treatment for TB is Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) for 2 months, then Isoniazid (H), and Rifampicin (R) alone for 4 months. To reduce mortality and morbidity due to TB, Government of India has initiated Revised National TB Control Programme introduced DOTS for controlling TB. [2,5]Tuberculosis is a deadliest communicable disease in the world. Revised National Tuberculosis Control Programmes (RNTCP) is the largest TB control programme in the world placing more than 1,00,000 patients on treatment every month.[6]

Government commitment to control TB, Diagnosis based on sputum smear examination, standardised treatment regimen directly observed by a health care provider, a regular drug supply and standardised recording and reporting system that allows assessment of treatment outcome results.[7]

DOTS therapy for newly diagnosed TB patient include 6 months of treatment with 2 months of initial phase ($2H_3$ R_3 Z_3 E_3) and 4 months of continuous phase ($4H_3$ R_3) given 3 times a week and it is intermittent dose regimen.

DOTS is the most effective strategy available for controlling the TB. DOTS will be given in intermittent doses which is provided by health care providers with direct observation.

Classification of patients in categories for standardized treatment regimen - DOTS

Category	***Type of patient***	***Regimen***	***Duration***
Category-1 Color of box: **Red**	New sputum positive Seriously ill sputum negative Seriously ill extra pulmonary Tuberculosis	2(HRZE)3 4(HR)3	6
Category-2 Colour of box: **Blue**	Sputum positive relapse Sputum positive failure Spum positive treatment after Default	2(HRZES)3 1(HRZE)3 5(HRE)3	8

However, due to varied reasons like Patient's discretion, Physicians choice, Non-availability of DOTS center near by residence etc., patients are put on Anti-tubercular regimen by Non-DOTS therapy.

Recommended Anti-tuberculous treatment regimens: Non-DOTS

Indication	Initial phase (I.P)		Continuous phase (C.P)	
	Duration months	**Drugs**	**Duration months**	**Drugs**
New smear positive or culture-positive cases	2	HRZE[a,b]	4	HR[a,c,d]
New culture negative cases	2	HRZE[a]	2	HR[a]
Pregnancy	2	HRE[e]	7	HR
Failure and relapses[f]	-	-	-	-
Resistance to H	Throughout (6)	RZE[g]		
Resistance to H+R	Throughout(12-18)	ZEQ+S		
Resistance to all first line drugs	Throughout (24)	1 INJ.S[h]+3 (Ethinamide, cycloserine, Q, PAS)		
Standardised re-treatment (susceptibility testing unavailable)	3	HRZES[i]	5	HRE
Drug intolerance to R	Throughout (12)[j]	HZE		
Drug intolerance to Z	2	HRE	7	HR

All drugs can be given daily during the initial phase of 2 months and continuous phase for 4 months. Streptomycin can be used in place of ethambutol but is no longer considered to be a first-line drug by ATS/IDSA/CDC. The continuation phase should be extended to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture– positive after the initial phase of treatment.[5,7]

Based on the following review of literatures the study was performed:

Mutasim Siddig et al., has conducted a study on intermittent chemotherapy compared to the daily regimen in Sudanese patients with pulmonary tuberculosis at Kosti teaching hospital. Smear positive new cases of TB of both the genders of all age groups were enrolled and randomized into two groups viz. Group A treated under intermittent therapy and Group B treated under Daily short course therapy for 12 months. Comparatively, intermittent therapy is as effective as the daily regimen and less expensive than daily regimen.[8]

Mrinalini Das et.al carried out a retrospective cohort study on Directly Observed Treatment Short course therapy (DOTS) and Self-Administered (SAT) tuberculosis treatment in a chronic low-intensity conflict setting in India during the period between January to December 2012. Sputum smear positive tuberculosis new cases of 55 under DOTS with 69% completed treatment and 17 under SAT with 53% treatment completion. Ratios of adverse outcomes, the ratio of loss to follow-up: failure: death in DOTS vs SAT was noted as 10:4:3 vs 7:0:1. This study revealed that SAT has better outcome than DOTS.[9]

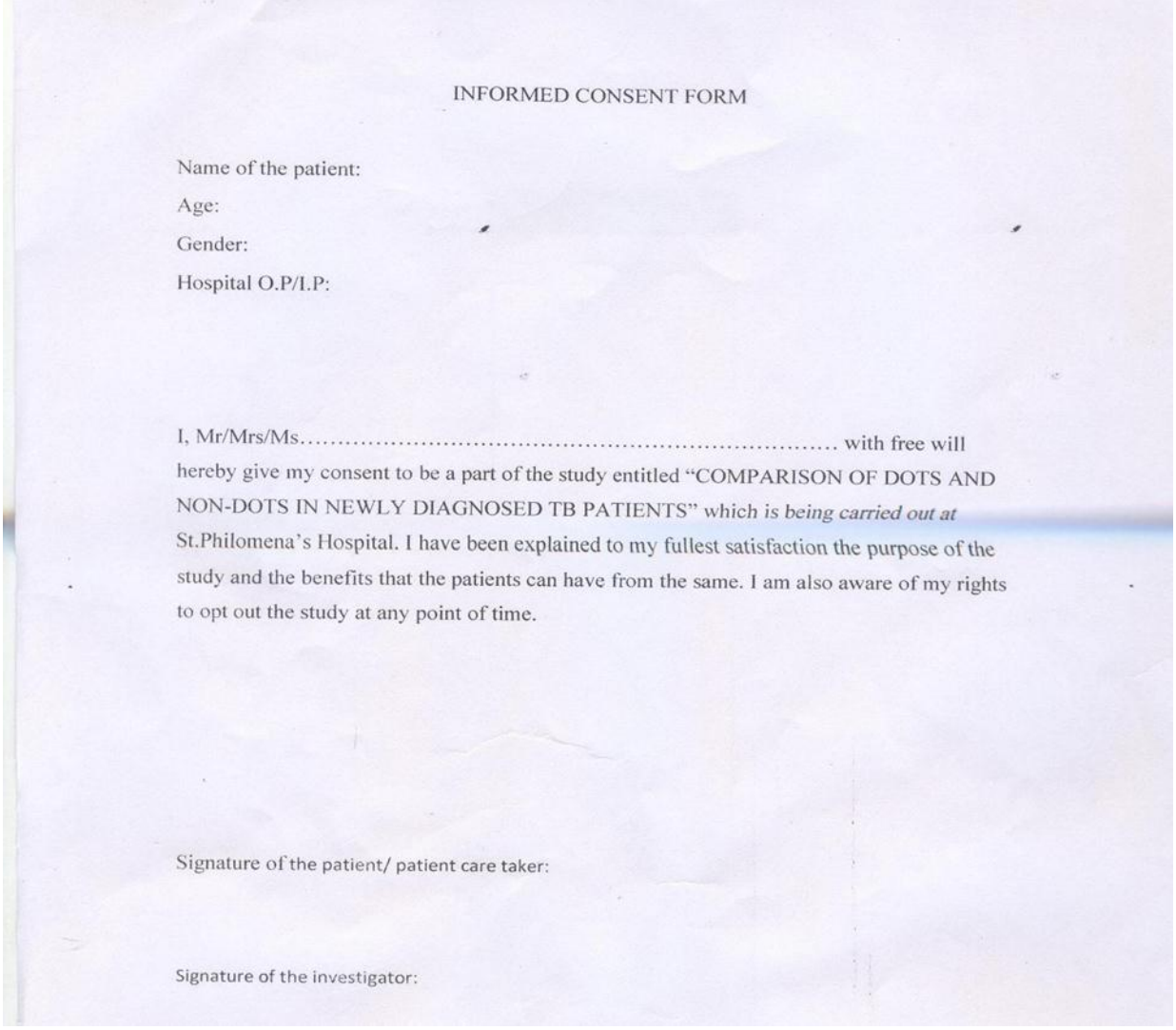
Amrita et.al conducted a retrospective study on comparison of Directly Observed Treatment Short Course (DOTS) with Self-Administered Therapy (SAT) in pulmonary tuberculosis at Manipal during the period between March 2011 to February 2012. 150 patients were enrolled in the study in which 75 under DOTS and 75 under SAT. The incidence rates in DOTS vs SAT were noted as 70.7% vs 68% cure rate, treatment completed 1.3% vs 4%, failure 5.3%vs 1.3%, ADR 5.4%vs 9.4%. 10.7% deaths, 8% defaulters and 4% transferred were observed in DOTS whereas in SAT 26.7% were lost to follow-up which includes death and defaulters. This study shows no statistical difference between success rate in patients taking DOTS and SAT.[10]

Hence, few studies had shown the controversies in safety and effectiveness between the DOTS and Non-DOTS groups. So, the present study was aimed to compare the study of

DOTS and Non-DOTS in newly diagnosed tuberculosis patients. The objectives of the study were to compare the Effectiveness, ADR's and Patient's Compliance between both the groups.

Methodology:

A Prospective observational was carried out after obtaining clearance from Institutional Ethical Committee, St. Philomena's Hospital, Bangalore during the period of July 2014-February 2015 after obtaining the informed consent.



INFORMED CONSENT FORM

Name of the patient:

Age:

Gender:

Hospital O.P/I.P:

I, Mr/Mrs/Ms..... with free will hereby give my consent to be a part of the study entitled "COMPARISON OF DOTS AND NON-DOTS IN NEWLY DIAGNOSED TB PATIENTS" which is being carried out at St.Philomena's Hospital. I have been explained to my fullest satisfaction the purpose of the study and the benefits that the patients can have from the same. I am also aware of my rights to opt out the study at any point of time.

Signature of the patient/ patient care taker:

Signature of the investigator:

Newly diagnosed 59 tuberculosis patients of both genders of all age groups were enrolled in the study. Out of 59 tuberculosis patients, 28 patients were undergoing DOTS regimen and 31 were undergoing Non-DOTS regimen. Data was collected by regular follow-up of the patient in out-patient department and wards. Patient's data was collected from the regular monitoring

of the prescription and personal interview with patient or attender using the patient profile proforma included socio-demographic details, clinical features, biochemistry values, reports of sputum investigations, chest x-ray, radiologic examinations, ADR, weight and treatment outcomes (cure/ treatment/ completed/ treatment failure/ defaulter, treatment success/ death).

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME

Treatment Card

State _____ City / District with code _____ _____ TB Unit with code _____

Name _____ Patient TB No / Year _____

Sex ☐M ☐F Age: Occupation _____ PHI: _____

Complete Address & Telephone number _____ Name and designation of DOT provider & Tel. No. _____

_____ _____

Name and Address of Contact Person & Telephone Number _____ DOT centre _____

_____ Signature of MO with date _____

Initial home visit by _____ Date _____

Disease Classification

☐ Pulmonary

☐ Extra Pulmonary site _____

Type of patient

☐ New ☐ Relapse

☐ Transfer in ☐ Failure

☐ Treatment after default ☐ Other (Specify) _____

Month	Date	DMC	Lab No.	Smear Result	Patient Weight
Pretreatment					
End IP/Extended IP					
2 Months CP					
End treatment					

H/o previous Anti-TB treatment with duration _____

I. INTENSIVE PHASE - Prescribed regimen and dosages:

Tick (✓) the appropriate Category below

☐ **Category I**

New Case
(Pulmonary Smear-Positive,
Seriously ill Smear Negative, or
Seriously ill extra pulmonary)

3 times / week

☐☐☐☐

H R Z E

☐ **Category II**

Retreatment,
(relapses, failure,
treatment after
default, others)

3 times / week

☐☐☐☐☐

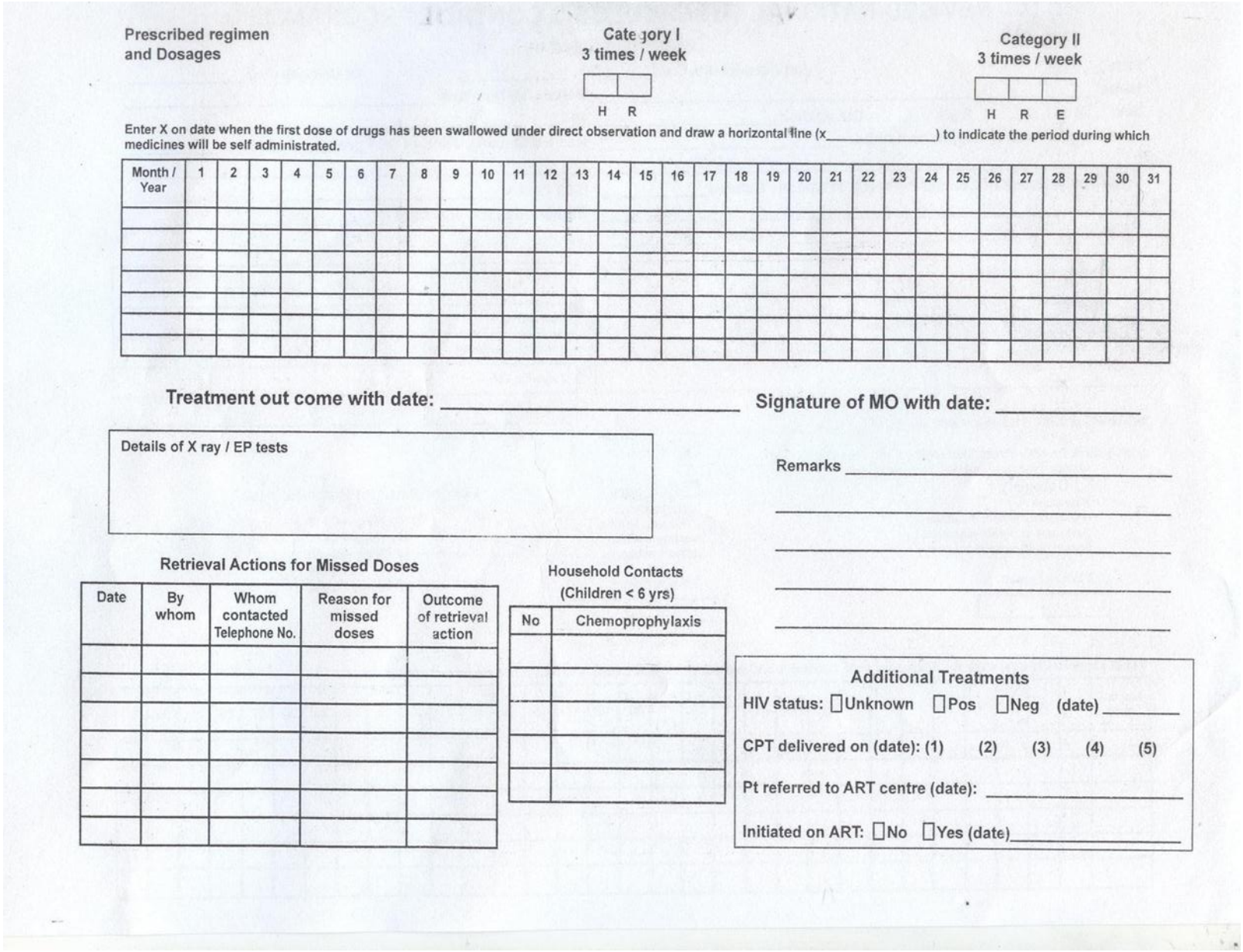
H R Z E S

Weight Band for Pediatric case

6 - 10 Kg - PC - 13
11 - 17 Kg - PC - 14
18 - 25 Kg - PC - 13
PC - 14
26 - 30 Kg 2 PC - 14

Tick (✓) appropriate date when the drugs have been swallowed under direct observation; Make a circle (O) on the date of missed doses

Month / Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31



Prescribed regimen and Dosages

Category I
3 times / week
H R

Category II
3 times / week
H R E

Enter X on date when the first dose of drugs has been swallowed under direct observation and draw a horizontal line (x_____) to indicate the period during which medicines will be self administrated.

Month / Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Treatment out come with date: _____

Signature of MO with date: _____

Details of X ray / EP tests

Remarks _____

Retrieval Actions for Missed Doses

Date	By whom	Whom contacted Telephone No.	Reason for missed doses	Outcome of retrieval action

Household Contacts
(Children < 6 yrs)

No	Chemoprophylaxis

Additional Treatments

HIV status: ☐Unknown ☐Pos ☐Neg (date) _____

CPT delivered on (date): (1) (2) (3) (4) (5)

Pt referred to ART centre (date): _____

Initiated on ART: ☐No ☐Yes (date)_____

Patient's data was assessed for effectiveness, ADRs, compliance and also additional factors like defaulters, relapses, loss of follow-up of medication, death due to TB or other comorbid conditions.

The data was analyzed and documented. Statistical Analysis was performed using student's t-test. Unpaired or independent sample t-test was used to find out the significant difference between both the groups in relation to effectiveness of the treatment included weight gain and decreased in ESR.

RESULTS AND DISCUSSION

Table No. 1: Distribution of patients based on age and gender:

Sl. No	Age in years	Number of patients							
		DOTS				NON-DOTS			
		No of patients				No of patients			
		Males	Percentage (%)	Females	Percentage (%)	Males	Percentage (%)	Females	Percentage (%)
1.	0-10	6	21.42	3	10.71	0	0	0	0
2.	11-20	1	3.57	4	14.28	0	0	0	0
3.	21-30	5	17.85	1	3.57	2	6.45	5	16.1
4.	31-40	1	3.57	1	3.57	4	12.9	4	12.9
5.	41-50	1	3.17	1	3.57	1	3.2	0	0
6.	51-60	2	7.14	2	7.14	3	9.6	3	9.67
7.	61-70	0	0	0	0	4	12.9	2	6.45
8.	71-80	0	0	0	0	0		1	3.2

In DOTS and non-DOTS, Patients above 18 years of old were more predominant. Male predominance was noted in both groups. In DOTS and non-DOTS, Patients above 18 years of old were more predominant. Our results are coinciding with the study carried out by R Verma et.al.[11.]

Based on gender distribution, in DOTS group 15(53%) males and 13(47%) females whereas in non-DOTS group 16(52%) males and 15(48%) females. Male predominance was noted in both the groups. The demographic reports of various TB studies cited a predominance of male which was coinciding with the studies carried out by Amrita et.al.[10]

Table No. 2: Distribution of patients based on types of TB and therapy:

SITE OF TB	DOTS	NON-DOTS
Pulmonary	6	10
Extra-Pulmonary		
Lymphadenitis	6	14
Abdominal Koch	0	3
Pleural effusion	2	3
Spine TB	2	1
Cold abscess	2	0
Meningeal TB	1	0
New smear sputum negative pulmonary TB	9	0

Based on type of tuberculosis, pulmonary was higher in DOTS than extrapulmonary whereas in case of non-DOTS it was vice-versa.

India's Revised National Tuberculosis Control Programme recommended DOTS strategy for controlling TB. RNTCP recommendations of DOTS has been widely advocated and adopted successfully.

DOTS therapy for newly diagnosed TB patient include 6 months of treatment with 2 months of initial phase ($2H_3$ R_3 Z_3 E_3) and 4 months of continuous phase ($4H_3$ R_3) given 3 times a week.

First line drugs used for treating TB are:

Isoniazid (H)- 300mg+Rifampicin (R)-450mg+Pyrazinamide (Z)-750mg+ Ethambutol (E) -800mg Whereas in Non-DOTS it is available as AKT-4 kit with the same doses.

Table No. 3: Number of ADRs

ADR	DOTS	NON-DOTS
Hepatotoxicity	1	2
Hepatomegaly	0	2
Elevated liver enzymes	2	2
Rashes	1	2
Jaundice	0	1
Diarrhoea	0	1
Drowsiness	0	2
Blurred vision	1	1
Vomiting	1	1
Itching	1	1

In our study, DOTS and non-Dots treatment outcome was equally effective even though non-DOTS had greater incidence of ADR, it was managed by withdrawing the drug, reducing dose, or alternate drug to treat that particular ADR but with the exception of one defaulter and death.

To strengthen and further emphasize the validity of the findings, causality assessment was done by using Naranjo's scale and WHO-UMC scale.

Naranjo's probability Assessment scale

Items and Score	Yes	No	Don't Know	Score
Are there previous conclusive reports on this reaction?	(+1)	(0)	(0)	
Did the adverse event appear after the suspected drug was administered?	(+2)	(–1)	(0)	
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	(+1)	(0)	(0)	
Did the adverse reaction reappear when the drug was readministered?	(+2)	(–1)	(0)	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	(–1)	(+2)	(0)	
Did the reaction reappear when a placebo was given?	(–1)	(+1)	(0)	
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	(+1)	(0)	(0)	
Was the reaction more severe when the dose increased, or less severe when dose was decreased?	(+1)	(0)	(0)	
Did the patient have a similar reaction to the same or similar drug in any previous exposure?	(+1)	(0)	(0)	
Was the adverse event confirmed by any objective evidence?	(+1)	(0)	(0)	
			Total	

It is emphasized that most of the reported ADRs were caused by drug. Upon assessing all the reported ADRs, according to WHO-UMC scale, most of the reactions during our study period were possible (50%), probable (43.75%) and definite (6.25%). No reports were found with Naranjo's assessment in the study of DOTS and non-DOTS regimen.

ADR was managed in DOTS vs non-DOTS by drug withdrawn (25%) and (14.28%), alternative drug (25%) and (64.29%), no change (continue same drug) (50%) and (14.28%) dose altered (0%) and (7.15%). Most of the ADRs had a clinical outcome but the exception of

one death. There was a study carried out by Dr. Manohar Lal Bhatia regarding good clinical outcome of ADR due to anti-TB which was similar to our study.[12]

Table No. 4: Comparison on Weight and ESR

PARAMETER	PRE-TREATMENT	POST TREATMENT
DOTS		
Weight	38.9	42.16
ESR	40.35	13.96
Non-DOTS		
Weight	42.83	46.39
ESR	46.41	12.63

Table No. 4a: Statistical analysis for weight gain after the treatment

Post treatment wt (Kg)	DOTS-GROUP	NON-DOTS-GROUP
N	15	10
Mean	36.80	58.00
SD	6.07	7.62
Df	19	
t-test	3.35	
P-Value	0.003	

Independent Sample t-test

*** P<0.05, which indicates that there was a significant difference.**

Effectiveness was compared based on differences in means of increased weight and ESR in DOTS and non-DOTS. Weight gain was observed in both groups. When comparing the weight gain between both the groups post treatment, statistically there was significant difference between 2 therapies. P value was found to be P<0.05. This indicates that weight gain was quite good in DOTS group than in non-DOTS.

Table No. 4b: Statistical analysis for ESR after the treatment

(Independent Sample t-test)

Post treatment ESR (mm/hr)	DOTS-GROUP	NON-DOTS GROUP
N	12	13
Mean	7.58	7.77
SD	2.75	2.79
Df	23	
t-test	0.11	
P-Value	0.91	

*** P>0.05, which indicates that there was no significant difference.**

Effectiveness was compared based on differences in means of decreased ESR in both groups. When comparing the ESR between both the groups post treatment, statistically there was no significant difference between 2 therapies. P value was found to be P>0.05 which indicates that ESR levels were decreased in both the groups.

Treatment outcome of the patient in DOTS vs non-DOTS included: completed treatment and cured- 96.42% vs 77.41%, loss to follow-up- 3.57% vs 3.22% defaulter and 3.22% death in non-DOTS were observed. There was no significant difference found in DOTS and non-DOTS regarding treatment outcome but with the exception of one defaulter and one death in non-DOTS.

In our study, patient's compliance was 100% in DOTS whereas 96.77% in non-DOTS. Patient's strict adherence to medication was found to be higher in DOTS than in non-DOTS. There were no reports found based on patient's compliance.

CONCLUSION

By analysing all the data, it was clear that both the therapies were equally effective though the number of adverse drug reactions is higher in Non-DOTS than in DOTS. The ADR were managed due to withdrawing the drug and supportive treatment. Effectiveness was compared

based on weight gain, ESR, sputum test. Sputum positive patients were sputum negative after the completion of treatment in both groups. Patients compliance were equal in both the groups but with the exception of one death and one defaulter in Non-DOTS.

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