CLINICAL EVALUATION AND MONITORING OF ADVERSE EFFECTS FOR FIXED MULTIDOSE COMBINATION AGAINST SINGLE DRUG THERAPY IN PULMONARY TUBERCULOSIS PATIENTS

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ABSTRACT
To evaluate the clinical and therapeutic value of 4 and 3 drug fixed dose combinations verses single drug formulations to treat pulmonary tuberculosis patients. The occurrence of adverse effects was also monitored.
A total of 293 patients having sputum positive pulmonary tuberculosis were enrolled (Male: 187 and Female: 106). Patients with renal, hepatic, diabetic, cardiac problem and pregnancy were excluded from study. Patients were randomly selected into three groups (A, B, C). Group A and B were given FDCs and group C was given single drug formulations. All patients received 4 drugs in the intensive phase and 3 drugs in the continuation phase.
Group A showed the highest percentage of patients who achieved sputum conversion (98.9%). The numbers of days taken to achieve sputum conversion on average were the least for Group B (32 days). When comparing the adverse effects, the patients of Group C suffered the most, with 22 patients who vomited repeatedly, 3 complaining of itching, 2 with Jaundice and 1 dead.
There was no significant difference in the efficacy among the three treatment regimens. However the side effects observed in all three groups strongly indicate that FDCs are safer for treating TB patients. There were no side effects in the continuation phase.

Keywords: Tuberculosis, fixed dose combinations, adverse effects.

INTRODUCTION

To evaluate the clinical and therapeutic value of 4 drug formulations [fixed dose combinations FDC] and 3 drug formulations versus single drug formulations and to compare the adverse effects of the different drug regimens being used. The study also assessed the pattern of age/sex distribution and socioeconomic involvement in the occurrence of tuberculosis. The 4 and 3 drug formulations used in the clinical study were manufactured by Schazoo Lab. (Pvt.), Ltd. and Wyeth Laboratories Pakistan. The single drug formulations used in the study were from different local manufacturers approved by Gulab Devi Chest Hospital [GDCH] for their annual supplies. The expected adverse effects of the anti Tuberculosis medication were studied (Martindale 32nd edition, 1999) and all patients were monitored for signs of toxicity.

MATERIALS AND METHOD

A total of 293 patients between the ages of 15-55 years, having sputum positive pulmonary tuberculosis were enrolled. Out of which 187 were male and 106 were female. Patients with renal, hepatic, diabetic, cardiac problem and pregnancy were excluded from study. Patients were randomly selected into three groups A, B and C.

Group A and B were given FDC's manufactured by Schazoo and Wyeth respectively and group C was given single drug formulations. All the tests performed on the drugs to ensure their quality were taken from Pharmacopeias (BP, 1998) and (USP 2000 and 2003). Consent was taken from all the patients prior to enrollment. The patients were kept in GDCH during the initial phase of therapy. They were allowed to go home during the continuation phase. During this time they returned to the hospital routinely for check ups once a month. The 3 drug medication of the continuation phase was issued to them on these visits.

A physician at GDCH, Lahore was assigned with the special duty of monitoring and recording the adverse effects if any of the anti-tuberculosis drug therapy. Any adverse effect was recorded, if complained by patient him/herself, or noticed by the nurse or the treating physician during the patients' routine check up. Physical examination and blood tests were taken on a regular basis. The results were recorded and action was taken by the physician to make the patient more comfortable.

Drug Regimen

In Pakistan, it is estimated that there are about 45 – 60 % new sputum positive cases each year, given that the estimated annual risk of infection of TB in Pakistan is about 261 cases per 1000. About 143831 x 1000 cases of all type of tuberculosis have been reported annually in Pakistan (Global Tuberculosis Control WHO Report 1999).

World Health Organization initiated a global TB control program in 1994 to be implemented in its member

Table 1: Daily Adult dose (mg) for patient weight

Drugs	Duration	Daily adult dose (mg) for patient weight	
		Below 50 Kg	Above 50 Kg
Rifampicin		450	600
Isoniazid		300	400
Pyrazinamide		1500	2000
Ethambutol	2 months	1200	
	4 months	900	

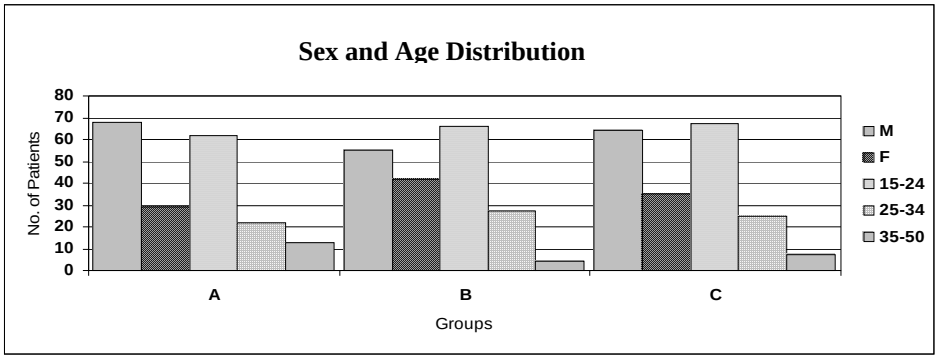

Fig. 1: Sex and age distribution.

countries for an effective treatment of tuberculosis and to check its spread. WHO has published a guideline and undertake the national program for the treatment of tuberculosis (WHO Geneva, Treatment of Tuberculosis, 1993). The guidelines include recommended regimens, patient selection and monitoring, program effectiveness, treatment costs and quality assurance of anti tuberculosis drugs. The aims of the WHO global TB control program at global level are to chart progress in TB control, and in particular, progress in implementing the Directly Observed Treatment, Short-course [DOTS], the WHO recommended strategy to control TB (WHO, 1994; WHO, 2000).

Short-course therapy regimens, recommended by the International Union against Tuberculosis and Lung Disease (IUATLD) are the treatment of choice for pulmonary tuberculosis (Mitchison, 1985). The regimens combine drugs with potent bactericidal activity; isoniazid, rifampicin with sterilizing activity against semi-dormant bacilli; rifampicin, pyrazinamide and with the ability to suppress drug resistant mutants; isoniazid, rifampicin & ethambutol (Committee on treatment of the International Union against Tuberculosis and Lung Disease 1988).

The use of combination therapy helps compliance and prevents monotherapy, which may result from selective compliance (WHO FDC treatment, Dec 1999).A fully supervised intermittent regimen may prove more successful for some patients. This represents a major departure from pre-1992 recommendations and is intended to decrease the potential for institutional transmission from persons with organisms initially resistant to one or more drugs (Angel J.H. 1992).

The Center for Disease Control (CDC) recommends four-drug treatment of tuberculosis in the multi drug era of rifampicin, isoniazid, pyrazinamide and ethambutol / streptomycin (The Center for Disease Control 1993).

Less adverse reactions are associated with the use of FDCs. In case of suspected side effects due to any of the component(s), the FDC can be switched to single-drug formulations. The withdrawal of FDC generally occurs in only 3-6% of patient on TB treatment. Although FDC can be given to patients with renal failure and liver disease, yet warrant consideration of risk-to-benefit ratio (Reider, 2002).

The standard dosage of anti-tuberculosis drugs is based on weight of the patients and all regimens for group A, B & C were according to them.

The standard drug dosages are mentioned in Table 1 (Ormerod, 1990; Edwards C.R.W and Bouchier, 1991; Angel, 1992; WHO Geneva Treatment of Tuberculosis, 1993; Physicians GenRx, 1993; Martindale, 1999):

Group A

Initial Phase of 2 months: Fixed four drug combination: Above 50 Kg body weight 5 tablets / Below 50 Kg 4 tablets; each tablet contains: Rifampicin 120 mg, isoniazid 75 mg, Pyrazinamide 350 mg & Ethambutol 250 mg.

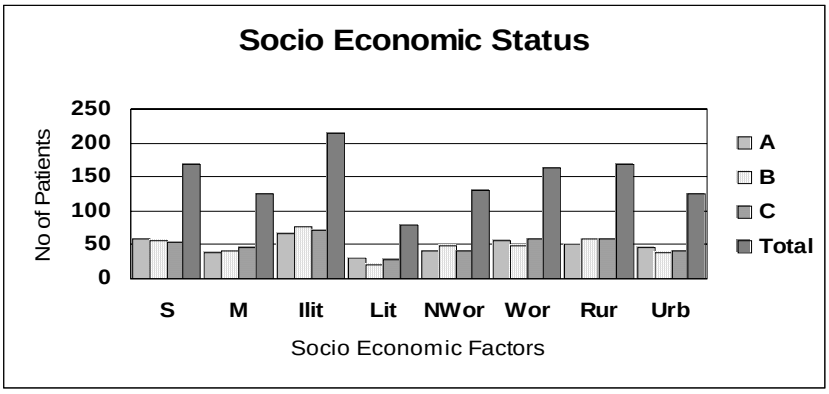

Fig. 2: Socio economic status.
Where S: Single, M: Married, Ilit: Illiterate, Lit: Literate, NWor: Non Working, Wor: Working, Rur: Rural, Urb: Urban

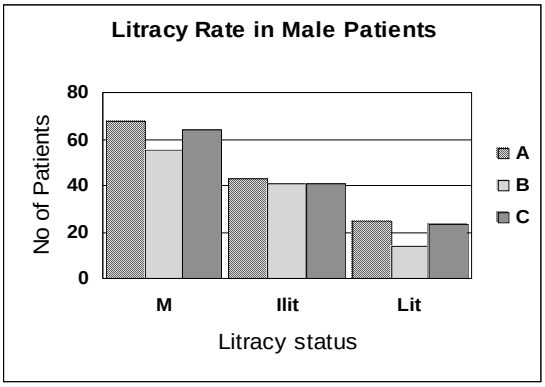

Fig. 3(a): Literacy rate in male patients.
M: Male, Ilit: Illiterate, Lit: Literate

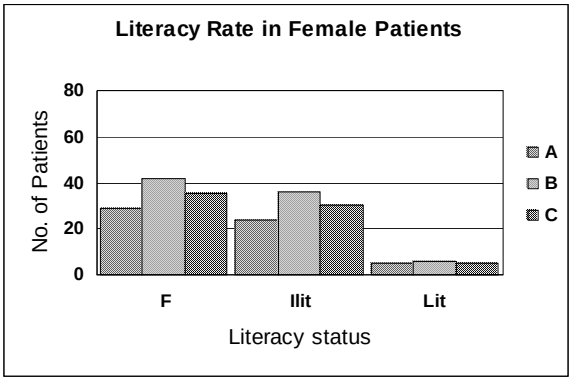

Fig. 3(b): Literacy rate in female patients.
F: Female, Ilit: Illiterate, Lit: Literate

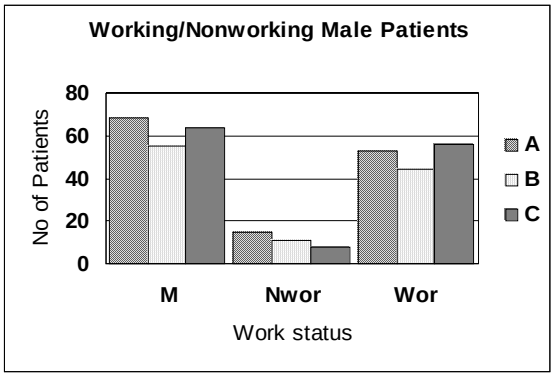

Fig. 4(a): Working/Nonworking male patients.
M: Male, Nwor: Nonworking, Wor: Working

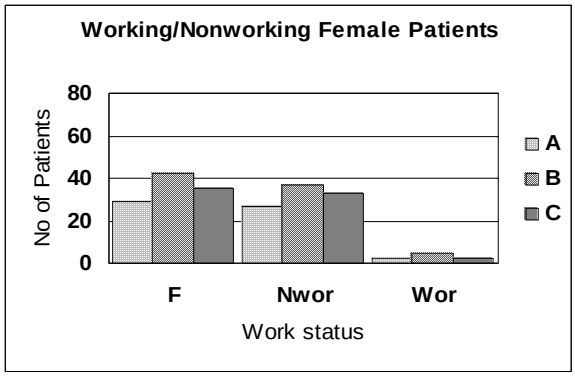

Fig. 4(b): Working/Nonworking female patients.
F: Female, Nwor: Nonworking, Wor: Working

Continuation Phase of four months: Fixed three drug combination; each tablet contains Rifampicin 150mg, isoniazid 100mg and Ethambutol 300mg. Above 50 Kg body weight 4 tablets / Below 50 Kg 3 tablets.

Group B

Initial Phase of 2 months: Fixed four drug combination: Above 50 Kg body weight 5 tablets / Below 50 Kg 4 tablets; each tablet contains: Rifampicin 120 mg, isoniazid 60 mg, Pyrazinamide 300 mg & Ethambutol 225 mg

Continuation Phase of four months: Fixed three drug combination; Each tablet contains Rifampicin 150 mg, isoniazid 75mg and Ethambutol 300 mg. Above 50 Kg body weight 4 tablets / Below 50 Kg 3 tablets.

Group C
Initial Phase of 2 months: Rifampicin 450 mg & 150 mg capsules / Isoniazid 100 mg tablets / Pyrazinamide 500 mg tablets / Ethambutol 400 mg tablets: Below 50 Kg body weight: Rifampicin 450 mg 1 Capsule, Isoniazid 3 tablets, Pyrazinamide 3 tablets, Ethambutol 3 tablets / Above 50 Kg body weight: Rifampicin 450 mg + 150 mg 2 Capsules, Isoniazid 4 tablets, Pyrazinamide 4 tablets, Ethambutol 4 tablets.

Continuation Phase of four months: Rifampicin 450mg and 150mg Capsules, Isoniazid 100mg tablets, Ethambutol 400mg tablets. Below 50 Kg body weight: Rifampicin 450 mg 1 Capsule, Isoniazid 3 tablets, Ethambutol 3 tablets / Above 50 Kg body weight: Rifampicin 450 mg + 150 mg 2 Capsules, Isoniazid 4 tablets, Ethambutol 4 tablets.

Drug Interactions from isoniazid are with anticonvulsants and pyridoxine 10 mg is advised for those at risk of peripheral neuropathy; Rifampicin reduces half-life of warfarin, phenytoin, corticosteroids, sulphonylureas and the oestrogen contraceptive pill (Drug Review III. 1993).

Clinical control of patients
Patients were kept In-House during the Intensive phase treatment till sputum conversion took place and Directly Observed Therapy (DOT) was followed for each patient on a daily basis. All the clinical tests were done in the Laboratory of Gulab Devi Chest Hospital under the supervision of properly trained and qualified professionals. The hospital ensured similar and adequate living quarters and proper balanced nutrition in the form of standard meals for the patients through out their Hospital stay.

The recovery of all the patients was closely monitored and recorded. All the data was then compiled and analyzed. For advanced statistical evaluation, the software, Statistical Package for Social Sciences (SPSS) was used. The means, standard deviations and standard errors were calculated and results were drawn on this basis.

RESULTS

Sex and age
Sex and age of patients was recorded to evaluate the ratio of TB in different segments of the population and to relate it with other socio economic factors observed.

All groups, A, B and C had more male patients as compared to female patients as shown in Figure 1.Group A had the highest number of males and group B had the highest number of females. More then 80 % patients were below 34 years old. Results show that prevalence of tuberculosis in this part of the world is more in the age group of 15-24 years.

Randomization of patients was ensured by sealed envelopes with group name in a bag, from which the patient chose an envelope. This was an effective randomization system as can be seen by the socio economic factors of patients and sex/age distribution among the three groups.

Socio economic factors
Socio economic factors like marital status, Literacy, rural/ urban living and working status were recorded which may have influenced the patients' life and then compared with each other to see the trend in different groups of patients. Socio economic factors of patients are shown in Fig.2. Ratio of Rural to Urban was higher for all groups shown in Fig. 2. As patients enrolled were young in majority therefore Fig. 2 shows that number of unmarried patients was higher.

Illiteracy seems to be high in all three groups and especially in female patients as compared to male patients, shown in Figs. 3 (a) and (b) reflecting the status of TB patients in Pakistan.

The working – non working ratio in the patients clearly shows that in Pakistan the men are considered the earners and the females are expected to stay at home.

Ratio of working to non-working was slightly higher in the case of Group A and C, non working patients were high in case of females patients while working males were higher seen in Figs. 4 (a) and (b).

Results of therapy in initial phase
TB patients are given drug dosage by weight therefore Patient's individual weight was recorded at the time of enrollment and periodically through out the study as a key factor which indicates recovery.

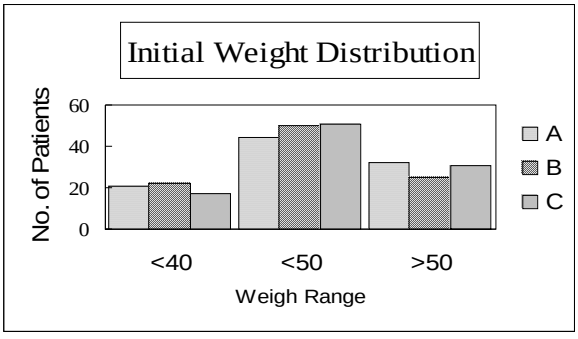

Fig. 5: Initial weight distribution.

Fig. 5 shows that majority of patients were below 50 Kg in weight at the time of enrollment.

The physical fitness condition of female patients was worse than male patients as their weight was less then 40 Kg in many cases as shown in Figs. 6 (a) and (b).

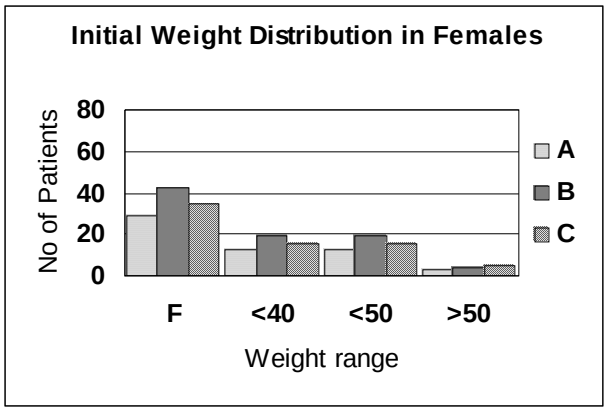

Fig. 6(a): Initial weight distribution in females.

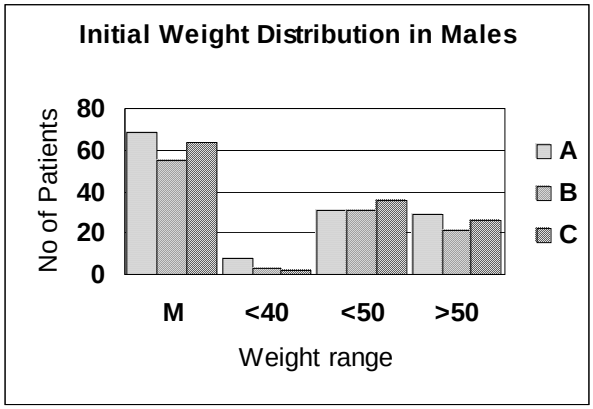

Fig. 6(b): Initial weight distribution in males.

Initial sputum positive results were considered essential for enrollment in the study. This was an important test which later on played a main role in the evaluation of level of recovery of the patients. The sputum positive ranges from (0-1)+ to (10-100)+ were checked. They have been presented in Fig. 7.

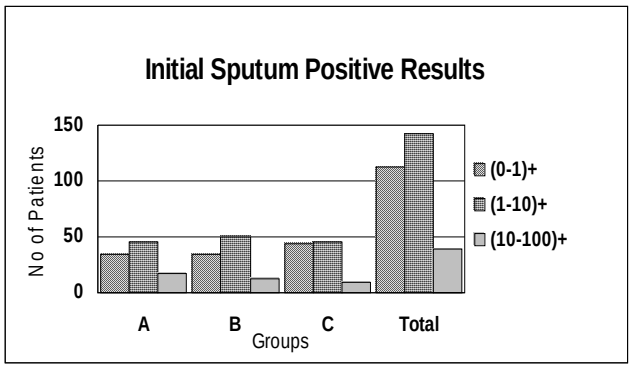

Fig. 7: Initial sputum positive results.
Sputum positive test ranges: (0-1)+, (1-10)+, (10-100)+

Initial sputum positive results in Fig. 7 show that more then 70 % patients were being identified at early stages of the disease in this hospital. This is confirmed by the Initial X-ray results which show disease status in the Lungs in Fig. 8. Majority of the patients in all three groups had minimum and moderate TB.

X-ray findings were also classified into Minimum, Moderate and Advanced TB based on the size of the lesions. The classification on the basis of X-ray findings is explained below:

Minimum TB
Showing minimal lesions of slight to moderate density, without demonstrable cavitations involving a small part of the lungs.

Moderate TB
Showing lesions of slight to moderate density throughout one lung or the equivalent in both lungs. Also showing cavities up to 4.0 cm.

Advanced TB
When lesions are spread over the total volume of the lungs or equivalent in both lungs and cavitations are greater than 4.0 cm.

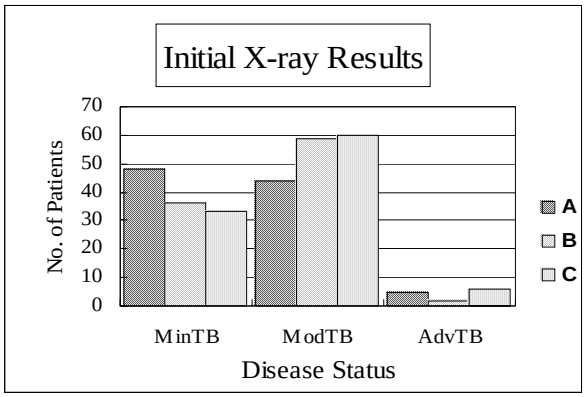

Fig. 8: Initial x-ray results.
Min TB: minimum TB, Mod TB: moderate TB, Adv TB: advanced TB.

According to the average patient weight and drug dosage shown in Fig. 9 Group C patients received more than the recommended standard maximum allowed dose in case of Ethambutol and Pyrazinamide.

A female patient died in Group C who was receiving higher than standard maximum doses of Ethambutol and Pyrazinamide. She suffered from excessive blood loss during vomiting leading to her death. Group B received fewer drugs per kilogram weight of Isoniazid, Ethambutol and Pyrazinamide as compared to other groups but it was above the acceptable recommended minimum standard range in all the three drugs.

Fig. 10 shows that the highest adverse effects like nausea/vomiting and jaundice were observed in Group C

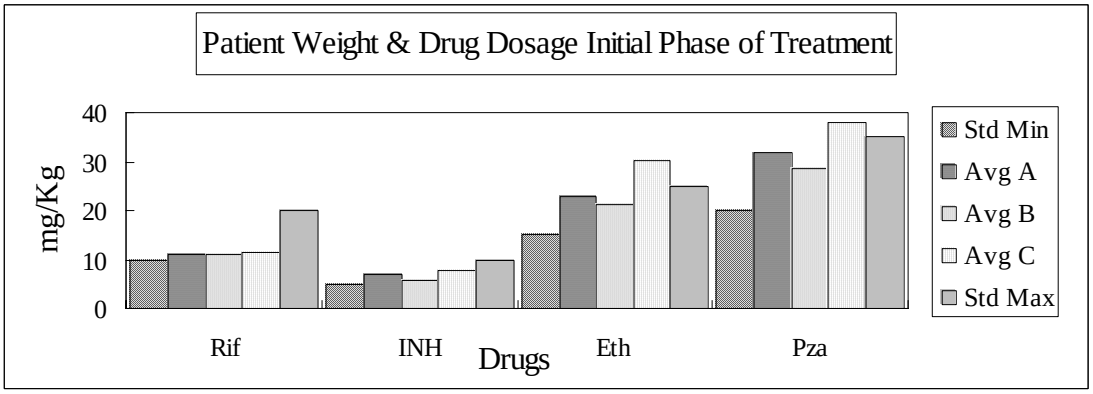

Fig. 9: Patient weight and drug dosage initial phase of treatment.
mg/kg: drug quantity / kilogram of patient body weight Rif: Rifampicin, INH: Isoniazid, Eth: Ethambutol, Pza: Pyrazinamide

patients, the reason for this could be due to the higher doses of ethambutol and Pyrazinamide received. Group B had some cases of skin irritation/itching and other kinds of complaints like numbness and joint pain.

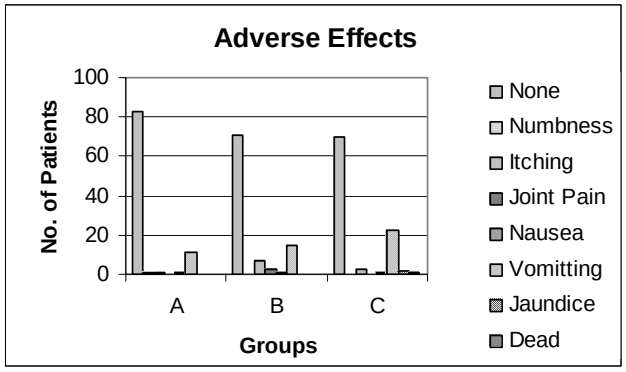

Fig. 10: Adverse effects.

Although it did take longer for some patients to achieve sputum conversion, there were only 16 patients who took longer than 2 months, a majority of them doing so in less than 60 days.

According to the results shown in Tables 2 and 3 analysis of different groups is given ahead:

Group A
The percentage of patients who achieved sputum conversion to negative was highest in group A, with maximum weight gain of 4.81 kg and minimum adverse effects. Average Hb. level improved by 1.4 gm % and average ESR values reduced by 43.93 mm. Shadows / Lesions in X-ray findings reduced on the average by 14.8 mm.

Group B
Group B also achieved satisfactory percentage of sputum conversion in the minimum number of average days. Lower Sputum conversion percentage was due to highest number of patients who left against medical advice (LAMA). Adverse effects were slightly higher and average weight gain of 4.30 kg was noted. Average Hb. level improved by 1.0 gm percentage and average ESR values reduced to 32.32 mm. Shadows / Lesions in X-ray findings reduced on the average by 14.1 mm.

Group C
Group C achieved satisfactory percentage of sputum conversion with an average weight gain of 4.47 kg. Average Hb level improved by 0.99 gm percentage and average ESR values reduced by 35.32 mm. Shadows / lesions in X-ray findings reduced on the average by 13.6mm. The toxicity and adverse effects observed were highest in Group C with two cases of Jaundice and one death. All the patients who suffered from Jaundice were females from Group C. The patient who expired was a young girl of 24 years whose sputum conversion had taken place. The exact cause of her death is not known but it is suspected that she could have developed TB meningitis.

Results of therapy in continuation phase
Table 4 gives the average results for all the parameters of recovery after 6 months of continuation therapy.

ESR reduction was very good during the continuation phase. Group C achieved maximum ESR reduction of 55.20 mm with Group A and B close behind. For most patients, it came within the accepted normal range. Haemoglobin improvement was also satisfactory, the Haemoglobin increased steadily. More than 50 patients in all three groups were relieved of all symptoms of Tuberculosis by the end of the intensive phase. The only symptoms that remained were coughing and dyspnea, coughing being much more common. By the end of six months of therapy, none of the patients complained of any ailments that are symptoms of Tuberculosis. During the continuation phase, only three antibiotics were given to

Table 2: Results of initial phase of therapy

Group	No. of Patients	LAMA Patients	Sputum Conversion	Ave. Days	Ave. weight Increase (kg)	Ave. decrease in ESR value (mm)	Ave. Hb increase (gm %)	Ave. decrease in X-ray lesions(mm)
A	97	1	98.9 %	37	4.81	43.93	1.4	14.8
B	97	6	93.8 %	33	4.30	32.32	1.0	14.1
C	99	5	95.9 %	38	4.47	35.32	0.99	13.6

LAMA: left against medical advice, Ave.: average, ESR: Erythrocyte sedimentation rate, Hb. Hemoglobin

Table 3: Adverse effects.

Groups	No. of Patients	Sputum Conversion	Average Days for Sputum Conversion	Adverse Effects							
				None	Nausea	Vomiting	Numbness	Itching	Jaundice	Joint pain	Died
A	97	98.9 %	37	83	1	11	1	1	0	0	0
B	97	93.8 %	32	71	1	15	0	7	0	3	0
C	99	95.9 %	38	70	1	22	0	3	2	0	1

Table 4: Results of continuation phase of therapy

Group	No. of Patients	LAMA Patients	Ave. weight increase (kg)	Ave. decrease in ESR (mm)	Ave. Increase in Hb (gm %)	Ave. decrease in X-ray lesions (mm) 2 -6 months	Total decrease in X-ray lesions (mm) 6 months
A	97	28	8.37	53.68	1.99	21.6	36.4
B	97	25	7.92	49.75	1.3	22.7	36.8
C	99	30	7.95	55.20	1.65	22.8	36.4

the patients, Rifampicin, Isoniazid and Ethambutol. As can be seen from Fig. 11 only Group C patients were receiving Ethambutol which was more than the required dose. Otherwise the dosage was well within the standards advised.

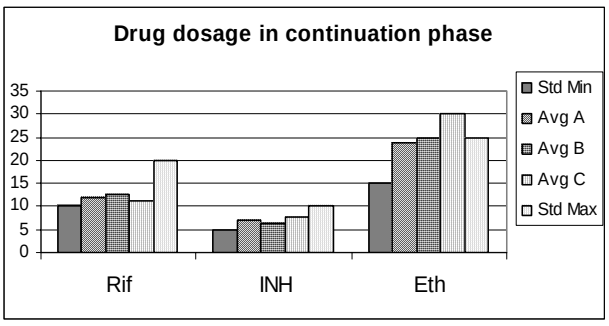

Fig. 11: Drug dosage in continuation phase.
Rif: Rifampicin, INH: Isoniazid, Eth: Ethambutol

Adverse effects

The most commonly suffered adverse effects were nausea, vomiting, rashes, itching, a few cases of jaundice and some others like numbness and joint pain. The patients of Group A showed the least adverse effects, while those of Group B showed a slightly higher number of adverse effects. In this respect, the patients of Group C showed the largest number of adverse effects, 2 patients coming down with jaundice and one female patient died. The FDCs give more accurate dosage of all the antibiotics as compared to the single drug therapy. Hence they show lesser adverse effects which resulted in lesser LAMA patients in these groups. For the statistical analysis of the adverse effects, the following grading system in Table 5 was suggested by the Medical Superintendent at the Gulab Devi Chest Hospital, Dr. Muhammad Akram.

There were a total of 82 Lama Patients. This 27.9 % ratio is quite high. 70 of these patients left during the

continuation phase and 12 during the intensive phase whose sputum conversion had not yet taken place. The 70 patients who did not complete the therapy had achieved sputum conversion. They did not show any symptoms of Tuberculosis. They were outwardly healthy and looked completely recovered. However, their anti biotic course had not been completed. They were mostly single males from rural areas who were illiterate and had manual jobs.

Table 5: Grading of adverse effects according to severity

Adverse effects	Grade
None	0
Numbness	1
Itching	2
Rashes	3
Joint pain	4
Nausea	5
Vomiting	6
Blurred Vision	7
Jaundice	8
Death	10

LAMA Patients (Left Against Medical Advice)

A large number of LAMA patients were not older than 24 years. Chances of relapse were very high in these patients due to discontinuation of therapy. All the efforts made to reach these patients were met with no response. There were a large number of patients who did not return after 6 months for final tests. No relapse case was reported until after six months of completion of the research in the cured patients.

CONCLUSIONS

The study shows that Literacy level in patients is very low especially in women. Single, young, illiterate and rural population is more at risk of getting Tuberculosis according to the Socio economic factors observed.

Treatment regimens of group A, B, and C produced satisfactory clinical results. There was no significant difference in the efficacy among the three treatment regimens as all groups achieved over 93% sputum conversion within two months. However the adverse effects observed in all three groups strongly indicate that FDC's are safer for treating TB patients. There was a significant difference in the severity of adverse effects suffered by the patients of Group C as compared to patients of Group A. Group B patients also suffered less adverse effects than the patients of Group C.

To prove that all the treatment regimens were comparable, Statistical Package for Social Sciences (SPSS) software was used for the t-test on the result data collected. This statistical t-test tells us if the difference between the mean results of different parameters of recovery is significant or not. The difference in means: mean, standard error, and confidence interval were then evaluated between the groups. When the values of different groups are compared, the 2-tailed significance is the deciding factor. If this is above 0.05, the difference is

Table 6: Final Result of Group A, B and C

Parameter	A			B			C		
	Mean *	Std. deviation	Std. error mean	Mean *	Std. Deviation	Std. error mean	Mean *	Std. deviation	Std. error mean
Days for sputum conversion	37.06	18.05	1.84	32.64	16.72	1.75	37.97	18.35	1.89
X-ray- 2 months	14.8	1.16	.12	14.1	1.20	.13	13.6	1.10	.12
X-ray- 6 months	21.6	1.01	.13	22.7	1.26	.16	22.8	.88	.12
Weight gained- 2 months	4.81	2.55	.267	4.30	2.40	.263	4.47	2.85	.208
Weight gained- 6 months	8.37	3.79	.49	7.92	4.03	.52	7.95	3.38	.45
ESR- 2 months	34.53	23.88	2.46	41.47	24.62	2.59	40.24	25.05	2.64
ESR- 6 months	24.78	13.22	1.89	24.04	16.48	2.24	24.34	20.36	2.72
Hb- 2 months	11.05	1.03	.11	10.90	1.22	.13	10.89	1.24	.13
Hb- 6 months	11.64	1.00	.14	11.20	1.04	.14	11.55	.93	.12
Adverse effects	0.14	0.35	3.59	0.27	0.45	4.52	0.40	1.10	0.11

Mean values for X-ray and ESR are in mm, in kg for weight gained, in gm percentage for Haemoglobin and according to the grading in table 3.4 for adverse effects.

Table 7: T-test results of Group A and C.

Parameter	t-test for equality of means					
	T	Sig. (2-tailed)	Mean Diff.	Std. Error Diff.	95% confidence Interval of the Difference	
					Lower	Upper
Days for sputum conversion	-.343	.732	-.91	2.64	-6.11	4.30
X-ray- 2 months	.736	.462	.12	.17	-.21	.45
X-ray- 6 months	-.646	.520	-.12	.18	-.49	.25
Weight gained- 2 months	.829	.408	.336	.406	-.465	1.13
Weight gained- 6 months	.631	.529	.42	.66	-.90	1.74
ESR- 2 months	-1.58	.115	-5.71	3.61	-12.83	1.40
ESR- 6 months	.129	.898	.44	3.40	-6.31	7.19
Hb- 2 months	.964	.336	.16	.17	-.17	.49
Hb- 6 months	.482	.631	0.091	.19	-.28	.47
Adverse effects	-2.54	.012	-.90	.35	-1.60	-.20

Table 8: T-test results of Group B and C.

Parameter	t-test for equality of means					
	T	Sig. (2-tailed)	Mean Diff.	Std. Error Diff.	95% confidence Interval of the Difference	
					Lower	Upper
Days for sputum conversion	-2.06	.040	-5.33	2.58	-10.43	-.23
X-ray- 2 months	.337	.737	0.05	.17	-.28	.40
X-ray- 6 months	-.063	.950	-.013	.21	-.43	.41
Weight gained- 2 months	-.432	.666	-.175	.406	-.977	.626
Weight gained- 6 months	-.043	.966	.029	.69	-1.39	1.33
ESR- 2 months	.330	.742	1.22	3.70	-6.08	8.53
ESR- 6 months	-.085	.932	-.30	3.54	-7.32	6.71
Hb- 2 months	.091	.928	0.016	.18	-.34	.38
Hb- 6 months	-1.86	.065	-.35	.19	-.72	.022
Adverse effects	-1.26	.208	-.46	.36	-1.17	.25

insignificant. If however, the value is less than 0.05, then there is a significant difference between the two groups being compared. The upper and lower limit of the 95% confidence interval of the difference gives a range. This is the range between which standard error would lie if the test is repeated. If zero is in that range, this means that if repeated, there might be no difference in the mean values of both groups.

Table 6 gives the final results of the research. The mean values, standard deviation and standard error mean values for the recovery parameters of all three groups have been calculated.

The mean values do differ slightly among the groups but this variation is irrelevant as proven by the t-test. The Table 7 summarizes the results of the T- test applied to the data collected from Group A and C. In only one of these cases does the t-test show a significant difference between the results of Group A and C. The significance highlighted between the adverse effects suffered by the patients. The patients of Group A showed significantly lesser adverse effects.

Table 8 summarizes the results of the T- test applied to the data collected from Group B and C. All the parameters of recovery including X-Ray improvement at 2 and 6 months, weight gained reduction in ESR and increase in Haemoglobin value shows no significant difference between Group B and C. Only days for sputum conversion have a lower value which could have been due to higher number of female patients in Group B.

The t-test when applied across the three groups showed that the differences were insignificant and that the two test regimens of Group A and B were equivalent to the accepted single drug regimen of Group C with lesser adverse effects.

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