RESEARCH PAPER

Intermittent or Daily Short Course Chemotherapy for Tuberculosis in Children: *Meta-analysis of Randomized Controlled Trials*

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Received: November 11, 2008; Initial review: December 11, 2008; Accepted: February 10, 2009.

Objective: To compare the effectiveness of intermittent with daily chemotherapy (both containing rifampicin) in childhood tuberculosis (age ≤16yrs) in achieving cure/ significant improvement.

Design: Systematic Review and Meta-analysis.

Methods: MEDLINE and the Cochrane Library were searched for randomized trials of antitubercular regimens containing rifampicin, in children 16 yrs or less with tuberculosis. Two reviewers independently assessed trial eligibility and quality. Data from full articles of selected studies were independently extracted by two authors and analyzed. The odds ratio was obtained for the pooled data in two groups (intermittent and daily therapy).

Outcome variables: Cure/significant improvement, relapse rate and adverse events.

Results: Four randomized controlled trials comparing twice weekly and daily therapy including 466 children (pulmonary 439; extrapulmonary 27) met the inclusion criteria. Baseline data were comparable. On quality assessment, 3 studies scored 2 and one study scored 3 out of 5 points. Per protocol analysis showed that children receiving intermittent regimen were less likely to be cured than those receiving daily therapy (OR 0.27; 95% CI: 0.14, 0.51). The results of intention to treat analysis suggest similar trend towards lower cure rates with twice weekly regimen (OR 0.66; 95% CI: 0.23-1.84).

Conclusion: Twice weekly intermittent short course therapy is less likely to cure tuberculosis in children as compared to daily therapy. There is a need for better quality randomized controlled trials for assessing efficacy of alternate schedule for intermittent therapy for childhood tuberculosis.

Key words: *Children, Intermittent therapy, Short Course chemotherapy, Treatment, Tuberculosis.*

Published online 2009 May 20. PII:S097475590800659-1

Childhood tuberculosis is a major public health problem. There have been efforts to improve the treatment and reduce the duration of therapy. DOTS was mainly introduced to improve the adherence to therapy and cut the cost of the medicines used. Several investigators in developing countries have found that high cure rates can be achieved with rifampicin-containing intermittent regimens(1) in adult patients with tuberculosis(2-4). Intermittent short course chemotherapy (SCC) improves adherence to treatment and cure rates(3,5,6) and is cost-effective(7). Intermittent therapy has been used in the National Tuberculosis programs in two large countries (India, China) and recently children suffering from tuberculosis have also been included as beneficiaries. It is, therefore, relevant to evaluate the available evidence on the efficacy of intermittent SCC in childhood tuberculosis.

We conducted a systematic review and meta-analysis of studies comparing intermittent (with or without an initial period of daily therapy) with daily short-course regimen (including rifampicin) in children ≤16 years with tuberculosis in achieving cure/significant improvement.

Accompanying Editorial: Pages 39-40.

METHODS

Search strategy: We attempted to identify all relevant studies without language restriction for the review. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 4, 2008), Cochrane Database of Systematic Reviews were searched. We combined the MEDLINE search (December 2008) with the highly sensitive search strategy for identifying controlled trials, as designed by Dickersin, *et al*.(8). The search terms used were: tuberculosis (text or MESH heading), children (text or MESH heading), therapy (text or MESH heading) with limits of age: 0-16 yrs, Randomized Controlled Trial. All the citations were screened from titles. Of those considered to be relevant, abstracts were screened. After screening of abstracts, full articles were obtained if considered relevant. References of all the studies were hand searched for potential inclusion. If a full article was not available, the authors were contacted.

Inclusion criteria: Randomized controlled trials (RCTs) in children aged 16 years or below with pulmonary/extrapulmonary tuberculosis, which compared intermittent and daily regimen (containing rifampicin), in hospital or ambulatory settings and recorded the outcome of cure/significant improvement (symptomatic relief and/or radiologic clearing at the completion of treatment course). Studies without any separate data for children were excluded.

Data extraction: Two reviewers independently extracted data pertaining to age, sex, history of contact with tuberculosis patient, demonstration of acid fast bacilli (AFB) by microscopy or culture, cure/significant improvement (symptomatic relief and/or radiologic clearing at the completion of treatment course), completion of treatment, relapse rate, adverse effects, and death.

Quality assessment: We used the previously validated Jadad five point scale(9), to assess randomization (zero to two points), double-blinding (zero to two points), and withdrawals and dropouts (zero to one point).

Definitions used

Intermittent short course therapy: Any rifampicin-containing multiple drug regimen, administered twice or thrice a week for a maximum of nine months; initial daily dosing phase not exceeding one month.

Daily short course chemotherapy: Any rifampicin-containing regimen given daily throughout (or five times a week in DOTS) for a maximum of nine months.

Pulmonary TB: Children with TB involving at least lungs (include disseminated tuberculosis with pulmonary involvement).

Extra pulmonary TB: Extra pulmonary tuberculosis involving pleura, lymph nodes, abdomen, bones and joints, disseminated, intestines, larynx, CNS.

Previously untreated patients: Patients who did not receive antituberculous drugs in the past.

Smear positive: AFB demonstrated by Ziehl-Neelsen stain on gastric lavage/ other fluid by direct microscopy.

Culture positive: *Mycobacterium tuberculosis* identified on culture from gastric aspirate/ sputum or other body fluid.

Treatment completed: Children completing regimen for assigned period.

Interrupted treatment: Children who interrupted treatment for 2 months (8 weeks) of chemotherapy due to various reasons (other than death).

Cure or significant improvement: A child who became free of clinical symptoms and/or showed significant radiological improvement at the end of assigned regimen.

Relapse rates: A child who showed cure/ significant improvement with assigned regimen but had recurrence of symptoms during follow up of up to 2 years.

Death: A child who died during the chemotherapy.

Statistical analysis

Intention to treat and per protocol analysis were performed using RevMan(4.2) program(10).

Baseline data were compared. Principal measure of effect of intervention (intermittent therapy) in terms of cure, relapse, side effects and death was assessed using odds ratio and 95% confidence interval. Random effects model was used in the analysis, wherever required. Heterogeneity was assessed using I^2 test(10). Level of significance was chosen as $P<0.05$. To see the impact of individual studies, sensitivity analysis was performed after excluding one study at a time from the pooled data.

RESULTS

***Figure* 1** depicts the inclusion of trials for meta-analysis. Four studies, enrolling 466 children met the inclusion criteria for the systematic review(17-20). ***Table* I** gives details of the 4 studies that fulfilled the inclusion criteria.

Baseline characteristics of patients: There were no statistically significant differences in distribution by age, sex distribution, nutritional status, history of contact with an infective case of tuberculosis, BCG vaccination status, positive tuberculin test and identification of acid fast bacilli between children enrolled to receive either intermittent or daily therapy.

Type of tuberculosis: A total of 439 children (of 466) had pulmonary TB(PTB). The distribution of cases of PTB in two groups were similar (P=0.67). One study enrolled ten cases of cavitary tuberculosis(17). Only one study enrolled 27 children with lymph-node tuberculosis with similar distribution between two groups (P=0.37)(19).

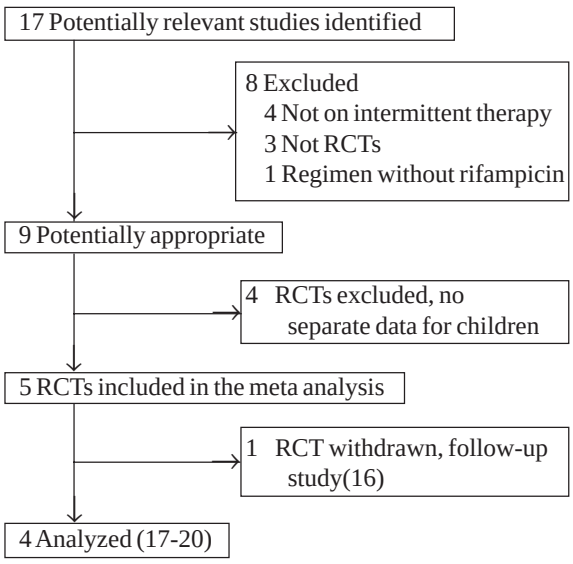

FIG.1 *Flow diagram of studies included for meta-analysis.*

Cure/significant improvement: Per protocol analysis revealed lower cure rates among children getting twice weekly regimen as compared to daily regimen (OR 0.27, 95% CI 0.15-0.51 (***Fig.* 2)**. Results of intention to treat analysis suggested that there was a trend towards lower cure rates in twice weekly intermittent therapy as compared to daily therapy (OR 0.66; 95% CI 0.23-1.84). Results of sensitivity analysis revealed that the cure rates were more in daily treatment except when study by Ramachandran, *et al*.(17) is excluded, but it did not reach statistical significance (***Table* II**). In study by Ramachandran, *et al*.(17), when only those who did not need extended regimen were considered cured, the pooled analysis shows trend towards better cure rates in daily regimen (OR 0.53, 95% CI 0.23-1.21), though it did not reach statistical significance.

Secondary outcomes: ***Table* III** gives the details of the outcomes of included studies. In the study by Kansoy, *et al*.(18), three children in daily treatment group were excluded because of poor compliance. In the study by Kumar, *et al*.(19), 13 children were excluded: 10 children, who belonged to migrant farm laborers, dropped out of the trial after a variable period of 2 to 4 months (interrupted treatment); all of them had pulmonary TB. Three children, two of whom had died soon after completing 2 months of therapy (reason not established) and one child who was diagnosed to have *Mycobacterium avium intracellulare* infection were excluded from analysis. Sixty-three children completed the study and had outcome determined. In the study by Te Water Naude, *et al.*(20), treatment records of seven children were described as lost for assessment of 4 weekly adherence data. However, the outcomes for these children have been included for analysis and the authors have stated that "it is unlikely that cases of relapse would not have come to our notice"(20).

The event rates for adherence, relapse, drug related side effects and deaths were very low but there was no significant difference between the two groups for these variables (P>0.05). Only one

TABLE I TRIALS COMPARING INTERMITTENT *VERSUS* DAILY THERAPY IN CHILDREN WITH TUBERCULOSIS

	Kansoy, *et al*. (18)		Ramachandran, *et al.* (17)		Kumar, *et al*.(19)		Te Water Naude, *et al*.(20)	
N, Place	36, Turkey		141, Chennai		76, Chandigarh		213, South Africa	
Age	mean 7.6 y		56% <5 y		<16 y		mean 2.1 y	
Diagnosis	PTB: history, tuberculin test, radiological findings, identification of *M tuberculosis.*		PTB: ICMR criteria with modifications (clinical and radio logical criteria)		PTB: clinically symptomatic children with ≥1 of the following positive tuberculin tests, AFB positivity, compatible histopatho-logy, and/or compatible radiological findings		PTB: modified WHO criteria (clinical and radiological criteria)(21)	
Exclusion criteria	Poor compliance on follow up		Massive pleural effusion, ETB, isolated bronchiectasis		< 1yr of age; CNS TB; abnormal renal / hepatic / cardiac status ; primary pulmonary complex		Child from rural areas; with extrathoracic tuberculosis	
Regimen* –	I	D	I	D	I	D	I	D
Intensive	*N*=18 SHR × 2 wk	*N*=15 SHR × 40d	*N*= 69 $H_3R_3Z_3$ × 2 mo	*N*= 68 HR × 9 mo	*N*= 37 $H_2R_2Z_2$ × 2 mo	*N*=39 HRZ × 2 mo	*N*= 95 $H_2R_2Z_2$ × 2 mo	*N*=118 $H_5R_5Z_5$ x 6 mo
Doses**	S -20; H- 15; R-15	S -20; H- 15; R-15	H- 15; R-12; Z- 45	H- 6; R-12	H- 20- 30; R- 10- 15; Z- 50- 60	H- 10- 15; R- 10- 15; Z- 20- 30	H- 15; R- 15; Z- 55	H-10; R-10; Z-25
Continuation	H_2R_2 × 8.5 mo H- 15; R-15	HR × 9mo, followed by H × 3 mo H- 15; R-15	H_2R_2 × 4 mo H- 15; R-12		H_2R_2 × 4 mo H- 20- 30; R- 10- 15	H_2R_2 × 4 mo H 10- 15; R 10- 15	H_2R_2 × 4 mo H- 15; R- 15	
Jadad score(17)	2		2		2		3	

*PTB=pulmonary tuberculosis; LNTB= lymph node tuberculosis; CNS TB= Central Nervous System Tuberculosis; ETB = extra -pulmonary TB H=isoniazid, R=rifampicin, Z=pyrazinamide; * I = Intermittent ; D = Daily; subscript in front of the drug suggests the number of doses in a week. No subscript indicates daily dosing; ** Doses of medications used in mg/ kg.*

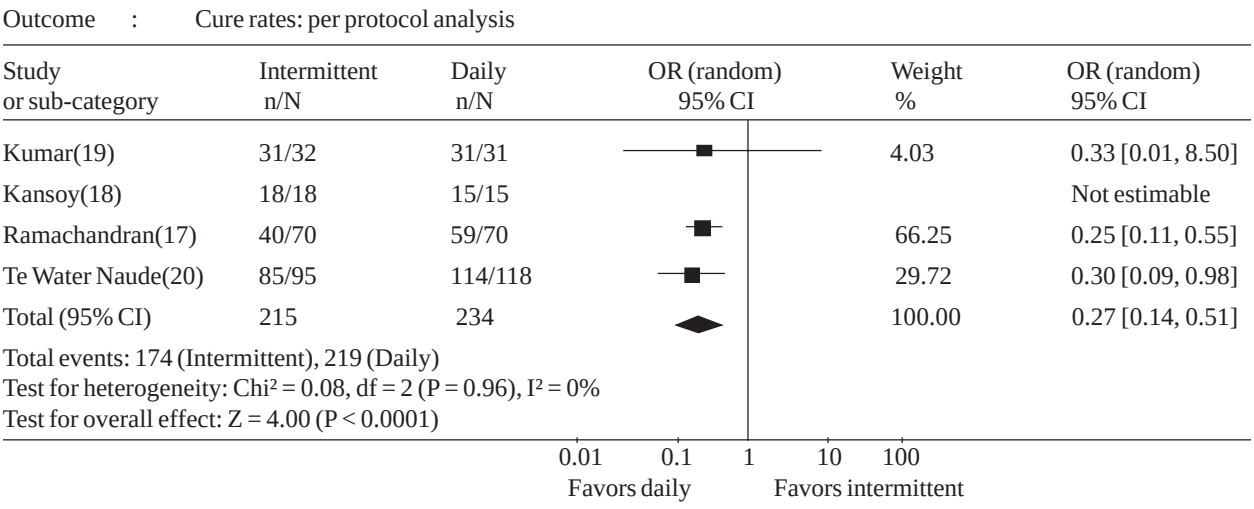

FIG.2 *Forest plot of cure rates in intermittent versus daily chemotherapy for tuberculosis in children.*

TABLE II RESULTS OF SENSITIVITY ANALYSIS

Study excluded	Cure rates (Cured/Total)		OR (95% CI)
	Twice weekly regimen	Daily regimen	
Kansoy, *et al*.(18)	160/208	211/237	0.48 (0.20-1.17)
Kumar, *et al*.(19)	142/185	188/210	0.48 (0.20-1.50)
Ramachandran, *et al*.(17)	128/156	167/185	1.02 (0.29-3.55)
Te Water Naude, *et al*.(20)	94/129	112/133	0.92 (0.17-5.05)

TABLE III PER PROTOCOL ANALYSIS FOR TREATMENT OUTCOME

	Kansoy, *et al*.(18)		Ramachandran, *et al*.(17)		Kumar, *et al*.(19)		Te Water Naude, *et al*.(20)	
Regimen*	I	D	I	D	I	D	I	D
Cure/ significant improvement	100% (18/18)	100% (15/15)	48% (33/69)	60% (41/68)	97% (31/32)	100% (31/31)	89% (85/95)	97% (114/118)
Relapse	0	0	0	1	0	0	1	0
Follow-up	12 mo		60 mo		24 mo		30 mo	
Adverse events	Transaminitis (*n*=1)		Jaundice (*n*=3)		Vomiting (*n*=6); joint pains (*n*=2)		Vomiting	

** I = Intermittent; D = Daily.*

study(19) reported data on children who interrupted treatment and there was no difference between the groups (*P*=0.56).

Out of four studies, three scored 2 on Jadad's 5 point scale while one study scored 3 points suggesting that these studies were not of very good quality.

DISCUSSION

We identified and analyzed four RCTs including 466 children comparing intermittent, twice weekly therapy with daily therapy; with mainly pulmonary tuberculosis. There was no RCT comparing the efficacy of thrice weekly regimen with daily treatment in childhood tuberculosis. Analysis of the pooled data revealed that daily therapy was superior to twice weekly intermittent therapy for children.

The major problem in assessment of treatment outcome in childhood tuberculosis is difficulty in defining outcome as documentation of conversion from AFB positive to AFB negative state (that is the gold standard for tuberculosis in adults) is extremely difficult as very small proportion of patients are positive in the beginning. In such a scenario, pediatricians have to rely on the clinico-radiologic markers of improvement, this may lead to some subjectivity. We tried to define outcome in the beginning and did multiple analysis (sensitivity analysis, per protocol, intention to treat, and defining cure when the patient did not require extension of treatment) to avoid bias in the results. All analyses showed trend towards better outcome in daily treatment group as compared to twice weekly regimen.

Directly observed therapy (DOT) may be conducted with regimens given 3 times/week, or 5 times/week(22) or daily, with equal efficacy depending on the drugs chosen. It is also postulated that intermittent therapy may be even more effective than daily therapy (in continuation phase) because it makes the organisms re-enter the phase of multiplication when the bactericidal drugs act best(23-24). Fewer doses, even if they are larger, usually reduce drug costs and may cause fewer side effects(7). A systematic review comparing daily and intermittent antituberculosis regimen in adults(22) found that there was no difference in cure rate (198

WHAT IS ALREADY KNOWN?

- Short course chemotherapy is effective in the treatment of childhood tuberculosis.

WHAT THIS STUDY ADDS?

- Twice weekly intermittent therapy is inferior to daily therapy in the treatment of childhood tuberculosis.

out of 199 in the intermittent group compared to all 200 in the daily group), but 5 patients relapsed in the group receiving intermittent therapy compared to one in the group receiving daily regimen. A recent review on long term efficacy of DOTS regimens for tuberculosis in adults concludes: "Although several clinical trials supported the use of daily treatment regimens, studies reporting tuberculosis recurrence after intermittent regimens were limited. Overall there was wide variation in recurrence after successful treatment, ranging from 0% to 14%. Considerable heterogeneity across studies precluded the systematic assessment of factors contributing to tuberculosis recurrence"(23).

The finding of inferiority of the intermittent regimen in our review may be due to the different regimens for treatment. Two out of the four studies had given twice weekly therapy during intensive phase which is no longer recommended(24). In all the studies, the therapy in intermittent regimen was directly observed, as recommended(25); even though there was loss to follow up. A single missed dose in an intermittent regimen represents a larger fraction of the total number of treatment dose than in a daily regimen increasing the risk of treatment failure. Adherence to therapy and hence, default rates may be influenced by other factors (like overcrowding in household, default in the first month in children with tuberculosis). One of the studies used a two drug regimen of isoniazid and rifampicin for 9 months for daily therapy(17); this will be considered as inadequate by current standards.

The main highlight of the review is that there are no RCTs in children comparing thrice weekly with daily regimen. The available studies comparing daily with twice weekly regimen lack uniformity in diagnosis and assessment of outcome. To overcome heterogeneity in the studies, we performed sensitivity analysis that revealed results in the same direction except when study by Ramchandran, *et al.*(17) was excluded. Even if it is presumed that in study by Ramachandran, *et al.*(17), even those who did not need extension of treatment were cured, the pooled analysis shows trend towards better cure rates in daily regimen. The study has some limitations, the results may not be valid for extrapulmonary tuberculosis as majority of the patient were having pulmonary TB. The data on relapse, adherence and interruption were limited to few patients, therefore, no valid conclusion can be drawn from this review for these outcomes.

Contributors: SKK planned the study, extracted data, conducted analysis and drafted manuscript and will act as the guarantor. PRM searched literature, extracted data, and drafted manuscript. RL conducted analysis and drafted manuscript. SS contributed to literature search and manuscript writing.

Funding: None.

Competing interest: None stated.

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