ORIGINAL RESEARCH PAPER

Paediatrics

A STUDY ON COMPARISON BETWEEN INTERMITTENT AND DAILY THERAPY FOR TREATING PULMONARY TUBERCULOSIS IN CHILDREN WITH SPECIAL REFERENCE TO EFFICACY AND OUTCOME.

KEY WORDS: pulmonary tuberculosis, intermittent therapy, daily therapyx

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ABSTRACT

This randomized controlled trial and prospective study "Comparison between intermittent & daily therapy for treating pulmonary tuberculosis in children with special reference to efficacy & outcome" was conducted in S.C.B. Medical College and Hospital & S.V.P. P.G.I.P., Cuttack under the supervision of R.N.T.C.P. Centre of S.C.B. Medical college, Cuttack. All the suspected cases, after screening, were diagnosed to have Pulmonary Tuberculosis according to WHO recommendation and then divided into two groups randomly comprising of 45 each. One group was given Daily regimen and other group Intermittent regimen therapy. Among the Daily Treatment group, majority of cases (2761.4%) became symptom free by 1 month, whereas, 9 (20.5%) and 8 (17.7%) children took 15 days and 2 months respectively to be free from the symptoms. Among the Intermittent Treatment group, majority of cases (2555.5%) became symptom free by 1 month, whereas, 7 (15.5%) and 8 (17.7%) children took 15 days and 2 months respectively. Majority cases had weight gain ranging from 2-4 kg. Complete radiological improvement was remarkable in daily treatment group. Gastric aspirate & sputum conversion. at 2 month is 100% for both daily as well as intermittent regimen. At 6 months after the completion of therapy, there was not a single case of relapse in both groups. Majority (4497.7%/4088.8 %) got cured. From the present study we can conclude that daily anti-tubercular therapy is better in terms of symptomatic relief as well as radiological changes at 6 months, than that of intermittent therapy in the treatment of childhood pulmonary tuberculosis.

INTRODUCTION

Discrepancies in national and international recommendations for treatment schedules of pulmonary tuberculosis in children extend across high-, low-, and middle-income countries and sometimes even within the same country. The WHO and the British Thoracic Society recommend either the daily or thrice-weekly intermittent regimens, whereas the American Thoracic Society, along with the Centers for Disease Control and Prevention (CDC), recommend a daily or twice-weekly regimen. The Indian Academy of Paediatrics recommends the use of the daily-dose regimen for the treatment of childhood TB and, although not proscribing intermittent therapy, cautions that compliance while on intermittent therapy is likely to be poor (IAP 1997). The Revised National TB Control Programme for India (RNTCP), the national authority for the control of TB in India, recommends a thrice-weekly regimen of drugs in both the intensive phase and the continuous phase. All cases of TB are to be reported to the RNTCP, which supplies free drugs for treatment under the DOTS programme (Chauhan 2004). These different guidelines have resulted in a myriad of regimens being used by clinicians. In India, the IAP recommendation of the daily regimen has led to paediatricians in the private sector preferring daily dosing for their patients. The national programme on the other hand, provides only intermittent therapy. Such a dichotomy will result in a substantial proportion of patients not being registered in the National TB Control Programme statistics, since they will not be accessing the drugs given under this programme. A Cochrane Review of fully intermittent dosing with drugs for treating tuberculosis in adults (Mwandumba 2001) produced inconclusive results. In this review, we hope to systematically evaluate fully intermittent dosing with drugs for treating childhood TB compared to daily dosing, to inform clinical practice and policy.

MATERIAL & METHOD

A Randomized controlled trial and prospective study was conducted by taking 90 patients diagnosed as a case of pulmonary tuberculosis basing on WHO recommendation, all are below 14 years of age, all cases are of category-1, categorised according to DOTS chemotherapy criteria followed in our country.

All confirmed cases of Tuberculosis were divided into two groups at random choosing from among both the categories and were given treatment regimens as follows:
- **Group-I** - Daily regimen therapy consisting of both Intensive (2 months) and Maintenance (4-10 months, depending upon the types of the Tuberculosis) phases. {Daily Short-course Chemotherapy}
- **Group-II** - Intermittent (Thrice a week) regimen therapy throughout the treatment period (6-12 months, depending upon the types of the Tuberculosis). {Fully Intermittent Drug Regimens}

After commencing treatment, all cases were followed up at regular intervals for clinical response, bacteriological clearance, any other result (Primary Outcome), death of the patient during the period of treatment, and adverse effects encountered, giving particular emphasis on definite ingestion of the drugs as per the schedule / regimen planned for the particular child. The duration of follow up will be as per the regimen assigned but not less than a minimum period of 6 months. All the data including the outcome were collected in a proforma prepared for the purpose, which ultimately, were tabulated and analysed for conclusion to be drawn. The study was conducted only after being duly approved and permitted by the ethical committee of the Hospital and cases were considered after written consent being taken from the parents/ guardian / older children, as the cases may be.

DISCUSSION

All the variations taken for comparison in daily versus Intermittent regimens in the treatment of childhood pulmonary tuberculosis such as age and sex distribution, nutritional status, socioeconomic status, presenting complain, past history, clinical findings, initial radiological status, tuberculin status, AFB test, have no significant charge as P value for each of them is> 0.05. Children receiving Daily therapy became symptom free relatively earlier in comparison to the Children receiving intermittent therapy **(Tables-11 A)**. P value of comparison shows no significant change.

Weight gain pattern in cases receiving either daily or intermittent therapy showed no significant difference **(Tables-12 A and B,)**. (P-Value of comparison > 0.05). Radiological changes at the end of 6 month of taking either daily therapy or intermittent therapy was remarkable. This change was better appreciated in daily therapy groups as compared to that of intermittent therapy. **(Tables-13 A)** (P = < 0.05). On the contrary, previous study report suggests no significance difference in cure rate in the intermittent group (198 out of 199) compared to daily group (200 out of 200). Accordingly, 5 patients relapsed in the group receiving intermittent therapy compared to the group receiving the daily group. As reflected in the study of, [Mwandumba HC, Squzre SB. Cochrane Database of Systematic Review 2001]. Again [Menon PR, Lodha R. Swanandans, Kabra SK (2004) in their study, showed that twice weekly intermittent short course therapy is less likely to cure tuberculosis in children as compared to daily therapy.

In our study, there was cent percent Sputum and / or Gastric aspirate conversion in both daily as well as Intermittent regiment treatment cases by 2 month **(Tables-14 A and B)**. During follow up of cases, Dropout cases were found more in Intermittent regiment treatment group in comparison to daily therapy cases but P value of comparison revealed no significant change **(Tables-15 A and B)**. Adverse effects were detected during the course of anti-Tubercular therapy in both the cases. G.I. disturbances, Hepatotoxicity, Rash and Fever were the findings noticed. These adverse effects were found relatively more in cases receiving Daily treatment regimen in comparison to the intermittent regiment. **(Tables-16 A and B)**. P value of comparison showed no significant change. During tuberculosis treatment in children with pulmonary tuberculosis increased level of ALT & AST were little higher in daily therapy regimen than that of children taking Intermittent regimen but P value of comparison showing no significant change.

Observation

Table – 11 (A): Time taken for symptomatic relief during daily therapy (n = (45-1) = 44

Duration	No.	%
15 days	9	20.5
1 month	27	61.5
2 month	8	18

As shown in Table-11 (A), majority of cases (27→61.5%) became symptom free by 1 month, whereas, 9 (20.5%) and 8 (18%) children took 15 days and 2 months respectively to be free from the symptoms.

Table – 11(B): Time taken for symptomatic relief during intermittent therapy (n=45-5)=40

DURATION	No.	%
15 days	7	17.5
1 month	25	62.5
2 month	8	20

As shown in Table-11 (A), majority of cases (2562.5%) became symptom free by 1 month, whereas, 7 (17.5%) and 8 (20%) children took 15 days and 2 months respectively to be free from the symptoms. *P value of comparison between time taken in symptomatic relief of two group: 0.9338.*

Table – 12 (A): Weight gain chart at the end of 6 months of daily chemotherapy (n = (45-1 = 44)

Weight gain (Kg)	No.	%
0-1 kg	0	0
1-2kg	4	9.4
2-3kg	14	31.8
3-4kg	17	38.6
4-5kg	8	18.
>5kg	1	2.2

It is evident from Table-12 (A) that, majority cases (31 →70.4 %) had weight gain ranging from 2-4 kg, whereas 4 children (9.4%) gained less than 2 kg and 8 children (18%) gained 4-5 kg. Single child (2.2 %) showed a gain of more than 5 kg. 2 cases were excluded from this study (One dropped out at 3rd month, and another died at 15th day of therapy).

Table – 12 (B): Weight gain chart at the end of 6 months of intermittent chemotherapy (n=45-5=40)

Weight gain(kg)	No.	%
0-1kg	0	0
1-2kg	5	12.5
2-3kg	14	35
3-4kg	15	37.5
4-5kg	6	15
>5kg	0	0

It is evident from Table-12 (B) that, majority cases (29 72.5 %) had weight gain ranging from 2-4 kg, whereas 5 children (12.5 %) gained less than 2 kg and 6 children (15 %) gained 4-5 kg. 5 cases were excluded from this study who dropped out during therapy. *P value of comparison of weight gain in two group: 0.3375 (Chi square test)*

Table – 13 (A): Radiological status (plain x-ray chest) at the completion of 6 months of daily therapy. (n=45-1=44)

Degree of Improvement	6 months No.	%
NO improvement	0	0
Slight	15	34
Moderate	21	48
Complete improvement	8	18

At the end of 6 months of therapy, each patient had some or more radiological improvement. Only 15(34%) had slight improvement, 21 (48%) had moderate and 8 (18%) had complete improvement.

Table – 13 (B): Radiological status(plain x-ray chest) at the completion of 6 months of intermittent therapy (n=45-5=40)

Degree of Improvement	X Ray taken	
No. Improvement	0	0
Slight	16	40
Moderate	23	57.5
Complete improvement	1	2.5

At the end of 6 months of therapy, each patient had some or more radiological improvement. Only 16 (40%) had slight improvement, 23 (57.5%) had moderate and 1(2.5%) had complete improvement. *P value of comparison of complete improvement vs less than it, between two group at the completion of 6 month: 0.0163. (Chi square test)*

Table – 14 (A): Sputum/gastric aspirate conversion in patients taking daily therapy

Sample	Conversion at (month)	No.	%
Sputum/Gastric aspirate smear (n=2)	2	2	100
Sputum/Gastric aspirate culture (n=4)	4	4	100

All the sputum and gastric aspirate positive cases were negative for mycobacterium tuberculosis on culture during the 2nd month of chemotherapy.

Table – 14(B): Sputum/gastric aspirate conversion in patients taking intermittent therapy

Sample	Conversionat (month)	No.	%
Sputum/Gastric aspirate smear(n=3)	3	3	100%
Sputum/Gastric aspirate Culture(n=1)	1	1	100%

All the sputum and gastric aspirate positive cases were negative for mycobacterium tuberculosis on culture during the 2nd month of chemotherapy.

Table - 15 (A): follow up study of the cases 6 months after the completion of daily therapy

Results	No.	%
Cured	44	97.7
Drop outs	1	2.2
Death	0	0
Relapse	0	0

As shown in **Table-15 (A)**, at 6 months after the completion of therapy, there was not a single case of relapse. Majority (44→97.7%) got cured evidenced by symptomatic, bacteriological, and radiological improvement. One case (2.2%) dropped out at 3rd months of chemotherapy.

Table – 15(B): Follow up study of the cases 6 months after the completion of intermittent therapy

RESULTS	No.	%
Cured	40	88.8
Drop outs	5	11.1
Death	0	0
Relapsc	0	0

As shown in **Table-15 (A)**, at 6 months after the completion of therapy, there was not a single case of relapse. Majority (4088.8%) got cured as evidenced by symptomatic, bacteriological, and radiological improvement whereas, five cases (11.1%) dropped out during chemotherapy. *P value of comparison between results of two group of therapy: 0.0910 (Chi square test)*

Table –16(A): Adverse effects of tubercular chemotherapy (daily regimen)(n = 45)

Adverse Effects	No.	%
GI Upset	4	8.9
Hepatotoxicity with jaundice	4	8.9
Rash	1	2.2
Fever	1	2.2

GI upset & hepatotoxicity were the major side effect which occurred in 4(8.9&) cases each. rash in 1(2.2%) and fever in 1(2.2%) children. Only 2 cases(Both having hepatotoxicity with jaundice) (i.e. 4.4%) needed transient withdrawal of chemotherapy. All others were managed symptomatically while continuing with chemotherapy.

Table – 16 (B): Adverse effects of tubercular chemotherapy (intermittent regimen)

Adverse effects	No.	%
GI Upset	4	8.8
Hepatotoxicity with Jaundice	2	4.4
Rash	1	2.2
Fever	1	2.2

GI upset was the major side effect which occurred in 4(8.9%) cases followed by hepatotoxicity with jaundice in 2(4.4%), rash in 1(2.2%) and fever in 1(2.2%) children. Only 4 cases (Both having hepatotoxicity with jaundice) (i.e. 8.8%) needed transient withdrawal of chemotherapy. All others were managed symptomatically while continuing with chemotherapy. *P value of comparison between adverse effect of two group: 0.9297 (Chi square test)*

CONCLUSION

Daily anti-Tubercular therapy is better in terms of symptomatic relief as well as radiological changes at 6 months, than that of intermittent therapy in the treatment of childhood pulmonary tuberculosis. Side effects, even though, seem to be more in recipients of daily therapy while comparing with Intermittent regiment, do not show significant variation statistically. The incidence of Dropout cases is observed to be more in Intermittent therapy; but does not satisfy the statistical variation significantly. Sputum conversion for AFB is seen to be equal (100%) in daily as well as intermittent regimen, by 2 months of therapy.

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