Safety Evaluation of Dots Therapy in Newly Diagnosed Tuberculosis Patients

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ABSTRACT
Introduction: TB is one of the top 10 causes of death worldwide. DOTS is the most effective strategy available for controlling TB. ATT has higher level of effectiveness and a lower level of toxicity, but combined treatment can cause serious adverse effects. As a result, adverse medication response must be closely monitored and effectively managed with proper counselling.

Objective: The main objective is to evaluate DOTS therapy in TB patients by monitoring ADRs during intensive phase of treatment and to analyse seriousness, predictability and preventability of ADRs in ATT with or without counselling.

Method: A case control observational study was conducted in a tertiary care hospital during six months period in which 100 samples were included. The samples were divided into test and control. Test was provided with proper counselling and both groups were analysed by Naranjo Scale and Schumock and Thornton criteria.

Result: In the total sample, 83% had ADR in which 83% was malesand 82% was females. Most of the ADR was observed in 41-60 age group. The test group had a high number of definite ADR with Naranjo scale while a least number of definitely preventable ADR.

Conclusion: Proper patient counselling was effective in detection and prevention of ADR as observed in the test group.

Keywords: ATT, ADR, Naranjo scale, Schumock and Thornton criteria, patient counselling, DOTS.

I. INTRODUCTION

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extra pulmonary TB). TB is curable and preventable.[1]

2019 marks another milestone year for TB surveillance effort in India, with a record high notification of 24 Lakh cases; an increase of over 12% as compared to 2018. Of the 24 lakh TB cases 90% (N=21.6 lakhs) were incident TB cases (New and Relapse/ Recurrent).[2] In response to the tuberculosis burden, the National Tuberculosis Program of India (NTP) was started in 1962 which was revised in 1997 as Revised National Tuberculosis Control Program (RNTCP) that used World Health Organization recommended DOTS (directly observed treatment short course chemotherapy) strategy for controlling TB.[3]

DOTS includes first-line anti-tuberculosis medicines. Because of improvements in treatment completion rates, cure rates, and rates of acquired multidrug resistant tuberculosis following introduction of the directly monitored therapy, it is the most successful technique available for managing TB.[4]

For the treatment of newly diagnosed TB patients, first-line medicines such as isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) were administered for 6-9 months. In India, anti-TB medicines were available as a single treatment regimen or as a fixed dosage combination.[5]Side effects from medications can range from moderate to severe.[6] Anti tubercular therapy (ATT) has a higher level of effectiveness and a lower level of toxicity, but combined treatment can cause serious side effects.[7]Complications might occur in any region of the body if there is a delay in presentation and poor adherence to therapy. Complications are widespread in Tb patients and are frequently the cause of morbidity and death.[8]

The WHO developed the Pharmacovigilance Program to track adverse medication reactions in the aftermath of the "Thalidomide crisis" in the 1960s.[9]Pharmacovigilance is the science of detecting, assessing, comprehending, and preventing adverse medication effects and other drug-related issues. After detection, the most important stage in the pharmacovigilance process is assessment, which may be accomplished through

causality assessment.[10]

Different algorithms exist for determining the causation of ADRs. Naranjo et.al algorithm is one of the most often utilised. It's a survey to see if an adverse reaction to a medication is truly caused by the drug rather than something else. The preventability of each ADR was classified as definitely preventable, probably preventable, or not preventable using a modified Schumock and Thornton scale. [11]

The most prevalent medicines that might induce hepatic damage are isoniazid, pyrazinamide, and rifampicin.

Anti-TB medication with pyrazinamide and ethambutol is well established to alter uric acid levels and cause polyarthralgia.

Peripheral neuropathy caused by isoniazid with ethambutol is characterised by numbness and prickling discomfort in the hands and feet. Pain, numbness, tingling, weakness, loss of muscular control, burning sensations, and loss of feeling are all symptoms of peripheral neuropathy.

Ocular toxicity is the most significant side effect of ethambutol, and it manifests itself as optic or retro-bulbar neuritis in one or both eyes.

The most common side effect observed by people using streptomycin was ototoxicity. Tinnitus, balance disturbances, ear discomfort, vertigo, and dizziness are all symptoms of ototoxicity.[4]

Objectives:
- To identify occurrence and frequency of ADRs associated with Anti-tubercular drugs
- To assess the causality and severity of ADRs occurring during DOTS therapy
- To analyze seriousness, predictability and preventability of ADRs in ATT
- To study the association of lifestyle factors such as alcohol consumption, smoking, diet, and occurrence of ADR

- To provide health education to patients taking DOTS

II. MATERIALS AND METHODS

This Case Control Observational Study was conducted for a period of six months, at Government TB & Chest Disease Hospital attached to Vijayanagara Institute of Medical Science Bellary,Karnataka,India with a sample size of 100 patients after obtaining Ethical clearance.

Inclusion criteria:
- Patients newly diagnosed with TB, undergoing ATT with first line drugs during the study period.

Exclusion criteria:
- Newly diagnosed patients of TB along with liver diseases (viral hepatitis, chronic liver failure or any other liver diseases).
- Patients taking ATT, which include medicines other than first line anti-tubercular medicines.
- Patients of age less than 20 and greater than 60 years.

Detection and monitoring of ADRs was done by direct interaction with the patients and from the case sheets by using data collection form.Samples collected were divided into two groups, test and control group in which the test group was provided with proper counselling before and after initiation of the therapy at proper time interval , specifically about ADRs . The two groups were followed up once in every week , through telephone to monitor ADRs .

Whole sample was assessed for predictability and preventability of ADRs with respect to Schumock and Thornton scale and severity of ADRs was assessed by using Naranjo Algorithm. The information obtained was analyzed and plotted on an excel sheet . Data was analyzed by using simple standard mean method and represented as percentage.

Definitely preventable
1.   Was there is history of allergy or previous reactions to the drug?
2.   Was the drug involved inappropriate for the patient's clinical conditions?
3.   Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4.   Was a toxic drug serum (or laboratory monitoring test) documented?
5.   Was there a known treatment for adverse drug reaction?
Probably preventable
6.   Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
7.   Was a drug interaction involved in the ADR?

8.	Was poor compliance involved in the ADR?
9.	Were preventive measures not prescribed or administered to the patient?
Not preventable	
	If all above criteria not fulfilled

Table 1: modified schumock and thornton scale

Sr.No:	Please answer the following questionnaire and give the pertinent score	Yes	No	Do Not Know	score
1.	Are there previous conclusive reports on this reaction?	1	0	0	
2.	Did the adverse event occur after the suspected drug was administered?	2	-1	0	
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	
4.	Did the adverse reaction reappear when the drug was readministered?	2	-1	0	
5.	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	2	0	
6.	Did the reaction reappear when a placebo was given?	-1	0	0	
7.	Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	
10.	Was the adverse event confirmed by any objective evidence?	1	0	0	
				Total	

Table 2: Naranjo algorithm

The ADR is assigned to a probability category from the total score as follows:

Definite	if the overall score is 9 or greater
Probable	for a score of 5-8
Possible	for 1-4
Doubtful	if the score is 0

III.   RESULTS
3.1 Demographic Details:
A total of 100 newly diagnosed Tubercular patients who received antitubercular drugs of age groups 20-60 years were studied in which 17 passed away during the study, and 68 were males and 32 were females.
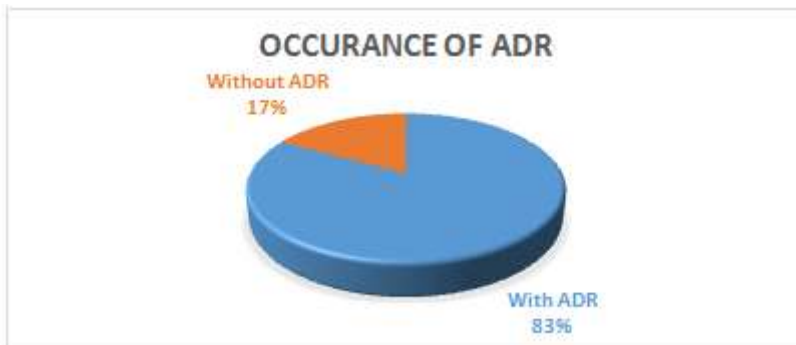
3.2 Occurance of ADR:

Figure 1: Occurance of ADR in total sample

	Male	Female
Total sample	68	32
With ADR	68.6% (57)	31.3% (26)
Without ADR	64.7% (11)	35.3% (6)

Table 3: ADR distribution among males and females

Out of total sample size 83 patients were observed with ADR after initiation of the therapy. Whereas, 17 did not had any ADR at any point of time of therapy. In the total sample size 68 were males and 32 were females. Among those 57 males were observed to develop ADR i.e., 83% of male populations. In females 26 developed with ADR, i.e., 82%, correspondent with males.

	Age groups	
	20-40	41-60
Total sample	43	57
With ADR	44.6% (37)	55.4% (46)
Without ADR	35.3% (6)	64.7% (11)
Males with ADR	31.4% (26)	37.3% (31)
Females with ADR	13.2% (11)	18.1% (15)

Table 4: ADR distribution among different age groups

Within 100 sample size, 43 were of age group 20-40 and rest 57 were of 41-60. Therein, 87% of the first age group, i.e., 37 samples and 80% of the second age group, i.e., 46 samples had ADR.

67% of samples in the starter age group were males out of which 90% of population generated with ADR. Whereas later age group has 70% of males and 79% of them generated with ADR.

Even though first and second age groups had only 33% and 30% of female populations respectively the percentage of female populations affected with ADRs were 80 and 83%.
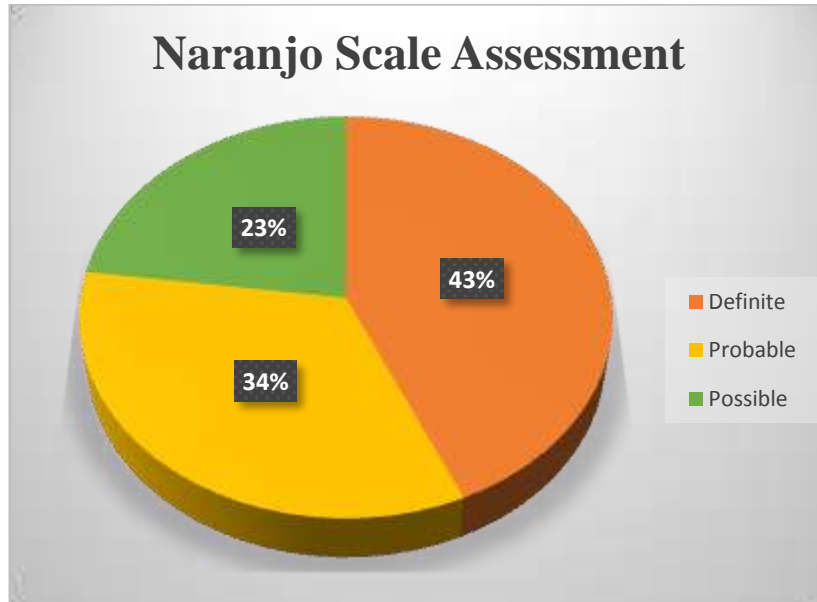
3.4 Naranjoscale Assessment:

Figure 2: Causality assessment with Naranjo's algorithm

The total number of ADRs reported during the study period was 83. Among this 36 were definite, 28 were probable, and 19 were possible.

The reason for considering Naranjo Scale was to assess whether there is a casual relationship between the identified untoward clinical event and the drugs used for ATT regimen.
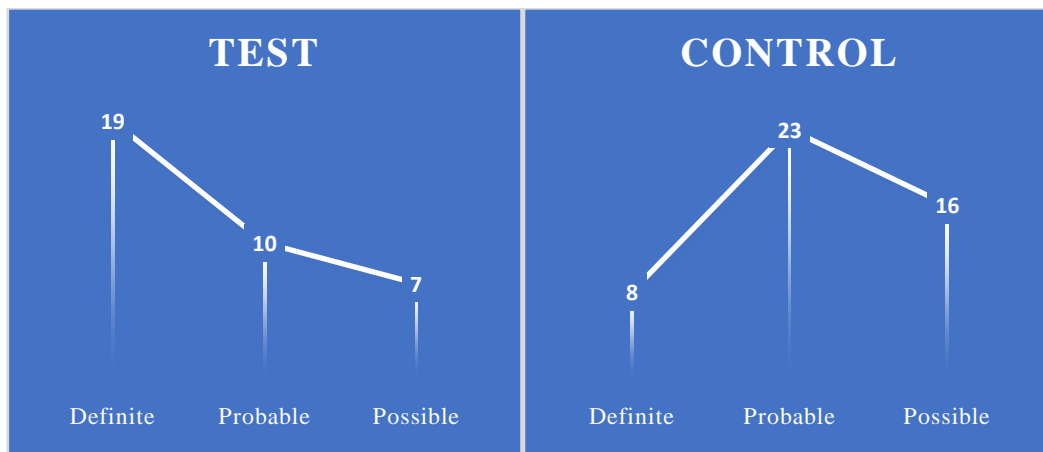

Figure 3: Causality assessment for test and control groups with Naranjo algorithm

The total sample was divided into test and control. In which, test was provided with proper counselling. The test group had 19 definite, 10 probable, and 7 possible ADRs. Whereas control group had 8 definite, 23probable, and 16 possible ADR.

3.5 Preventability assessment with Schumock and Thornton scale:

Scale	Control	Test
Definitely preventable	23	05
Probably preventable	13	10
Not preventable	11	21

Table 5: Preventability assessment with Schumock and Thornton scale for test and control group

ADRs were categorized into definitely preventable, probably preventable, and not preventable to assess preventability based on Schumock and Thornton scale.

In each category, number of ADR reports belonged were 23, 13 and 11respectively in control group and 5,10 and 21 respectively in test group.
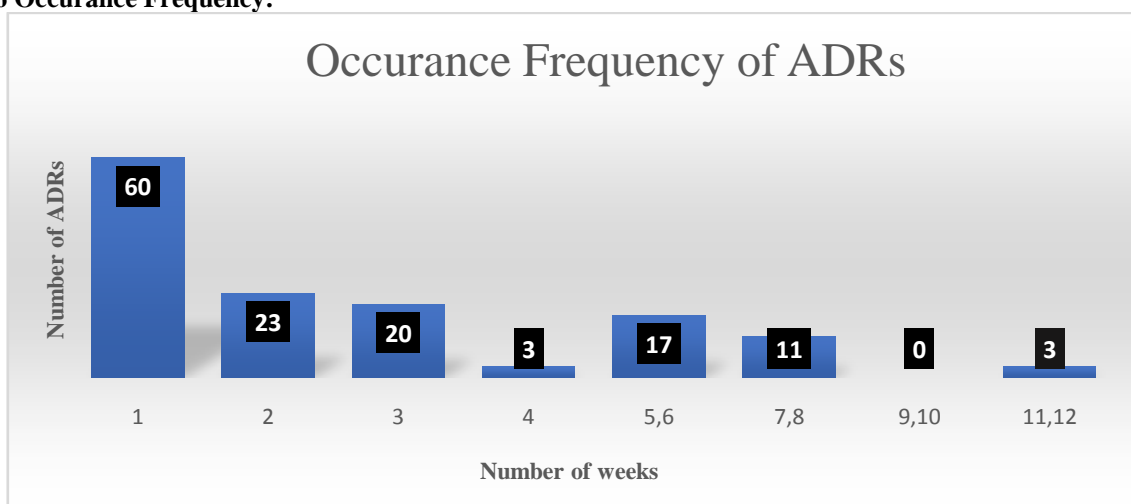
3.6 Occurance Frequency:

Figure 4: Occurance of ADRs during intensive phase of treatment

The samples were followed up each week with proper counselling to each patient. Information was gathered regarding ADRs with simple reference to signs and symptoms.

During first week, the highest number in complaint of ADR were received, i.e., 60 followed by second and third week as 23 and 20 respectively.

A gradual decrease in ADRs was seen. But a drastic change was observed in week 4. When it dropped to 3 cases from 20 on previous week and then raised to 17 on next week.

3.7 Lifestyle Factors and occurrence of ADRs:

In the total sample, 29 were alcoholic and 26 were smokers. All the smokers and alcoholic were observed with at least one ADR.Also, none of the non-smokers and non-alcoholic had any ADR.

IV. DISCUSSION

In our study, it was noted that out of 100 patients studied, 83% developed one or more ADRs. In studies conducted by Anupa Khatri Chhetri et al., in 2008 from nepal and Arjun H et al., the occurance of ADRs were 54.74% and 58% respectively.

In the total no. Of ADRs observed, 57 were males (69%) and 26 females (31%) which was found similar to the study conducted by Athira B et al., where more no. Of ADRs were observed in males (68.81%). We also found that among the total males (68), 83% and from the total females (32), 82% were with ADR. Hence it indicated the occurance of ADRs in males and females were found to be identical.

In the present study, more no. Of ADRs were observed during the first week of ATT which was similar to the study of Arjun H et al., where more no. Of ADRs were observed within 7days

after start of ATT. A gradual decrease was seen over consecutive weeks and a steep dip was observed in the 4th week.

We observed that majority of the ADRs (55%) were reported by the age group 41-60 years in both sex (31% males and 15% females) was similar to a study by Arjun H et al., were the incidence was high in the same age group due to ATT, while contradict to Kumarjit Sinha et al., as in his study less no.of ADRs were observed in this age group.

Maximum number Of ADRs were observed in males of age group 41-60 (37.3%) whereas minimum was observed in females of age group 20-40 (13.2%).

Causality assessment using standard method is probably the best way to establish the casual relationship between a drug and its identified untoward clinical event. The Naranjo algorithm is used widely in causality assessment of ADRs. It is based on score calculated on the basis of points assigned to each of the ten questions. As per Naranjo scale, majority of the reactions were definite. Out of 100 samples, 36 were definite, 28 were probable and 19 were possible. The total samples divided into test and control, in which test provided with proper counselling. The test group had 19 (53%) definite, 10(36%) probable, 7 (37%) possible, whereas control group had 8 (22%) definite, 23 (82%) probable and 16 (84%) possible ADRs.TejasA.Acharya et al., conducted a study, which had probable reaction the most. The difference observed may due to proper counselling.

Preventability was assessed based on Schumock and Thornton scale, ADRs were categorised in to definitely preventable, probably preventable or not preventable. In our study, 23 (82%) were definitely preventable, 13 (57%) were probably preventable, 11 (34%) were not preventable in control and in test 5 (18%) were definitely preventable, 10 (43%) were porbably preventable, 21 (67%) were not preventable. In JihanaShajahan et al., 0.3% were definitely preventable, 18% were probably preventable and 81.7% not preventable respectively and also supported the same findings.

The prevalance of ADRs among the population with varying life style factors like smokers, non smokers, alcoholics, non alcoholics. In our total samples of 100, 29 were alcoholics and 26 were smokers. All the smokers and alcoholics were observed with atleast one ADR which is in contradiction to Anupa Khatri Chhetri et al., as in her study most of the ADRs were observed in non smokers and non alcoholics.

V. CONCLUSIONS

The study was conducted to evaluate the safety of DOTS therapy in the patients during intensive phase of treatment. By providing proper counselling to the test group, the occurance of ADRs were preventable on the basis of schumock and thornton scale. Occurance of ADRs were found to be high during the initial weeks of ATT, as per the hypothesis since the patient's body was getting adjusted with the treatment. Hence, as an outcome of counselling, patients were able to answer questionnaire more specifically and number of definite ADRs were more in test group on the basis of Naranjo's algorithm. Also it is concluded that ADRs are triggered by life style factors such as smoking and alcohol cosumption.

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