INITIAL DRUG RESISTANCE AMONG TUBERCULOSIS PATIENTS IN SHRI KRISHNA MEDICAL COLLEGE, MUZAFFARPUR, BIHAR

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ABSTRACT

BACKGROUND

Tuberculosis is an infectious disease which is prevalent worldwide, especially in developing nations and shows difficulty in elimination of disease due to resistant strains. So, there is a need of better and more effective control programs for tuberculosis patients and periodical survey for drug resistance patterns to formulate better treatment regimen and to make national tuberculosis program more strong and effective.

MATERIALS AND METHODS

A Prospective study has been conducted on 700 newly detected smear-positive TB patients who initiate receiving anti Tubercular drugs and had no history of previous anti tuberculosis treatment from April 2015 to April 2016. Sputum for AFB was done to detect the infection and Gene expert method and culture & sensitivity method done for detection of drug resistance of Isoniazid, Rifampicin, Ethambutol, Pyrazinamide & Streptomycin.

RESULTS

Out of 700 smear positive patients 628 patients were found culture positive and of them 560 were sensitive to all drugs, 48 patients shown resistance (7.8947%). Most common drug showing resistance is Rifampicin (3.94%) then Isoniazid (2.3%). Resistant pattern more for females, illiterate persons, married persons, rural patients with mean age 40.1 years, median age 38.5 years, S.D. 18.7, p-value 0.024112215.

CONCLUSION

In our study more resistant pattern seen for Rifampicin, which is more in married, illiterates, rural, female patients. So, a periodical assessment of the prevalence of drug resistance pattern is very essential not only to know the effectiveness of the program but also to plan suitable regimens in areas of high prevalence.

KEYWORDS

AcDRS-Acquired Drug Resistance, DOTS- Directly Observed Therapy Short Course, IDR-Initial Drug Resistance, SKMCH-Shri Krishna Medical College and Hospital.

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BACKGROUND

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis & it becomes the second leading infectious Cause of death in the world after HIV-AIDS. Drug resistant Tuberculosis has become a worldwide threat and constitute a challenge for disease control. In 2008 WHO estimated more than 4,40,000 individuals had Multidrug resistant (MDR) TB worldwide. Such patients are drugs. MDR patients constituted 3.6% of all TB patients registered globally.[1] and almost 50% of MDR TB cases are estimated to occur in China and India.[2] In 2015, 4,80,000 new MDR TB cases estimated.

The tuberculosis program in India, till 1993, had short course chemotherapy regimen, given under unsupervised conditions.[3] and the performance of program in terms of success rate was poor. This together with the easy availability and the haphazard use of Rifampicin, both in public and private sectors from mid-eighties had created the fear of increasing level of acquired drug resistance (AcDR), particularly the multi-drug resistance tuberculosis (MDR TB).[4] AcDR is bound to influence the level of initial drug

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resistance (IDR) in the community.[5] There has been increased awareness that drug resistant TB poses a major threat to the patients as well as to the TB Control Program. The frequency of IDR, especially MDR TB, varies from place to place and is found to be generally low, even in high prevalence countries such as Malawi.[6] Tanzania.[7] and China.[8] where DOTS strategy is implemented. In contrast, a poor or suboptimal tuberculosis control program can lead to a rapid emergence of drug resistance, especially in the area with high prevalence of TB.[5]

In India, Revised National Tuberculosis Control Program (RNTCP) based on DOTS strategy had shown a success rate of 82.0% among newly diagnosed smear positive patients evaluated from 1993 to 1998.[3] In contrast, the cure rate was 40.3% among patients treated with unsupervised SCC (Short course chemotherapy) regimen during the year 1999.[9] Efficiency of the treatment program determines the level of AcDR (Acquired drug resistance).[10] Due to continued transmission of infection with resistant bacilli, AcDR leads to increase in the levels of IDR (Initial drug resistance), which in turn may cause increase in treatment failure cases, thereby decreasing the success rate of the existing program. The level of initial drug resistance and its trend is a sensitive indicator of the program efficiency and provides indirect reflection of the quality of tuberculosis services in the area. The level of IDR would serve as useful information to assess the impact of DOTS strategy on the levels of IDR subsequently.

Aims and Objective of Study

- To study the proportion of initial drug resistance (IDR) among urban & rural patients attending DOTS.
- To specifically investigate the extent of resistance to Rifampicin and INH (Isoniazid), which could have an impact on the success of SCC (Short Course Chemotherapy).

MATERIALS AND METHODS

The patients are selected from Department of Medicine & paediatrics as well as Department of TB & chest including DOTS Centre and who were newly detected smear-positive pulmonary tuberculosis and initiate receiving anti tubercular drugs and had no history of previous anti tuberculosis treatment.

Patients suspected of having Tuberculosis detected by

1> X-ray chest.

2> Sputum smear examination one spot and other next day morning by Centre staff.

Smear microscopy examination was carried out with Ziehl-Neelsen technique and smear grading was as per RNTCP guidelines. Isolation of mycobacteria was done using Lowenstein Jensen (LJ) media, smear positive patients are treated with CAT-I RNTCP regimen.

A Prospective study was conducted and patients taken for study from April 2015 to April 2016 and reviewed for initial 2 months of treatment for improvement of symptoms i.e., till June 2016. If patients show no improvement in their condition even after 2 month of treatment they are suspected for resistance pattern .One sputum specimen was collected from each patient, and sent on the same day to laboratory for culture of M. tuberculosis.

All sputum collected were subjected to the following-

1. Smear for AFB by microscopy.
2. Gene Xpert method to detect resistant pattern of Rifampicin.
3. Culture for mycobacteria.
4. Sensitivity to Isoniazid, Rifampicin, Ethambutol, pyrazinamide and Streptomycin.

The criterion used for declaring a strain as resistant was: growth of >20 colonies at the following concentrations:-
Isoniazid: MIC of > 1 /µg/ml.
Rifampicin: MIC of >64/µg/ml.
Ethambutol: MIC of >8/µg/ml.
Pyrazinamide: MIC of >100 mg/dl.
Streptomycin: Resistance Ratio of >8.

Complete patient history has to be obtained to distinguish IDR from AcDR. Drug susceptibility testing should be in accordance with international standards with an ongoing internal quality control and external quality assessment. The socio-demographic variables considered for analysis to compare the resistant and susceptible groups were age, sex, literacy, marital status, employment and history of contact.

Study Groups

1. Sputum positive patients on CAT-I Anti tubercular regimen who developed Initial drug resistance after prospective study.
2. Sputum positive patients on CAT-I Anti tubercular regimen who developed Initial drug resistance and documented early in journals and from review of books and literature.

Inclusion Criteria

Any patients of any age group and any ethnicity, any sex who are sputum positive and on CAT-I Anti tubercular treatment from Department of Medicine, Department of Paediatrics or DOTS centre in SKMCH, Muzaffarpur, Bihar.

Exclusion Criteria

1. Any Patients on Anti Tubercular regimen but sputum negative cases,
2. Any patients on Anti Tubercular regimen but other than CAT-I cases
3. Culture negative or contaminated cases.

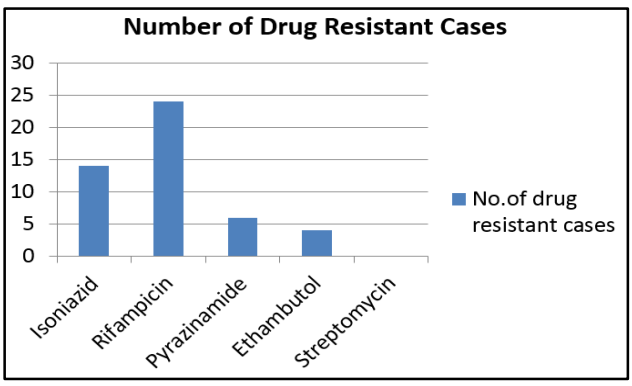
RESULTS AND ANALYSIS

A total of 800 patients taken CAT-I treatment from April 2015 to April 2016, out of which 700 patients are sputum smear positive pulmonary cases and 100 negative cases .All these cases are registered as new cases. Out of 700 patients 628 patients are culture positive and 72 are either culture

negative or contaminated cases. On further interrogation, it was found that 20 patients had previous history of anti-TB treatment of >4 weeks and had been wrongly classified as 'new smear positive'. The remaining 608 patients correctly identified as "new", formed the study group. Among these 608 patients, 560 patients were susceptible to all drugs and 48 patients showed resistance to anti tubercular drugs.

Any drug#	Number	Percentage
H	14	2.3
R	24	3.95
S	0	0
E	4	0.66
Z	6	0.97
One Drug+		
H	2	0.33
R	15	2.47
S	0	0
E	1	0.164
Z	1	0.164
Two drugs+		
HR	5	0.82
HE	1	0.164
HZ	2	0.33
Three drugs+		
HRZ	2	0.33
HRE	1	0.164
HRZE	1	0.164
Any drug	48	7.8947

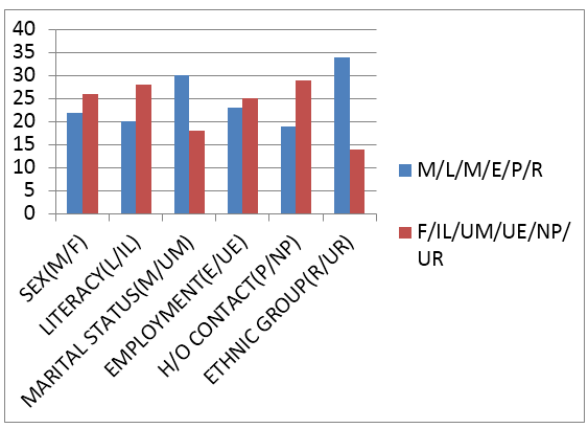
Table 1. Resistant Drugs- Resistance Pattern in New Culture Positive Cases (N=608)



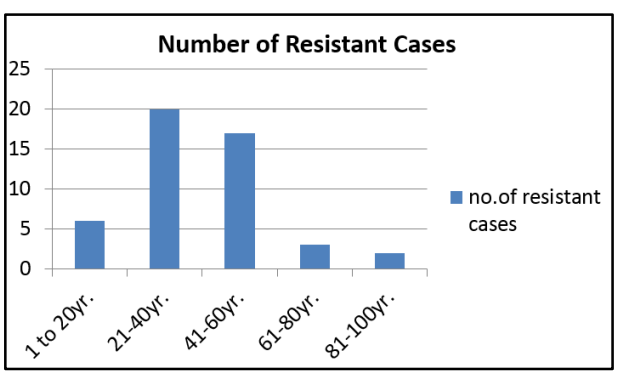
Graph 1. Number of Drug Resistant Cases

Characteristics Sex	Total Number of Patient	Resistant to Any Drug
Male	378	22 (5.8%)
Female	230	26 (11.3%)
Literacy		
Illiterate	200	28 (14%)
Literate	408	20 (4.9%)
Marital status		
Married	338	30 (8.87%)
Unmarried	270	18 (6.67%)
Employment		
Employed	318	23 (7.23%)
Unemployed	290	25 (8.62%)
History of contact		
Present	200	19 (9.5%)
Absent	408	29 (7.17%)
Ethnic Group		
Rural	400	34(8.5%)
Urban	208	14 (6.7%)

Table 2. General Characteristics of New Culture Positive Cases



Graph 2. Showing Relation of Different Factors with Resistance of Drugs



Graph 3. Number of Resistant Cases

Age in Years	Modified Age	Xi	di= (Xi-A)/h	fi	cf	fidi	fidi2
1-20	0.5-20.5	10.5	-2	6	6	-12	24
21-40	20.5-40.5	30.5	-1	20	26	-20	20
41-60	40.5-60.5	50.5=A	0	17	43	0	0
61-80	60.5-80.5	70.5	1	3	46	3	3
81-100	80.5-100.5	90.5	2	2	48	4	8
				N=∑fi= 48		∑fidi= -25	∑fidi2= 55

Table 3. Age Group Characteristic of Resistance

Here,
Xi= Mid point of class, di=deviation, A=Assume mean, h=class size, N=total number, Fi=frequency, cf= cumulative frequency.

Now,

Mean X = A +∑fidi×h /N=50.5+(-25)×20/48= 50.5-10.4=40.1 years

Varince (σ2) = h2/N2[N.∑fidi2-(∑fidi)2]=20×20/(48×48)[48×55-(-25)2]=

400/2304[2640-625] = (400/2304) × 2015=349.82

Now,

Standard Deviation (S.D.) = √σ2=√349.82=18.70

Now,

Median M=L+ (N/2-cf) × h/f

Where,

Median class=Where cf is Just above N/2 =48/2=24 i.e, 20.5- 40.5

L=lower limit of class, f = frequency, Cf=cumulative frequency of class just before median class, h=class interval=20

So, L=20.5, N/2=48/2=24, c=6, f=20.

So, M= 20.5+ (24-6) ×20/20=20.5+18 =38.5 year.

P-value =.024112215

DISCUSSION

Drug resistance in mycobacteria is defined as a decrease in sensitivity to a sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never come in contact with the drugs.[11]

Types of Drug Resistance

Drug resistance in TB may be broadly classified as primary or acquired. When drug resistance is demonstrated in a patient who has never received anti- TB treatment previously, it is termed primary resistance. Acquired resistance is that which occurs as a result of specific previous treatment. The level of primary resistance in the community is considered to reflect the efficacy of control measures in the past, while the level of acquired resistance is a measure of on-going TB control measures. However, the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Diseases (IUATLD), in the light of discussions in several international fora, have replaced the term primary resistance by the term "drug resistance among new cases" and acquired resistance by the term "drug resistance among previously treated cases.

The current study was undertaken to assess the level of IDR in Smear positive tuberculosis patient on CAT-I treatment. The history of treatment was elicited meticulously by using the pre-tested questionnaire adopted from WHO.[10,12] This resulted in exclusion of 20 patients who wrongly classified as 'new' and hence, the drug resistance identified in this study could be termed as Primary Drug Resistance.

Studies conducted by Tuberculosis Research Centre (TRC), Chennai from 1956 to 1997 have clearly shown a gradual increase in the prevalence of resistance to H, S and SH.[8] Resistance to R started appearing in 1990s and had remained at almost 1%.

The IDR has been reported from Bangalore in the studies done in 1980.[13] and 1985– 86.[14] by NTI (National Tuberculosis institute) (5.7% and 4.8% respectively). The results did not differ much in these two studies, probably because of the short interval between the two studies.

In our present study Rifampicin resistant cases are more while most of the study shows more resistance in Isoniazid, it may be due to two reasons

1 > Use of Rifampicin has increased in treatment of other cases as for Gut sterilization and in treatment of leprosy.

2 > We use gene expert method to detect resistance firstly which detect Rifampicin resistance.

A total of 48 cases are detected to show resistance out of 608 cases i.e the percentage of patient showing resistance is 7.8947% out of which 3.95% of Rifampicin and 2.303% of Isoniazid.

CONCLUSION

A prospective study has been carried out in Medicine Department, Paediatric department and Department of TB and Chest including DOTS Centre in Shri Krishna Medical College, Muzaffarpur, Bihar from April 2015 to April 2016 and following conclusions derived from the study-

- Most common drug affected from resistance is Rifampicin then Isoniazid.
- Females are affected more in comparison to male for resistant cases while tuberculosis is more prevalent in males.
- Illiterate persons are affected more as compared to literates.
- Resistant cases are more in married persons as compared to unmarried.
- Statistical data of affected persons
  1> Mean age =40.1 years
  2> Standard deviation = 18.7
  3> p-value =0.024112215
  4> Median age = 38.5 years
- A total of 48 cases are detected to show resistance out of 608 cases i.e. the percentage of patient showing resistance is 7.8947% out of which 3.95% of Rifampicin and 2.303% of Isoniazid.
- Rural population is affected more in comparison to Urban both for prevalence of Tuberculosis as well as anti Tubercular drug resistance.

Ethical Consideration

Ethically approved by Institutional ethical committee.

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