Original Article

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Internal Medicine Section

Comparing the Daily Versus the Intermittent Regimens of the Anti-Tubercular Chemotherapy in the Initial Intensive Phase in Non-HIV, Sputum Positive, Pulmonary Tuberculosis Patients

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ABSTRACT

Background: Tuberculosis (TB) is a major health problem in the universe and India is no longer exempted from this crisis. The emergence of HIV and MDRTB (Multi Drug Resistant Tuberculosis) have further made the situation critical.

Aims: Our aim was to compare the efficacy of the daily and the intermittent doses of the Anti Tubercular Drug (ATD) therapy which is under the Revised National Tuberculosis Control Programme, amongst the sputum positive pulmonary tuberculosis in terms of the sputum conversion rate at the end of the initial phase , the default rate and the adverse drug reactions.

Methods: This was an observational prospective study.

Material: Eighty three patients were selected from the out patient and the inpatient departments of a tertiary medical centre in India.

Results: Forty three cases received an intermittent regimen, where the major age group belonged to the under 40 years age group, the default rate to the therapy was 9.3%, the sputum conversion rate was 94.87% and adverse drug reactions were found in 25.58% of the patients. In the daily regimen, there was an equal proportion of the age group of the patients, both above and below 40 yrs, the sputum conversion rate was 94.74%, a default rate was found in 5% cases and adverse reactions were found in 35% of the cases.

Conclusion: Both the intermittent and the daily regimens showed equal sputum conversion rates and the drug default cases were found more in the intermittent group. However, the adverse reactions were found more in the daily regimen category.

Key Words: Anti tubercular drugs, Daily regimen, Intermittent regimen, Sputum

INTRODUCTION

Tuberculosis is a major public health problem in India and worldwide. According to the recent World Health Organization (WHO) global report of 2011, 1.1 million people died from tuberculosis among the HIV negative cases and an additional 0.35 million people died among the people who were HIV positive. There were 8.8 million new TB cases worldwide in 2011, out of which 2 million cases were from India [1]. There were 14 million prevalent cases of tuberculosis in 2009 ,which was equivalent to 164/100000 populations. In India, the mortality which is caused by tuberculosis was in 2,80000 patients in 2009 [2]. India bears the highest TB burden . One in every 5 TB patients in the world is from India [3]. The TB cases are increasing worldwide, also in India, after an HIV epidemic and after the development of multidrug resistance tuberculosis.

Tuberculosis is a treatable condition and the tuberculous treatment can be given daily or intermittently. The intermittent regimen can be as effective as the daily regimen [4]. It has the advantage of a directly observed therapy which ensures a compliance [5]. After the failure of the National Tuberculosis Control Programme in India, as per the WHO guidelines which were followed since 1993 , RNTCP was started initially as pilot project and then as a public sector programme.

The main principle of DOTS is that a directly observed therapy which ensures compliance and a regular treatment with high quality drugs prevents drug resistance. DOTS is the internationally recommended strategy for ensuring the cure of TB. The case detection is done by sputum smear microscopy. So, the main focus is to stop the chain of the transmission to decrease the new TB cases and the development of multidrug resistant tuberculosis.

Unfortunately, even with the introduction and the functioning of DOTS in India for more than a decade, tuberculosis is still one of the leading causes of mortality in India (two persons in every three minutes, nearly 1000/day) [6]. The number of new smear positive cases has increased from 28/1,00,000 population in 1997 to 41/1,00,000 population in 2003 [7]. Even in these patients who have been declared as cured, the chance of a relapse is more in the intermittent regimen. In India, in 2008, 1.51 million TB patients were treated and in the past year, according to the estimate, there were approximately 1,10,000 new cases of MDR TB [8]. In India, 10-15% of all forms of TB are extrapulmonary. It has been shown in various studies, that some forms of extrapulmonary tuberculosis need chemotherapy for more than six months.

The WHO revised the situation, it published a guideline in 2010 and recommended that wherever feasible, in the daily regimen,

the optimal dosing frequency for the new patients with pulmonary tuberculosis was daily [9].

So, there is confusion whether the daily regimen or the intermittent regimen is superior to combat the global tuberculosis emergency and to prevent the development of multidrug resistance. There are few studies which have compared the daily and the intermittent regimens in non HIV persons. In our study, we have tried to fill up this lacuna.

AIMS AND OBJECTIVES

With this background, we compared the daily and the intermittent regimens in the initial intensive phase of ATT to evaluate the

1. Sputum conversion rate at the initial intensive phase.
2. Default rate.
3. Adverse drug reactions if any, in the initial intensive phase of the TB chemotherapy.

MATERIALS AND METHODS

This was an observational, prospective study.

This study was done in a tertiary care centre in Kolkata. The diagnosis of pulmonary tuberculosis was done by 2 sputum smear examinations for Acid Fast Bacilli (AFB) by the Z.N.stain method at DMC of NRS Medical College and Hospital. All the cases, irrespective of their ages and sexes, with a history of cough for more than 2 weeks, were advised sputum smear examinations by the Z.N.method. The data were collected regarding the age, sex, duration and the nature of the symptoms and a past history of tuberculosis or the antitubercular chemotherapy. The data on a family history of tuberculosis, habits like alcoholism and comorbid illnesses like Diabetes mellitus also were collected.

INCLUSION CRITERIA

√ Age greater than 10 years, irrespective of the sex.

√ Sputum smear positive for AFB

√ HIV seronegative

√ Willing to participate in the study and to give an informative consent.

The cases were divided into two groups; the daily regimen and the intermittent regimen groups. All the cases were advised to take the treatment under RNTCP. The patients who did not give their consents to take the DOTS therapy were given the daily regimen. The regimen was given in the following dosage in the initial intensive phase.

- H=300mg, R=450/600mg, Z=1500mg, E=800mg, S=0.5g/0.75g
- H=5mg/Kg , R=10 mg/Kg , Z=30 mg/Kg , E=15 mg/Kg, S=15 mg/Kg(in daily regime).
- H=10 mg/Kg ,R=10 mg/Kg ,Z=30 mg/Kg ,E=15 mg/Kg ,15 mg/Kg (in intermittent regime).

During the initial intensive phase, the cases were followed up every 15 days with regards to the default and any adverse reactions in the form of

√ GI intolerance

√ Peripheral neuropathy

√ Hypersensitivity reactions

√ Hepatic dysfunction

√ Vertigo/deafness

At the end of the intensive phase i.e. 2 months in CAT I and 3 months in CAT II, repeat sputum smears of AFB were done. The results were analyzed and compared by using the appropriate statistical methods.

RESULTS AND ANALYSIS

This observational study was done in a tertiary care hospital in Kolkata during the period From January 2010 to December 2011. Out of a total of 83 patients, 43 cases were included in the intermittent regimen group. Of these, 30 new cases were put on CAT I and 13 cases had relapsed or were defaulters, who received CATII. The male:female ratio was 3.3:1. A majority of them were in the age group of 21-40 years [17(39.54%) patients] [Table/Fig-1] .Follow up sputum smears were done at the end of 2 months in the CAT I patients and at the end of 3 months in the CAT II patients. Four patients (9.30%) defaulted for more than 2 weeks in the initial intensive phase. Among the remaining 39 patients, 37patients (94.87%) showed a sputum smear conversion at the end of the intensive phase [Table/Fig-2] .In the intermittent regimen group, adverse reactions (25.58%) were noted in the initial intensive phase of the chemotherapy, of which the most common side effect was a gastrointestinal disturbance (9.30%), followed by raised serum transaminase levels (6.98%) [Table/Fig-3].

Another 40 patients received the daily regimen.25 cases were on CAT I and 15 cases were on CATII. The male:female ratio was 3:2.50%. The patients were below the age of 40 years [Table/Fig-4]. At the end of the initial intensive phase, two patients had

Sl. No.	Age group (yrs)	Male (%)	Female (%)	Total (%)
1	0-20	12(27.91)	2(4.65)	14(32.56)
2	21-40	12(27.91)	5(11.63)	17(39.54)
3	41-60	7(16.28)	3(6.98)	10(23.26)
4	Above 60	2(4.65)		2(4.65)
Total		33(76.74)	10(23.26)	43(100)

[Table/Fig-1]: Age and sex distribution in intermittent regimengroup (n-43)

Case Category	Total no of Patient	No of Default	Sputum Conversion	Non-Conversion
Cat 1	30(69.77%)	1(2.32%)	29(67.44%)	0(0%)
Cat 2	13(30.23%)	3(6.98%)	8(18.60%)	2(4.65%)
Total	43(100%)	4(9.30%)	37(94.87%)	2(4.65%)

[Table/Fig-2]: Treatment category default and sputum conversion rate in intermittent regimen group (n-43)

Adverse Reaction	Number of Patients	%
GI disturbance	4	9.30%`
Raised Serum Transaminase (SGPT > 250)	3	6.98%
Clinical Jaundice	1	2.32%
Vertigo	2	4.64%
Itching & Rash	1	2.32%
Peripheral Neuropathy	0	0
Arthralgia	0	0
Total	11	25.58%

[Table/Fig-3]: Adverse Reaction To Atd – Intermittent Regimen (N=43)

Sl. No.	Age group (yrs)	Male (%)	Female (%)	Total (%)
1	0-20	6(15)	4(10)	10(25)
2	21-40	6(15)	4(10)	10(25)
3	41-60	7(17.5)	6(15)	13(32.5)
4	Above 60	5(12.5)	2(5)	7(17.5)
Total		24(60)	16(40)	40(100)

[Table/Fig-4]: Age and sex distribution in daily regimen group (n-40)

Case Category	Total no of Patient	No of Default	Sputum Conversion	Non-Conversion
Cat 1	25(62.5%)	1(2.5%)	23(57.5%)	1(2.5%)
Cat 2	15(37.5%)	1(2.5%)	13(32.5%)	1(2.5%)
Total	40(100%)	2(5%)	36(94.74%)	2(5%)

[Table/Fig-5]: Treatment category default and sputum conversion rate in daily regimen group (n-40)

Adverse Reaction	Number of Patients	%
GI Disturbance	6	15%`
Raised Serum Transaminase (SGPT > 250)	0	0
Clinical Jaundice	3	7.5%
Vertigo	0	0
Itching & Rash	2	5%
Peripheral Neuropathy	1	2.5%
Arthralgia	2	5%
Total	14	35%

[Table/Fig-6]: Adverse Reaction To Atd – Daily Regimen (N=40)

defaulted (5%). Among the remaining 38 patients, 36 showed a sputum smear conversion (94.74%) [Table/Fig-5]. Adverse drug reactions were found more in this category in about 35% cases.

The commonest adverse reaction which was found in the daily regimen was GI intolerance, chiefly, epigastric pain and fullness in 15% of the cases [Table/Fig-6].

DISCUSSION

Tuberculosis is a treatable disease and the tuberculosis treatment can be given daily or intermittently (various regimens have been tried in various clinical trials and studies). Even with the availability of an effective chemotherapy for more than 60 years, the incidence of tuberculosis is increasing worldwide, with the emergence of the MRD strain.

Worldwide, there are very few studies which have compared the daily regimen with the intermittent regimen and most of the studies were done in HIV positive patients.

Tuberculosis affects the younger age group [10]. In our study, most of the affected patients were in the age group of 10-40 years. In a study which was done in AIIMS on 266 patients, the median age was 25 years [11]. So, an effective, safe and acceptable chemotherapy should be formulated to prevent the loss of human resources.

In our study, both the regimens showed a comparable sputum conversion rate at the end of the initial intensive phase, but the intermittent regimen group showed a greater default rate. In a study which was done by Shahina Qayyum et al., [12] , the sputum conversion rate at the end of the intensive phase was 83% in the intermittent therapy group and it was 80% in the daily therapy group. The default rate was 20.51% in the intermittent therapy group and it was 15% in the daily therapy group in the whole treatment period. The serious events which were reported with the intermittent therapy was itching in 2.8% of the cases, jaundice in 4.2% cases and vomiting in 9.9% of the patients.

In a study which was done by Chennaveerappa P K et al., [13], the cure rates among the new smear positive and the retreatment patients were 84% and 83% respectively with the DOTS intermittent therapy. The treatment default rate was 8%. The same finding was found in a study which was done by Mohamed Taher and the treatment success rate was 92%, with 7% defaulters. There were no treatment limiting adverse reactions, with nausea and vomiting in 11% cases, transient gastritis in 9% cases and a change in SGPT in 3% cases [11].

In a study which was done in a DOTS centre in northern India, the treatment success rate in the sputum smear positive cases was 85.6% and the default rate was 1.4%, while in a study which was done by Anil Kashyap et al, the mean age of the TB cases was 35.39 years. The sputum conversion rate at the end of the initial intensive phase was 87.27%. Regarding the adverse drug reactions, 6.62% showed elevated LFT levels, 2.65% developed skin rashes, and only 1.99% developed severe gastritis with tinnitus in 1.32% cases. The default rate was 2.65% [14]. So, the study on the daily regimen dates back to the eighth and ninth decades of the last century.

In the second East African trial (EA)/British Medical Research Council(BMRC) (1974), the third and fourth EA/BMRC (1978) with the use of the 2SHRZ regimen Bacterial index (BI) were 83% and 87% respectively [15,16]. In the Hongkong) [17] trial (1978), with the use of the same regimen, the BI was 95%.Whereas in a study which was done by the Research Committee of TB (1988), the sputum conversion rate was 92.2% [18]. In Agra, a study which was done by Mehrotra et al., (1982) achieved a BI of 93% [19].

Regarding the overall adverse drug reactions with the use of the HRZE regimen with/without Streptomycin in the initial intensive phase, they were 17.39% in the Agra Study [19], 28.7% in the Singapore study [20] and in two Hongkong studies [17], they were 29.27%. In the Singapore study (1979), cutaneous reactions were found to be commonest type of reactions and in the Agra study, arthralgia was the commonest type of reaction.

In the present study, the overall toxicity was found in 35% cases in the daily regimen group, whereas it was found in 27.9% cases in the intermittent regimen group. Inspite of having a fully supervised chemotherapy for TB, the overall default rate was 17.4%, the default rate which was due to the side effects of drugs was 50%, an early relief of symptoms was seen in 25% cases, visit to the relatives' housees (12..5%) and unwilling to come thrice weekly (25%) [21].

In our study, 39% of the cases refused DOTS, as they were unwilling to lose 3 days' earnings in a week. This has to be kept in mind during the implementation of DOTS in the rural and urban areas.

Our study was unique in the sense that there are only few studies which have compared the daily and the intermittent regimens. But, it has some limitations:-

1. The study materials were done in a limited number of patients. Large multicenter studies are required to arrive at an

evidence based conclusion.

2. We considered only the initial intensive phase, but the efficacy of a regime is judged not only by the sputum conversion rate, but also by the relapse rate. Some adverse reactions appear late in the course of the therapy. So, we could not estimate the overall default rate throughout the chemotherapy period.

CONCLUSIONS

In conclusion, while comparing the fully intermittent and the daily regimens of the anti-tubercular chemotherapy, both the regimens showed comparable sputum conversion rates at the end of the initial intensive phase. The treatment default rate was significantly higher in the intermittent regimen group. But, due to the higher pill burden, the incidence of the adverse reactions was higher in daily regimen group.

This study was done only on a very small number of patients and only on the initial intensive phase. Though the two regimens showed comparable sputum conversion rates, the cases should be followed up to see the rates of relapse in the two regimen groups to come to a conclusion about the efficacy of the regimen.

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