Short Report

**Randomized controlled trial of DOTS versus conventional regime for treatment of ileocecal and colonic tuberculosis**

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There is limited information regarding the efficacy of ‘directly observed treatment short course’ (DOTS) in the treatment of intestinal tuberculosis. We randomized patients with ileocecal or colonic tuberculosis to receive daily tuberculosis chemotherapy (Group A) or DOTS (Group B). Patients received isoniazid, rifampicin, pyrazinamide and ethambutol daily for two months in group A and thrice weekly for 2 months in group B, followed by isoniazid and rifampicin daily for 7 months in group A and thrice weekly for 4 months in group B. Patients were followed up at 2 and 4 weeks and monthly thereafter until the end of treatment. Follow up colonoscopy was done at 2 and 6 months after starting treatment. The improvement in clinical symptoms was not different between Groups A (24) and B (23) at 2 and 6 months. Mean increase in weight was 5.1 (0.5) Kg and 5.7 (0.6) Kg at 2 months and 7.1 (1.7) Kg and 6.9 (1.9) Kg at 6 months in Group A and B, respectively. Complete healing of ulceration was noted in 75% of Group A patients and 79% of Group B patients at 2 months and in all patients in both groups at 6 months. We conclude that DOTS and daily chemotherapy are equally effective for treating ileocecal and colonic tuberculosis.

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Abdominal tuberculosis is common in India and ileocecal area is the most common site of involvement.¹ The treatment duration for intestinal tuberculosis is not well defined. Treatment regimes vary from long-term treatment for 12 to 18 months to short-term treatment for 6 months.² According to the Revised National Tuberculosis Control Program (RNTCP), intestinal tuberculosis should be treated with directly observed treatment short course (DOTS) for 6 months under category I.³ However, literature regarding the efficacy of DOTS in the management of intestinal tuberculosis is very limited.

**Methods**

This prospective, randomized, controlled study was conducted between January 2002 and December 2006 after getting the approval of the institutional ethics committee. Patients diagnosed to have tuberculosis of the ileocecal region, colon or both sites on the basis of clinical, radiological and endoscopic features and with histological evidence of epithelioid granuloma with or without caseation and AFB positivity were studied. Patients without microbiological confirmation but with resolution of symptoms, increase in weight and healing of lesions after treatment were also included. The exclusion criteria were: HIV positivity, prior antitubercular treatment (ATT), patients unwilling for follow-up colonoscopy, lack of confident diagnosis of tuberculosis by pathologist, co-morbid illnesses and involvement of areas of small intestine other than terminal ileum.

Random numbers were generated by a computer program. Patients in Group A received daily isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1500 mg and ethambutol 800 mg for 2 months, followed by isoniazid and rifampicin daily for 7 months. Those in Group B received DOTS regime of isoniazid 600 mg, rifampicin 450 mg, pyrazinamide 1500 mg, ethambutol 1200 mg thrice weekly for 2 months, followed by isoniazid and rifampicin thrice weekly for 4 months. All patients who received DOTS treatment were enrolled in the RNTCP cell at the Institute of Chest Diseases, Calicut Medical College and were referred to the nearest primary health centre (PHC) where a medical officer was in charge of DOTS treatment. Drug compliance was ensured by anganwadi workers who provided drugs uninterruptedly.

Patients were followed up at 2 and 4 weeks and every month thereafter until the end of treatment; dur-
ing each visit, clinical examination was done and bio-
chemical parameters (ESR, liver function tests) were
checked. Compliance was evaluated by questioning the
patient as well as by checking the treatment card. Im-
provement of clinical symptoms and general well being,
weight gain and ESR were compared at 2 and 6 months.
Colonoscopy was done at 2 and 6 months by two senior
consultants in the department who were not aware of
the treatment allocation. Healing was assessed by compar-
ning post-treatment findings with pretreatment colonos-
copy images.

A sample size of 45 in each group was calculated
to get 90% power for the study for a difference of 30%
between conventional and DOTS regime. After evalu-
ating 47 patients it was observed that the results were
similar at 6 months in both groups; we therefore con-
sidered it unethical to continue the study further and new
recruitment was stopped. Statistical comparisons were
done using chi square test and p value of <0.05 was
taken as significant.

**Results**

Forty-seven (Group A 24 [14 men], Group B 23 [13
men]) of 88 patients evaluated satisfied the study crite-
ria. The mean (SD) age of patients in Group A was 37.8
(11.6) years, and in Group B was 39.9 (13.5) years. The
pretreatment clinical features, laboratory parameters and
colonoscopic appearances were comparable between two
groups (Table 1). Histological examination of biopsy
specimens from involved areas showed epithelioid gran-
uloma and Langhan’s giant cells in all patients in both
groups. Four patients in Group A and three in Group B
had caseating necrosis. Three patients in Group A and
four in Group B had radiological evidence of active
pulmonary tuberculosis.

Follow-up data are given in Table 2. Data are re-
ported for intent-to-treat analysis. Mean increase in
weight was 5.1 (0.5) Kg and 5.7 (0.6) Kg at 2 months
and 7.1 (1.7) Kg and 6.9 (1.9) Kg at 6 months in Groups
A and B, respectively. One patient from Group A was
lost to follow-up after the first follow-up colonoscopy.
Follow-up colonoscopy at 2 months showed complete
healing of ulceration in 75% of Group A patients and
in 79% of Group B patients (p=ns).

Two patients in Group A and three in Group B
developed intermittent abdominal pain during the treat-
ment period due to stricture formation. Seven patients
in Group A and five in Group B developed vomiting in
the early treatment period, which responded to symptom-
atic management. Three patients in Group A and two in
Group B developed mild elevation of liver enzymes up
to 1.5 X ULN. None of the patients discontinued treat-
ment due to this. There was no recurrence of tuberculo-
sis on clinical evaluation at median follow-up of 26 (3-
52) months and 27 (3-55) months.

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<tr>
<th>Table 1: Baseline data</th>
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<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>Number</td>
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<td>Age (years)</td>
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<td>M:F ratio</td>
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<tr>
<td><strong>Clinical features</strong></td>
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<tr>
<td>Abdominal pain</td>
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<td>Loose stools</td>
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<td>Fever</td>
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<td>Weight loss</td>
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<td>Anorexia</td>
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<tr>
<td>Hematochezia</td>
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<td><strong>Laboratory parameters</strong></td>
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<tr>
<td>Mantoux positivity</td>
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<tr>
<td>ESR (&gt;30 mm/1st hr)</td>
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<tr>
<td>Active pulmonary tuberculosis</td>
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<tr>
<td><strong>Endoscopic appearances</strong></td>
</tr>
<tr>
<td>Ulceration alone</td>
</tr>
<tr>
<td>Nodularity alone</td>
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<tr>
<td>Ulceration + nodularity</td>
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<tr>
<td>Stricture + ulceration</td>
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Values are as number of patients

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<tr>
<th>Table 2: Improvement in clinical features and colonoscopic findings at the end of 2 and 6 months after initiating treatment in both groups</th>
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<tbody>
<tr>
<td><strong>Time</strong></td>
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<tr>
<td>Group</td>
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<tr>
<td>Number</td>
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<tr>
<td>Symptom improvement ** *</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Loose stools</td>
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<tr>
<td>Hematochezia</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>ESR*</td>
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<tr>
<td>Weight gain (Kg)</td>
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<tr>
<td>Colonscopic findings</td>
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<tr>
<td>Ulcer healing</td>
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<tr>
<td>Complete</td>
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<tr>
<td>Partial</td>
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<td>Disappearance of nodularity</td>
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</table>

*dropout 1; **Values are as number with symptom/total number with symptom at baseline; *ESR <30 mm/1st hr p=ns for between group comparison
**Discussion**

Our study showed that the clinical improvement and weight gain was similar between the groups at 2 and 6 months. Complete healing of ulceration was noted in 75% of Group A patients and 79% of Group B patients at 2 months and in 100% of patients in both groups at 6 months. There was no clinical recurrence on follow-up.

The principles of treatment for pulmonary tuberculosis are applicable in intestinal tuberculosis also. Treatment for nine months had been found to be useful in tuberculous enterocolitis. The recent recommendation by the World Health Organization for 6-month therapy is not strongly supported by published randomized controlled trials. Balasubramanian et al found that 6-month short-course chemotherapy regimen was as effective as the standard 12-month regimen in the treatment of all forms of abdominal tuberculosis. Decreased compliance and increased cost are two problems associated with long-term treatment regimes. DOTS regime has been proven to have better compliance without compromising the efficacy at a low cost. There are no reports in literature regarding the efficacy of DOTS in intestinal tuberculosis.

A sense of well-being usually appears within ten days of treatment; fever and abdominal pain subsides within 3 weeks and usually there is rapid weight gain. In our study, almost all patients had improvement of symptoms and general well-being by two months in both treatment groups. Colonoscopic follow-up study of patients receiving ATT is limited. It is not clear whether intestinal lesions heal correspondingly with symptom improvement. Our results show that tubercular lesions of colon healed at two months of treatment with both these treatment regimes.

Small sample size and absence of blinding of patients are the drawbacks of this study. It was very difficult to get a large population of patients satisfying all inclusion and exclusion criteria. Patients could not be blinded as it was not technically possible to alter the strategy of administering drugs under the DOTS regime. The parameters of improvement however were assessed objectively. Even though we wanted to enroll 90 cases, the study was stopped earlier due to ethical considerations.

We conclude that treatment of intestinal tuberculosis by both conventional and DOTS regime has equal efficacy. Clinical and endoscopic improvement is similar in both treatment regimes.

**References**


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