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# SHORT COURSE CHEMOTHERAPY FOR PULMONARY TUBERCULOSIS IN CHILDREN

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*Summary* : A total of 137 children with pulmonary tuberculosis were treated with one of the following 2 regimens : the first regimen consisted of two drugs namely isoniazid and rifampicin administered daily for nine months (9HR) and the second of isoniazid, rifampicin and pyrazinamide thrice a week for the first two months followed by isoniazid and rifampicin twice a week for the next 4 months ($2\ H_3R_3Z_3/4\ H_2R_2$). The diagnosis was based on radiological abnormality which was classified as most probable (category A) and probable (category B). On admission, 56% of the patients were aged less than 5 years, tuberculin test with 1 TU was positive in 72% and a history of contact with a known case of tuberculosis present in 78%. Of the 137 patients, 50% were treated with regimen I and the remaining 50% were treated with regimen II while 41% of the patients were classified as category A and 59% as category B. Culture was positive for *M. tuberculosis* in a total of 44 (32%) patients.

The results were similar in both the regimens indicating that 6 months' intermittent therapy with 3 drugs in the initial 2 months' is as effective as the 9 months' daily therapy with 2 drugs. Both the nodal and parenchymal lesions resolved to the same extent at the end of treatment. The residual lesions continued to improve even after stopping treatment. Mortality and drop out rates were very low and adverse reactions negligible.

## Introduction

Tuberculosis in children is a serious and challenging problem both from diagnostic and treatment perspectives. This is mainly because of the paucibacillary nature of the disease and the absence of a gold standard like isolation of tubercle bacilli for confirmation in the majority of patients. The diagnosis is usually presumptive, based on a positive tuberculin test, contact with a known case of open pulmonary tuberculosis and an abnormal chest radiograph suggestive of tuberculosis.

There are a number of reports on the efficacy of SCC in the treatment of adult pulmonary tuberculosis but information regarding the value or the same in the treatment of childhood tuberculosis is limited. A chemotherapy study was, therefore. undertaken by the Tuberculosis Research Centre in collaboration with the Institute of Child Health and Hospital for Children, Chennai, from where the patients were drawn. The findings of the same are presented in this paper.

## Plan and conduct of the study

Children aged between 1 and 12 years, who had not received more than 2 weeks of previous anti-tuberculosis treatment and had no evidence of renal or hepatic disease were admitted to the study. Patients with associated lymphadenitis and minimal pleural effusion not warranting a pleural tap were also considered eligible while those with massive pleural effusion, other forms of extrapulmonary tuberculosis and isolated bronchiectasis were excluded.

## Criteria for diagnosis

The diagnosis was based mainly on the radiological abnormalities which were classified as most probably TB (Category A) and probably TB (Category B). The criteria recommended by the Task Force set up by the ICMR were adopted with slight modifications. The radiographs were read by an independent assessor (Dr. Elizabeth John, Professor of Radiology, Institute of Child Health, Chennai), who was not posted with the clinical findings about the patients. Category A included patients with a primary focus plus hilar adenitis, mediastinal adenitis, miliary tuberculosis and progressive primary complex. These patients were started on anti-tuberculosis drugs. Patients with a doubtful radiological

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abnormality (category B) were started on antibiotics alone and a repeat chest radiograph taken at the end of 2 weeks. If the abnormality persisted, they were admitted to the study.

**Investigations**

A 1 TU Mantoux test (PPD batch R T 23 with tween 80) was done and read at 2, 3 (or occasionally 4) days. A full plate radiograph of the chest was taken at the time of admission and repeated at 2, 6 and 9 months. In category A patients, in addition, the X-ray was repeated at the end of 2 weeks of starting anti-tuberculosis treatment. Estimations of liver function tests, blood urea, plasma creatinine, routine haematological investigations including platelet count were done on admission and repeated subsequently only if necessary. Gastric lavage for *Mycobacterium tuberculosis* culture was done on admission. Wherever possible, sputum for smear and culture was done. Urine tests for albumin, bile pigments. acetyl isoniazid and rifampicin were done on admission, and thereafter for albumin and isoniazid at monthly intervals till the treatment was completed. Lymphnode biopsy for histopathological examination and culture for *M. tuberculosis* was undertaken for patients with lymphnode enlargement.

**Chemotherapeutic regimens**

Patients were randomly allocated after stratification according to the 2 categories (A and B), to one of the following 2 regimens :

Regimen I : 9HR

Isoniazid and rifampicin daily for 9 months.

Regimen II : $2H_3R_3Z_3/4H_2R_2$

Isoniazid, rifampicin and pyrazinamide thrice a week for the first 2 months followed by isoniazid and rifampicin twice a week for the next 4 months.

The dosages were as follows : Rifampicin was administered in a dose of 12 mg/kg (maximum 300 mg), isoniazid 6 mg/kg (maximum 150 mg) for the daily phase and 15 mg/kg (maximum 300 mg) for the thrice weekly and twice weekly phases. The dose of pyrazinamide was 45 mg/kg (maximum 1 gm).

**General management**

As far as possible, patients were hospitalised for a minimum period of 2 weeks and more, if necessary. Subsequent to discharge, patients admitted to regimen 1 (9 HR) attended once a week to collect drugs. They were given the drugs under supervision on the days they attended. In regimen II $2H_3R_3Z_3/4H_2R_2$ patients attended thrice a week for the first 2 months followed by twice a week for the next 4 months for supervised chemotherapy. The progress was assessed at monthly examinations. After completion of treatment. patients attended once a month till 24th month.

***Table 1. Pre-treatment Characteristics***

| | |
|---|---|
| Age less than 5 years | 56% |
| Positive tuberculin test | 72% |
| Contact with TB patient | 78% |
| BCG scar present | 57% |
| Gastric lavage positive | 38 (28%) |
| Sputum culture positive | 2 patients |
| Lymphnode culture alone positive | 4 patients |
| Lymphnode histopath alone positive | 3 patients |
| Total culture positive | 43 (32%) |
| Confirmation of TB | 47 (34%) |

**Results**

A total of 141 patients were admitted to the study. Of these, 4 were excluded from analysis (1 patient missed 26% of the prescribed treatment, 2 others were discharged against medical advice before completing treatment and the last patient died of a non-tuberculous cause). Thus. the analysis of response to treatment was based on 137 patients.

Table 1 shows the pretreatment characteristics. On admission, 77 (56%) patients were aged less than 5 years. Fifty six (41%) patients were classified as category A and the remaining 81 (59%) as category B. Of the total patients. 68 (50%) received regimen I and 69 (50%) regimen II. Tuberculin test with 1 TU was positive with an induration of 10mm or more in 98 (72%) patients and BCG scar was present in 78 (57%). A history of contact with a known case of pulmonary tuberculosis was present in 107 (78%). Resting gastric juice was positive for *M. tuberculosis* in 38 (28%) patients and sputum culture alone in 2 patients. Lymphnode biopsy was undertaken in 12 patients, of whom, in 10 the

*Table 2. Radiological findings on admission*

| Type of lesion | No. of patients | % |
|---|---|---|
| Parenchymal | 68 | 50 |
| *Adenitis* | | |
| Mediastinal | 19 | |
| Hilar | 13 | 25 |
| Both | 2 | |
| Adenitis + Parenchymal | 25 | 18 |
| Cavitary | 10 | 7 |
| All | 137 | 100 |

*Table 3. Response to therapy (regimen wise)*

| Regimen | Normal | | Residual lesion | | TB. death | | Total patients |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| 9HR | 41 | 60 | 26* | 38 | 1 | 1 | 68 |
| $2H_3R_3Z_3$/ $4H_2R_2$ | 33 | 48 | 34@ | 49 | 2 | 3 | 69 |
| All | 74 | 54 | 60** | 44 | 3 | 2 | 137 |

* In 5 patients ATT continued for 3 months
@ In 4 patients ATT continued for 3 months
** includes 2 patients with calcification

histopathological examination was confirmatory. Lymphnode culture was positive for *M. tuberculosis* in 7 of 12 patients (including 3 patients for whom gastric lavage was also positive). Lymphnode histopathology alone was confirmatory in 3 patients. Thus, culture was positive for *M. tuberculosis* in a total of 44 (32%) patients and the diagnosis of tuberculosis was confirmed in 47 (34%). Of the 44 culture positive patients (22 in regimen I and 22 in regimen II) the organisms were resistant to SHR in 1 (2%), to SH in 2 (5%), to HR in 1 (2%), S alone in 1 (2%) and H alone in 1 (2%) patient.

**Type of lesions**

Table 2 shows the type of lesions present in the patients on admission. Majority, namely, 68 (50%) patients had parenchymal lesions alone, 34 (25%) had adenitis alone (mediastinal, hilar or both), 10 (7%) had cavitary lesions while the remaining 25 (18%) had combined lesions.

**Response to treatment**

Table 3 gives the status at the end of therapy, regimen wise. The results were similar in both the regimens (P = 0.3). Of the 137 patients, 3 (2%) died, in 74 (54%) the radiological lesions disappeared completely and 60 (44%) had residual lesions (including 2 patients with calcified lesions). Of the 74 patients, 41 were in regimen I and 33 in regimen II. Of the 60 with residual lesions, 26 were regimen I patients while 34 were in regimen II. Of these, in 9 patients (5 in regimen I and 4 in regimen II) the treatment was continued for a further period of 3 months - in 8 because the lesions showed minimal or no clearance even though clinically they had no respiratory symptoms and the ninth patient developed tuberculous meningitis during the first month of treatment. Three (2%) patients, 1 in regimen I and 2 in regimen II died.

Table 4 shows the response to therapy according to the type of radiological lesion. Of the 68 patients with parenchymal lesions, in 34 the lesions cleared completely while 33 had residual lesions. One patient died. Of the 25 patients with combined lesions (adenitis plus parenchymal), in 8 the radiographs became normal at the end of treatment, in 2 there was calcification and the remaining 15 had residual lesions (adenitis in 5 and both adenitis and parenchymal in the remaining 10). Of the 34 patients with adenitis alone, in 28 the nodes disappeared completely and the remaining 6 had residual lesions. Lastly, of the 10 patients with cavitary lesions, 2 patients died, 4 had complete clearance of the radiological abnormality and in the remaining 4 there were residual lesions. The findings in Table 4 give an impression that the rate of clearance in nodal lesions was more than that in parenchymal lesions. This is because the residual lesions in the combined group (Adenitis + parenchymal) which accounts for 1.5 patients have not been taken into account. In all the 15 patients, the nodes persisted at the end of treatment (even though the size was considerably reduced) and in 5 patients the parenchymal lesions alone cleared completely. Thus, of the total 100 patients with parenchymal lesions, the clearance was complete at the end of treatment in 51 (51%). Similarly, of the total 59 patients with adenitis, there was complete resolution in 36 (61%) patients (Table 5).

**Deaths**

Three patients died while on treatment. All were culture positive (gastric lavage in 2 patients and sputum in the third). Two patients died in the second month - the first due to sudden development of pneumothorax and the second deteriorated despite regular treatment and had extensive parenchymal lesions. Both had organisms sensitive to all the drugs. The third patient died during the fourth month of treatment and had organisms resistant to SH and R.

**Hepatic toxicity**

Three patients developed jaundice - the first (in Regimen II) during the second month and the second (in Regimen I) in the third month. The last patient (in Regimen I) developed hepatitis B infection in the sixth month. In these patients anti-tuberculosis treatment was modified. H, R and Z in the first patient and HR in the remaining 2 patients were withheld and substituted with SE till the liver function tests became normal. The allocated chemotherapy was subsequently resumed.

**Exclusions**

Two patients who had extensive bronchopneumonic changes were discharged against medical advice before completing 1 month of treatment (one in each regimen). In the first patient gastric lavage was positive with organisms resistant to H and she continued treatment from a private practitioner irregularly after discharge. On follow up she was reported to have died in the third month. The second patient did not receive any treatment after discharge and died in the second month. Gastric lavage was positive with sensitive organisms.

One patient (9HR) missed 26% of the prescribed treatment and did not report for the 9th monthly examination. He was doing well with no complaints when seen 2 weeks earlier.

***Table 4. Response to therapy according to the type of radiological lesion***

| Type of lesions | No. of patients | X-ray status at end of treatment | | | TB. deaths |
|---|---|---|---|---|---|
| | | Nor-ma1 | Calci-fied | Resi-dual | |
| Parenchymal | 68 | 34 | 0 | 33 | 1 |
| Adenitis + parenchymal | 25 | 8 | 2 | 15* | 0 |
| Adenitis | 38 | 28 | 0 | 6 | 0 |
| Cavitary | 10 | 4 | 0 | 4 | 2 |
| All | 137 | 74 | 2 | 58 | 3 |

* in 5 only adenitis and in 10 both

**Non-TB death**

One patient died of a non-tuberculous cause in the first month of treatment.

**Discussion**

Short Course Chemotherapy studies for pulmonary tuberculosis arc limited. Dingley[1] in 1980 used four different regimens, namely, 26 weeks of HZE, HPT, HZR and 78 weeks of HT for treating pulmonary tuberculosis in children. He concluded that the radiological response was satisfactory in all the groups but better with rifampicin containing regimens. Abernathy[2] *et al* treated 50 children with tuberculosis (47 with pulmonary TB. 2 with cervical adenitis and 2 with tuberculous arthritis) with 9 months of rifampicin and isoniazid (1 HR/8$H_2R_2$). They found that most of the pulmonary infiltrates cleared in 10 months while hilar adenopathy rarely cleared in less than 2 years. Varudkar[3] treated 20 children with one of the three regimens - 2 RHE/4 HE, 2 HZE/4 HE and 6 $HRE_3$ and found excellent results in 90% of the patients. Residual lesions were found only in 10%. Kulkarni *et al* [4] compared a 6 month regimen (3 $S_3H_3Z_3/3H_7E_7$) with regimens of 9, 12 and 18 months in all forms of tuberculosis and found patient compliance to be excellent with SCC. Francisco *et al* [5] treated 117 children with pulmonary tuberculosis with 6 months of daily INH

***Table 5. Response of nodal/parenchymal lesions***

| Type of Lesion | Total patients | Resolved | | Calcified | | Residual | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| Adenitis | 59* | 36 | 61 | 2 | 3 | 21 | 36 |
| Paren-chymal | 100* | 51 | 51 | 0 | 0 | 49 | 49 |

* Some patients had combined lesions

and rifampicin. The results indicated that SCC was efficacious and did not cause any relapse. Thus, conclusion drawn by the various authors was that SCC for tuberculosis in children is safe, effective and inexpensive.

The results with the 2 regimens used in this study are similar, indicating that intermittent short course chemotherapy for six months using 3 drugs initially is as effective as the nine months daily therapy with 2 drugs. The clearance of radiological lesions was complete at the end of treatment in 61% of the patients with adenitis and 51% with parenchymal changes. In 2 there were calcified lesions. Only in 9 patients, treatment had to be continued for a further period of 3 months. The residual lesions in the other patients continued to improve even after stopping treatment. Of the total 60 patients with residual lesions at the end of therapy, on follow up, there was total clearance in 37, calcification in 3 and in only 20 patients, minimal residual lesions persisted. All the patients were clinically asymptomatic.

In this study, we observed that the time taken for both nodal and parenchymal lesions to resolve was similar while Abernathy *et al*[2] and Seth[6] reported that nodal lesions take upto 1% - 2 years to clear.

To ensure accuracy in diagnosis we undertook categorisation of the lesions. In all the patients with radiological lesions classified as 'most probable', anti-tuberculosis treatment was started, chest radiographs were repeated at the end of 2 weeks : in none of the patients did the lesion disappear or decrease in size. To avoid over-diagnosis, patients with consolidation (which could be either due to tuberculosis or non-tuberculous infection) were treated with a course of antibiotics for a period of 10-13 days and a repeat radiograph taken. Only if the lesions persisted, anti-tuberculosis treatment was started. An important feature is that all the radiographs were read by a radiologist, an independent assessor, who was not aware of any details pertaining to the patients.

**In conclusion, SCC with intermittent 6 month regimen was found to be as effective as daily 9 month regimen. The adverse reactions were negligible. The mortality and the drop out rates were very low. Radiological clearance at the end of therapy was similar in both nodal and parenchymal lesions and the improvement continued even after stopping the treatment.**

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**References**

1. Dingley, H.B. Short term chemotherapy in tuberculosis in children. Ind. J. Tub. 1981, 29, 48.
2. Abernathy, R.S., Dutt, A.K., Steed, W.W. and Moers D.J. Short course chemotherapy for tuberculosis in children. Pediatrics. 1983, 72, 801.
3. Varudkar, B.L. Short course chemotherapy for tuberculosis in children. Ind. J. Pediatrics. 1985, 52, 593.
4. Kulkarni, Vidyagouri *et al.* Proceedings of the 21 st National Conference of Indian Academy of Pediatrics. Bombay, December 1984, 104.
5. Francisco, J.C., Ries., Maria B.M., Bedran., Jose A.R. Moura, Assis and Mary E.S.M. Rodrigues Six month Isoniazid - Rifampicin Treatment for Pulmonary Tuberculosis in Children. Amer Rev. of Resp Dis. 1990, 142, 996.
6. Seth, V. Essentials of Tuberculosis in Children. Jaypee Brothers Medical Publishers (P) Ltd. 1997; 361.