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Effect of Different Types of Drugs in Tuberculosis

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ABSTRACT: Tuberculosis (TB) remains an important infectious disease and public health concern worldwide. This disease is caused by the bacteriaMycobacterium tuberculosis. This bacterium are slender bacilli that sometimes show branching filamentous forms resembling fungal mycelium. Hence the name "mycobacteria" meaning fungus like bacteria. Tuberculosis is a treatable, communicable disease that has two general states - latent infection and active disease. In MDR-TB, organisms are resistant to 2 key drugs – Rifampicin and Isoniazid (drugs in the treatment of TB). Since 2006, It has been recognized the presence of more resistant strains of M. tuberculosis labelled as extensively drug resistant (XDR-TB). DOTS- plus for MDR-TB is a comprehensive management initiate built upon 5 elements of DOTS Strategy. There are many ways to detect the patient for tuberculosis. They are as follows: -Chest x-ray, Acid-fast stain and culture, Tuberculin skin test (TST) or interferon-gamma release assay (IGRA), When available nucleic acid–based testing. Drug susceptibility tests (DSTs), should be done on initial isolates from all patients to identify an effective anti-TB regimen. Rifampicin drug is mother drug of tuberculosis. It is more effective and more curable for the tuberculosis patient.

I. INTRODUCTION

Tuberculosis (TB) remains an important infectious disease and public health concern worldwide. This disease caused by the bacteria: -Mycobacteriumtuberculosis. This bacterium are slender bacilli that sometimes show branching filamentous forms resembling fungal mycelium. Hence the name "mycobacteria" meaning fungus like bacteria. Tuberculosis is a treatable, communicable disease that has two general states: -latent infection andactive disease. With few exceptions, only those who develop active tuberculosis in the lungs or larynx can infect others, usually by coughing, sneezing, or otherwise expelling tiny infectious particles that someone else inhales. Usually affects the lungs, but it can also affect the brain, kidney, spine. The disease is usually chronic with varying clinical manifestations. The disease also affects animals like cattle, this is known as "bovine tuberculosis" which may sometimes be communicated to man. "Pulmonary tuberculosis," the most important form of tuberculosis which affects man.

According to WHO report every year there are 9 million people suffer from this disease and 2 million people die. In 2015, there were a 350,000 case of MDR-TB and 140,000 deaths due to this. DOTS remain central to the public health approach to tuberculosis control which is now presented as stop TB strategy. The advantages of DOTS are: - a) accuracy of TB is more than doubled b) treatment success rate is up to 95 percent c) prevent failure of treatment and the emergence of MDR-TB by ensuring patient adherence and uninterrupted drug supply.

Drug resistant tuberculosis is the major problem in controlling tuberculosis. People who have been in faced with drug resistant strains need 2 years of treatment instead of 6 months. In MDR-TB, organisms are resistant to 2 key drugs – Rifampicin and Isoniazid (drugs in the treatment of TB). Since 2006, It has been recognized the presence of more resistant strains of M. tuberculosis labelled as extensively drug resistant (XDR-TB). This strains in addition to being MDR are also resistant to any fluoroquinolone and at least one of the injectable second line drugs -kanamycin,capreomycin or amikacin. More recently a worrying situation has emerged with the M. tuberculosis strains that have been found resistant to all antibiotics that are available for testing this situation labelled as totally drug resistant (TDR-TB).

Drug resistance can be detected using special laboratory tests which test the bacteria for sensitivity to the drugs or detect resistance pattern. These tests can be molecular in type (such as expert MTB/RIF) or else culture based. Molecular

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technique can provide results within hours and have been successfully implemented even in low resource settings. DOTS- plus for MDR-TB is a comprehensive management initiate built upon 5 elements of DOTS Strategy. The goal of DOTS-plus is to prevent further development and spread of MDR-TB.

Early detection of all forms of drug resistant in TB is a key factor to reduce and contain the spread of these resistant strains. But people with this disease can die if they do not get proper treatment and proper drugs. The WHO has launched global plan for stop TB strategy (2006-2015), with the objective of reducing incidence of tuberculosis.

II. AIM AND OBJECTIVES

The aim of the study is:

- Evaluating the effect of different types of drug for tuberculosis.
- To examine the effectiveness of drug against TB patient.
- To prevent the development of acquired drug resistance.
- Minimize risk of death and disability.

III. MATERIALS AND METHODS

Equipment:

- Slide
- Acid fast stain
- Burner
- Disc
- Swab
- Scale
- gloves
- Specimen collection: -For diagnostic purposes, all persons suspected of having TB disease at any site should have sputum specimens collected for an AFB smear, culture, and antibiotic susceptibility test. At least three consecutive sputum specimens are needed, each collected in 8- to 24-hour intervals, with at least one being an early morning specimen.
- **Staining: - (acid fast staining): -**
  - Prepare bacterial smear on clean and grease free slide, using sterile technique.
  - Allow smear to air dry and then heat fix.

Alcohol-fixation: This is recommended when the smear has not been prepared from sodium hypochlorite (bleach) treated sputum and will not be stained immediately. M. tuberculosis is killed by bleach and during the staining process. Heat-fixation of untreated sputum will not kill M. tuberculosis whereas alcohol-fixation is bactericidal.

- Cover the smear with carbolfuchsin stain.
- Then Heat the stain until vapour just begins to rise. Do not overheat. Allow the heated stain to remain on the slide for 5 minutes.

Heating the stain: Great care must be taken when heating the carbolfuchsin especially if staining is carried out over a tray or other container in which highly flammable chemicals have collected from previous staining. Only a small flame should be applied under the slides using an ignited swab previously dampened with a few drops of acid alcohol or 70% ethanol or methanol.

- Wash off the stain with clean water.
- Cover the smear with 3% v/v acid alcohol for 5 minutes or until the smear is sufficiently decolorized. i.e. pale pink.
- Wash well with clean water.
- Cover the smear with malachite green stain for 1–2 minutes, using the longer time when the smear is thin.
- Wash off the stain with clean water.
- Wipe the back of the slide clean, and place it in a draining rack for the smear to air-dry (do not blot dry).
- Examine the smear microscopically, using the 100 X oil immersion objective.

When acid-fast bacilli are seen in a smear, they are counted. According to the number of acid-fast bacilli seen, the smears are classified as 4+, 3+, 2+, or 1+. The greater the number, the more infectious the patient.

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➢Disc diffusion method: -

•Principle of the method:

The media used in this test has to be the MuellerHinton (15x150mm) agar because it is an agar that is thoroughly tested for its composition and its pH level. Also, using this agar ensures that zones of inhibitions can be reproduced from the same organism, and this agar does not inhibit sulphonamides. The agar itself must also only be 4mm deep. This further ensures standardization and reproducibility.

The size of the inoculated organism must also be standardized (using the McFarland 0.5 Latex standard with the Wickersham Card. The reasons are because if the size of the inoculum is too small, the zone of inhibition will be larger than what it is supposed to be ("the antibiotics will have a distinct advantage") and if the inoculum is too large, the zone of inhibition will be smaller.

A. Procedure:

➢Preparation of Bacterial Suspension

- Remove a Hardy Diagnostic Saline 0.85%, 1.8mL tube from the box, label with the patient name and place in a test tube rack.
- Using a 1ul loop, pick several isolated mycobacterium colonies from the agar surface.
- Immerse the loop in a labelled saline tube.
- Using a Wickersham Card and a vortexed McFarland Latex 0.5 standard, compare the turbidity of the inoculated saline tube with the Standard. If the turbidity is comparable, proceed with the inoculation of the Mueller Hinton Plate. If not, adjust the turbidity by adding more isolated colonies in the same manner if the turbidity is less than the standard or more saline if the turbidity is greater. Once the turbidity is comparable to the standard, proceed with the inoculation of the labelled Mueller Hinton plate.
- The bacterial suspension should be used within 6 h of preparation. If not used immediately after preparation, shake vigorously to resuspend the bacteria just prior to use.

B. Inoculation of Mueller Hinton Agar

- Allow plates to come to room temperature before use.
- Dip a sterile cotton swab into the bacterial suspension. To remove excess liquid, rotate the swab several times with a firm pressure on the inside wall of the tube above the fluid level.
- Using the swab, streak theMueller-Hinton agarplate to form a bacterial lawn.
- To obtain uniform growth, streak the plate with the swab in one direction, rotate the plate 90° and streak the plate again in that direction.
- Repeat this rotation 3 times.
- Allow the plate to dry for approximately 5 minutes.
- Use an Antibiotic Disc Dispenser to dispense disks containing specific antibiotics onto the plate.

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- Using sterile sticks or loops, gently press each disc to the agar to ensure that the disc is attached to the agar.
- Plates should be incubated overnight at anincubationtemperature of 37°C.

C. Reading and Interpreting Zone Sizes

After overnight incubation measure the zone sizes (area of no growth around the disk) in millimetres using a ruler or template.

Enter the zone sizes into the Kirby Bauer sensitivities log along with the patient's information.

Interpret the results as Resistant, Intermediate or Sensitive for each antimicrobial according to the ranges listed on the log for Enteric gram-negative rods.

IV. RESULT AND ANALYSIS

Tabular representation of different parameters of effect of different drugs in tuberculosis: -

Sl.no.	Patient ID	Age	sex	test	stain	HIV status	Diabetes status	Zone of inhibition in rifampicin	zone of inhibition in isoniazid
01	100	36 yrs.	M	1+	Zn	NR	N	2.1	1
02	101	46 yrs.	M	1+	Zn	NR	N	2.5	4
03	102	26 yrs.	F	2+	Zn	NR	D	3.5	2
04	103	24 yrs.	M	1+	Zn	NR	N	4	3.6
05	104	32 yrs.	F	2+	Zn	NR	N	5.1	0

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06	105	45 yrs.	F	1+	Zn	NR	N	1.4	5
07	106	56 yrs.	M	1+	Zn	NR	N	2	3.6
08	107	25 yrs.	M	1+	Zn	NR	N	1.5	4.5
09	108	36 yrs.	M	2+	Zn	NR	N	2.6	5
10	109	48 yrs.	F	2+	Zn	NR	N	3.2	2.1
11	110	55 yrs.	F	1+	Zn	NR	N	3.3	2.13
12	111	42 yrs.	F	1+	Zn	NR	D	2.8	0
13	112	30 yrs.	M	1+	Zn	NR	N	3.5	2.1
14	113	18 yrs.	F	1+	Zn	NR	N	7	3
15	114	46 yrs.	M	1+	Zn	P	N	6.3	1.3
16	115	40 yrs.	F	2+	Zn	NR	N	4	2
17	116	50 yrs.	F	1+	Zn	NR	N	5.1	0.8
18	117	22 yrs.	M	1+	Zn	NR	N	3.1	0
19	118	36 yrs.	F	1+	Zn	NR	D	4	3.1
20	119	47 yrs.	F	2+	Zn	NR	N	4.3	0
21	120	29 yrs.	M	1+	Zn	NR	N	3.6	5
22	121	30 yrs.	F	1+	Zn	NR	N	2.6	2
23	122	52 yrs.	F	1+	Zn	NR	D	4.11	1.3
24	123	54 yrs.	F	1+	Zn	NR	N	5	2

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25	124	44 yrs.	M	1+	Zn	NR	N	6	1
26	125	32 yrs.	M	2+	Zn	NR	N	2.5	4
27	126	52 yrs.	F	2+	Zn	NR	N	3.9	1.2
28	127	50 yrs.	F	1+	Zn	NR	D	6.5	1
29	128	31 yrs.	M	2+	Zn	NR	N	2.2	0
30	129	27 yrs.	F	1+	Zn	NR	N	0	1.29
31	130	29 yrs.	M	2+	Zn	NR	N	4.1	2.64
32	131	39 yrs.	M	2+	Zn	NR	N	3.44	0
33	132	20 yrs.	F	1+	Zn	NR	D	2.22	6
34	133	45 yrs.	M	1+	Zn	P	N	3.4	5
35	134	41 yrs.	F	1+	Zn	NR	N	4.7	1.1
36	135	50 yrs.	M	1+	Zn	NR	N	5.3	1
37	136	28 yrs.	F	1+	Zn	NR	N	7.12	3
38	137	46 yrs.	M	1+	Zn	NR	N	3.5	0.3
39	138	37 yrs.	M	2+	Zn	NR	D	6.5	0.6
40	139	56 yrs.	F	3+	Zn	NR	N	6.8	2.1
41	140	51 yrs.	M	1+	Zn	NR	N	5.9	1.2
42	141	33 yrs.	F	1+	Zn	NR	N	0	1.48
43	142	40 yrs.	F	1+	Zn	NR	D	7.54	2

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44	143	48 yrs.	M	1+	Zn	NR	N	2.2	3.22
45	144	38 yrs.	M	1+	Zn	NR	N	6.5	2.1
46	145	36 yrs.	F	2+	Zn	NR	N	0	0
47	146	46 yrs.	M	2+	Zn	NR	N	7.9	1
48	147	39 yrs.	M	1+	Zn	NR	N	7.5	2.1
49	148	32 yrs.	F	2+	Zn	NR	N	6.4	3.1
50	149	23 yrs.	M	1+	Zn	NR	D	6.7	5
51	150	55 yrs.	F	1+	Zn	NR	N	3.5	2
52	151	30 yrs.	M	1+	Zn	NR	N	6.2	1.1
53	152	19 yrs.	M	1+	Zn	NR	N	2.9	0
54	153	24 yrs.	M	1+	Zn	NR	N	3.1	7
55	154	50 yrs.	M	1+	Zn	NR	N	2.1	7.8
56	155	40 yrs.	M	2+	Zn	NR	N	3.6	0.3
57	156	42 yrs.	M	2+	Zn	NR	D	3	1.5
58	157	38 yrs.	M	2+	Zn	NR	N	4.2	3
59	158	47 yrs.	M	1+	Zn	NR	N	3.1	1
60	159	40 yrs.	M	1+	Zn	NR	N	5	4.1
61	160	55 yrs.	M	2+	Zn	NR	D	2.5	2
62	161	36 yrs.	M	1+	Zn	NR	N	3.1	3

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63	162	39 yrs.	M	1+	Zn	NR	N	4.8	3.6
64	163	36 yrs.	M	1+	Zn	NR	N	5.4	1
65	164	51 yrs.	M	1+	Zn	NR	N	5.8	7
66	165	36 yrs.	M	2+	Zn	NR	N	3.1	5
67	166	26 yrs.	M	2+	Zn	NR	N	2.6	6

ANALYSIS OF DATA

The calculated data was analysed by the mean value, standard deviation, standard error and T-test with the help of computer package.

❖**Mean: -**

Mean is the arithmetic average of the observed scores. The Sample mean is representing by the symbol X, where X represent each individual score of samples, LX is the sum of all scores and n is the sample size or the total frequency of cases in the sample.

❖**Standard Deviation: -**

Standard Deviation (SD) is the positive square root of the mean of squared deviation of all the scores from the mean. It is an absolute measure of deviation and is expressed in the same unit as the original scores.

❖**Standard Error: -**

Standard Error (SE)of a statistic is a measure of the deviation of that statistic from the corresponding parameter and consequently serves as an index of the sampling error of that statistic. It is the standard deviation of the sampling distribution of the relevant statistics.

❖**T-test: -**

To test the significance of the different between the means of two small samples that difference ($X_1 - X_2$) is converted to student's t-score which is then interpreted with reference to the appropriate t-distribution.

TABLE NO.-1

RIFAMPICIN DRUG	SEX	NOOF PATIENT	MEAN
	Male	40	4.1685 (59%)
	female	27	2.9473 (41%)
	Total	67	7.11580 (100%)

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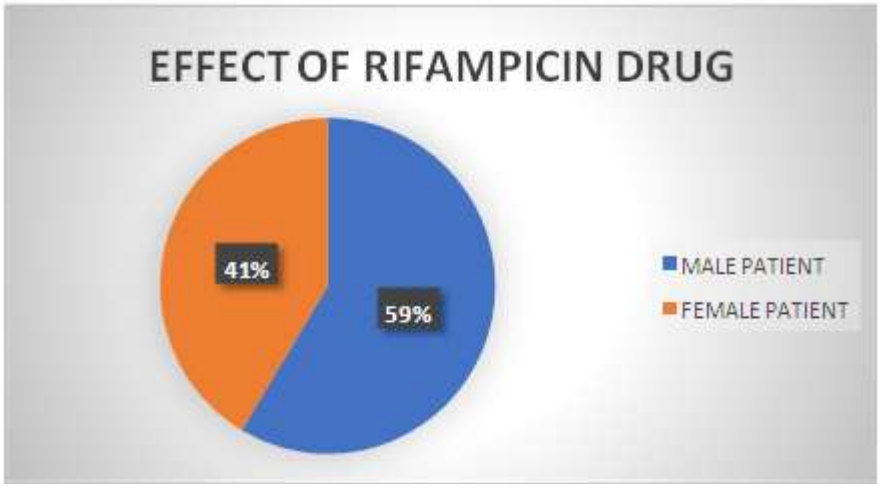

Fig: - comparative study of effect of rifampicin drug in male and female between the mean

TABLE NO: - 2

ISONIAZID DRUG	SEX	NO OF PATIENT	MEAN
	Male	40	2.8415(38%)
	Female	27	1.74230(62%)
	Total	67	4.58380(100%)

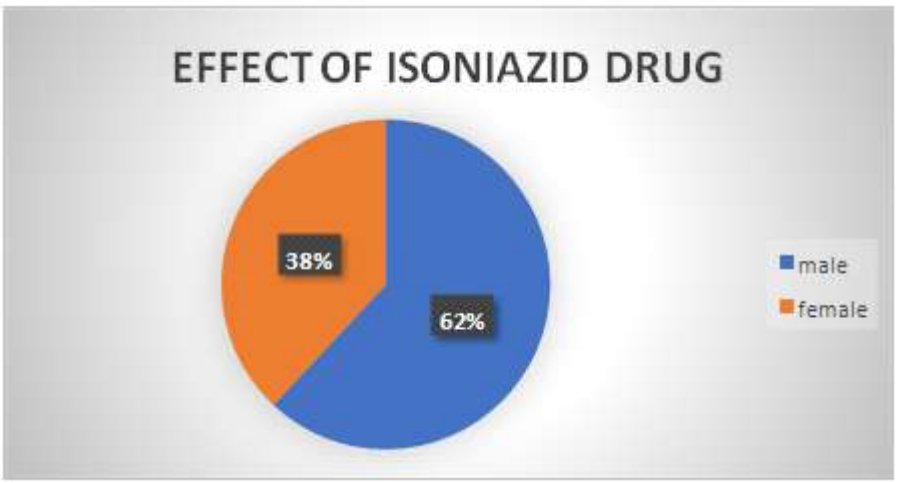

Fig: -comparative study of effect of isoniazid drug in male and female between the mean

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•**Statistical analysis of effect of different drug among the mean in tuberculosis patient:** TABLE-3

PARAMETER	MEAN	Standard deviation	t-test	P value
RIFAMPICIN	3.687434	1.714578	6.27964	<0.06
ISONIAZID	2.408485	1.835821		

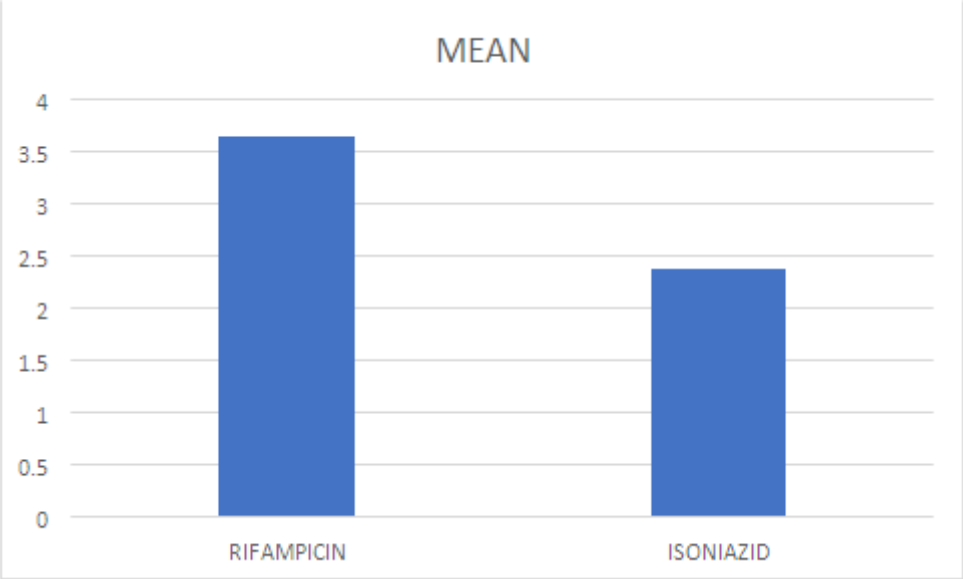

Fig: - comparative study of effect of different types of drug in tuberculosis patient

V. DISCUSSION

In this work, tuberculosis was the main I select 67 positive patients. I never tested all the patient sample but I tested some patient sample. I prepare my project through record. I collected patients some personal data and calculate mean, standard deviation, standard error.

I tested patients' sample (sputum) by staining and drug susceptibility test and I measure the zone of inhibition. I choose two first line drug Rifampicin and Isoniazid because I saw these two drugs are more effective for tuberculosis.

These data show the male patient are more affected than female.

In table-1 represents that the drug rifampicin gives higher zone of inhibition for male than the female. So, in this case the rifampicin drug is more effective for male. That are show by the pie diagram. In 67 patient 40 are male patient and 27 are female patient. In the pie diagram 41% female are affected by the rifampicin and 59% male are affected by the rifampicin.

In table-2 I take isoniazid drug. This drug is also affected and better for the male patient.it gives higher zone of inhibition for male. That is seen by the pie chart, in that case 38% female are affected by isoniazid and 62% male are affected in this drug.

In table-3 I saw overall comparation of two drugs.in that case I calculate that rifampicin drug is more affective and curable and it give high zone of inhibition than the rifampicin that shown by the bar diagram in that case the mean value of rifampicin is 3.687434 and the mean value of isoniazid is 2.408485 and the standard deviation of rifampicin drugs is 1.714578 and the standard deviation of isoniazid is 1.835821.

The study showed that tuberculosis is most finding disease and it is commonly spread .in this disease patient are given many first line and second line drugs, commonly two first line drugs rifampicin and isoniazid are used. Rifampicin drug

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is mother drug of tuberculosis. It is more effective and more curable for the tuberculosis patient.

VI. CONCLUSION

Tuberculosis is a specific infectious disease caused by Mycobacterium tuberculosis. The disease primarily affects lungs and causes pulmonary tuberculosis. It can also affect intestine, meningitis, bones, lymph nodes skin etc.

Tuberculosis is leading infectious cause of morbidity and mortality in adults worldwide, killing about 1.7 million people in 2016, most of them in low and middle income countries.in 20th century TB was leading cause of death in the united states. Today most cases are cured with antibiotic. But it takes long time up to 6 to 9 months.

The resurgence of tuberculosis and increases in the resistance of M. tuberculosis to antituberculosis agents have focused attention on the need for simple and rapid means that help to diagnose tuberculosis. The rapid diagnosis of M. tuberculosis and accurate antituberculosis susceptibility tests are essential for treatment of infected patients and to control the spread of the disease.

The aim of this work is to detect the prevalence of isoniazid and rifampicin resistant mycobacterium tuberculous clinical isolates among the newly diagnosed tuberculosis patients and to assess the value of apoptosis as a laboratory technique in the diagnosis of tuberculosis in comparison to the conventional identification methods (Z.N stain and culture on L.J medium).

This study was carried out on 67 cases suspected of having tuberculosis based on full history, clinical and radiological examination.Three successive morning sputum samples were collected from each patient and subjected to bacteriological study which includes: 1- Microscopical examination of Z.N stained sputum smears before and after concentration and decontamination by NALC-NaOH method. 2- Culture on L.J media and identification of isolates by biochemical reactions.

Antimicrobial sensitivity testing was done for the isolated strains to two antituberculosis drugs, INH & RIF, using the drug susceptibility method. Drug susceptibility tests (DSTs) should be done on initial isolates from all patients to identify an effective anti-TB regimen. These tests should be repeated if patients continue to produce culture-positive sputum after 3 mo. of treatment or if cultures become positive after a period of negative cultures. Results of DSTs may take up to 8 wk. if conventional bacteriologic methods are used, but several new molecular DSTs can detect drug resistance to rifampicin and isoniazid in a sputum sample within hours.

In my project work I use two drugs and I saw that rifampicin drug is more affective and curable and it give high zone of inhibition than the rifampicin that shown by the bar diagram.

The study showed that tuberculosis is most finding disease and it is commonly spread through the droplet .in this disease patient are given many first line and second line drugs, commonly two first line drugs rifampicin and isoniazid are used. Rifampicin drug is mother drug of tuberculosis. It is more effective and more curable for the tuberculosis patient.

AUTHOR CONTRIBUTIONS

Study design was done by AheliGuha. The first draft of the paper was written by Maitri Chakraborty. Data collection and interpretation was done by MonishaNath. Analysis work was being carried out by Maitri Chakraborty and Aheli Guha. All authors approved the final version.

CONFLICTS OF INTEREST

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analysis, in the writing of the manuscript, and in the decision to publish the results.

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