Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report

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SUMMARY

OBJECTIVES: To assess and compare the efficacy of a 6-month short-course chemotherapy regimen (SCC) with that of a 12-month standard regimen in the treatment of abdominal tuberculosis.

DESIGN AND SUBJECTS: A total of 193 adult patients with evidence of abdominal tuberculosis were randomly allocated to one of two daily regimens: 1) a 6-month SCC regimen with rifampicin, isoniazid and pyrazinamide for 2 months followed by rifampicin with isoniazid for another 4 months (6R series) and 2) a 12-month standard regimen of ethambutol and isoniazid with streptomycin supplemented for 2 weeks (12E series). Surgery was undertaken only for patients suspected to have obstruction or perforation of the intestine.

RESULTS: A total of 163 (85 6R, 78 12E) patients were available for efficacy analysis after exclusion of 30 patients for various reasons. At the end of treatment clinical status was normal in 84 (99%) in 6R patients and in 73 (94%) in 12E patients. Of these, 147 patients completed follow-up for 5 years; none had relapsed requiring treatment for abdominal tuberculosis.

CONCLUSION: A 6-month SCC regimen has been found to be as effective as the standard 12-month regimen in the treatment of all forms of abdominal tuberculosis.

KEY WORDS: short-course chemotherapy; abdominal; tuberculosis

ABDOMINAL TUBERCULOSIS as a clinical entity was recognised in the era of Hippocrates, long before the discovery of Mycobacterium tuberculosis. It continues to be a common medical condition with worldwide occurrence. Since the clinical presentation closely simulates other inflammatory and neoplastic lesions of the intestines and other viscera, a high index of suspicion is required to make a prompt diagnosis; failure to do so may lead to avoidable morbidity and mortality. The management varies from early surgery to a trial of anti-tuberculosis chemotherapy. Many chemotherapeutic regimens of 8-12 months’ duration have been tried in India.1-3 Both conservative and radical surgery have been recommended by various workers.

Short-course chemotherapy (SCC) regimens have been found to be very effective in the treatment of bacteriologically proven pulmonary tuberculosis, spinal tuberculosis, tuberculous lymphadenitis and brain tuberculosis.4-9 As the commonest drug combination in SCC regimen, rifampicin with isoniazid and pyrazinamide, is potentially hepatotoxic, it is necessary to assess the toxicity and side effects in patients with abdominal tuberculosis, who might have covert involvement of liver without clinical manifestations.

A randomised controlled clinical study was undertaken by the Tuberculosis Research Centre (TRC), Madras, in collaboration with the Departments of Medicine, Medical and Surgical Gastroenterology of the Government General Hospital, Madras, and Gastroenterology Department of the Government Peripheral Hospital, Anna Nagar, Madras, to compare the efficacy of a 6-month SCC regimen with that of a standard 12-month regimen in the treatment of abdominal tuberculosis. Surgery was undertaken only if a patient presented with or developed signs of obstruction or perforation. This report presents the results of the study during treatment and up to five years from admission.

SUBJECTS AND METHODS

Adult patients attending the medical and gastroenterology clinics at Government General Hospital (GGH), Anna Nagar Peripheral Hospital and the TRC, with the following symptoms and signs were investigated

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at the TRC. Patients with 1) abdominal pain for more than 1 month duration, after investigations had excluded acid peptic disease, 2) distension of abdomen of more than 1 month duration with or without features suggestive of sub-acute obstruction, or 3) persistent diarrhoea associated with loss of weight, were examined. A detailed clinical examination was performed for all patients.

Patients with diabetes, hypertension, hepatic or renal dysfunction, blood dyscrasias, neurological or cardio-vascular disorders, history of previous anti-tuberculosis chemotherapy for more than 6 months or patients in moribund condition were excluded from the study.

Investigations on admission

A chest radiograph, a plain radiograph of the abdomen and barium enema (including double contrast) and barium meal follow-through pictures were taken for all patients. They were read independently by a radiologist. In addition, examination of 3 early morning specimens of urine by culture for *M. tuberculosis*, liver function tests, complete haemogram and tuberculin test with 1 TU PPD RT 23 with Tween 80 were also done. Cytological, biochemical and bacteriological examinations were done with ascitic fluid from patients presenting with ascites. For patients with chest radiograph suggestive of pulmonary tuberculosis, two sputum specimens were examined by smear and culture for *M. tuberculosis*. Laparoscopy was done for patients with ascites or with symptomatology suggestive of peritoneal tuberculosis. Laparotomy was undertaken for patients with signs of obstruction or perforation. Percutaneous liver biopsy was done in patients with hepatomegaly. All the biopsy specimens were subjected to both bacteriological and histopathological examinations for confirmation of tuberculosis.

Bacteriological procedures

All the biopsy specimens, urine and ascitic fluid specimens were cultured for *M. tuberculosis* in multiple solid and liquid media, namely Lowenstein-Jensen’s medium alone and with pyruvate, Middlebrook’s 7H11 medium and Kirschner’s medium. 10

Diagnostic criteria for admission to the study

Patients with one or more of the following criteria were admitted to the study.

1) Presence of acid fast bacilli on smear/positive culture for *M. tuberculosis* in biopsy specimens and ascitic fluid.
2) Histopathological evidence of tuberculosis in biopsy specimens.
3) Radiological findings suggestive of abdominal tuberculosis:
   a) irregular narrowing of multiple loops of small intestine with or without features of obstruction,
   b) deformity or reduced distensibility of caecum in association with involvement of terminal ileum, or
   c) intestinal internal fistulae.
4) Clinical features suggestive of abdominal tuberculosis without laboratory confirmation as decided by the Professor of Medicine at the GGH.

Treatment regimens and dosage

Eligible patients were allocated at random in equal proportions to one of the two daily regimens, after stratification on the basis of diagnostic criteria, a) laboratory/radiological confirmation, and b) clinical confirmation (Table 1):

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugs</td>
<td>Duration</td>
</tr>
<tr>
<td>2HRZ/4HRSE/SEH</td>
<td>HRZ</td>
<td>2 mths</td>
</tr>
<tr>
<td></td>
<td>SEH</td>
<td>2 wks</td>
</tr>
</tbody>
</table>

H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin; E = ethambutol

Change of chemotherapy

Chemotherapy was modified or changed before the end of the scheduled period of treatment if a patient developed severe adverse reactions to drugs or had clinical deterioration as judged by an independent assessor (Professor of Medicine at the GGH). If a patient developed signs of acute abdomen (obstruction or perforation), the case was referred to the surgical gastro-enterologist for opinion regarding surgical intervention and change of chemotherapy.

General management

All patients were treated as out-patients from the start of treatment. They attended the TRC clinic daily for the first 14 days, for supervised drug administration; thereafter drugs were supplied twice a week up to 2 months, then once a week for patients residing in Madras and once per fortnight or per month for patients coming from outside the Madras area for self-administration at home. Patients were hospitalised if they were too sick, if their residence was outside Madras City or for sociological reasons.

Investigations and assessments during follow-up:

A detailed clinical examination was done every month up to 24 months and once every 6 months up...
RESULTS

CHARACTERISTICS ON ADMISSION: A total of 193 (96 6R series, 97 12E series) patients were admitted to the study. The pre-treatment characteristics were broadly similar in the two series (Table 2). The mean age was 30 years (range 13-72 years); there were 85 males and 108 females. An initial induration of 10 mm or more to 1 TU was observed in 75% of the patients. Of the 193 patients, 135 (70%) had intestinal lesions, 84 (44%) had peritoneal tuberculosis, 25 (13%) had hepatic tuberculosis, 17 (9%) had mesenteric tuberculosis and 2 (1%) had retroperitoneal tuberculosis; 61 patients had combined lesions.

CLINICAL PROFILE: In all, 143 (74%) patients presented with abdominal pain in association with one or more of the following: tenderness of abdomen, alteration in bowel habits, increased borborygmi, or distension of abdomen. Another 13% had loss of weight in association with one or more symptoms such as alteration of bowel habits, distension of abdomen or anorexia (Table 2).

DIAGNOSTIC PROCEDURES: Laparoscopy was performed in 60 cases of suspected peritoneal tuberculosis; 49 (82%) of them had either histopathological or bacteriological confirmation or both (Table 3). Fifty-four had undergone laparotomy, 42 for suspected obstruction or perforation and the remaining were exploratory laparotomies; 45 (83%) patients had histopathological or bacteriological proof or both. Three had colonoscopy for suspected ileocaecal tuberculosis and one was confirmed by histopathological examination. Liver biopsies were done in 43 cases and 7 (16%) had histopathological or bacteriological proof or both. Ascitic fluid aspiration was done in 37 patients and examined by smear and culture. Bacteriological proof was available in 11 (30%) patients.

LABORATORY CONFIRMATION OF DIAGNOSIS: Of the 193 patients, direct proof in the form of bacteriological confirmation by culture of the biopsy specimens was obtained in 15 (7 6R, 8 12E; 8%) patients and by smear in 4 (2 6R, 12 12E; 2%) patients. Ascitic fluid culture was positive for M. tuberculosis in 9 (5 6R, 4 12E; 5%) patients and smear alone was positive in 2 (one in each series; 1%) patients. Histopathological evidence of tuberculosis was available in 77 (36 6R, 41 12E; 40%) patients. Indirect confirmation, such as chest radiograph abnormality suggestive of pulmonary tuberculosis, was present in 93 (46 6R, 47 12E; 48%) patients; among them 28 (12 6R, 16 12E; 15%) patients had positive sputum culture for M. tuberculosis. In another 2 patients, one in each series, urine culture examination yielded M. tuberculosis. One other patient in the 6R series had histopathologically proven cervical lymphadenitis. In all, laboratory confirmation of tuberculosis (direct or in-
short-course chemotherapy for abdominal TB

Response at the end of treatment

<table>
<thead>
<tr>
<th>Status</th>
<th>2HRZ/4HR</th>
<th>Total</th>
<th>6R</th>
<th>12E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom free</td>
<td>DE</td>
<td>IE</td>
<td>Ra</td>
<td>Clin.</td>
</tr>
<tr>
<td>Clinically improved but still</td>
<td>DE</td>
<td>IE</td>
<td>Ra</td>
<td>Clin.</td>
</tr>
<tr>
<td>TB death</td>
<td>DE</td>
<td>IE</td>
<td>Ra</td>
<td>Clin.</td>
</tr>
</tbody>
</table>

DE: Direct evidence; IE: Indirect evidence; Ra: Radiological evidence; Clin: Clinical evidence
Table 5: Status of patients at 60 months

<table>
<thead>
<tr>
<th>Series</th>
<th>Eligible for follow-up</th>
<th>Completed 60 months</th>
<th>Requiring retreatment</th>
<th>Death due to TB</th>
<th>Other reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>6R</td>
<td>84</td>
<td>79 (94)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>12E</td>
<td>73</td>
<td>68 (93)</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

1 each for: Intestinal obstruction, renal TB, suspected tuberculous lymphadenitis, TB of the spine
2 each for: tuberculous lymphadenitis, brain tuberculoma, renal TB, pulmonary TB

12E) patients completed 48 or 54 months of follow-up (Table 5). Among them, 7 (3 6R, 4 12E) required retreatment. In the 6R series, one following surgery for intestinal obstruction in the 13th month from the start of treatment (without confirmatory evidence); one for renal tuberculosis in the 12th month, and the other for suspected tuberculous lymphadenitis and tuberculosis of the spine in the 42nd month, but the lesion was later proved to be squamous cell carcinoma with secondaries in the spine. In the 12E series, one for TB lymphadenitis in the 43rd month, one for multiple brain tuberculoma in the 21st month (who took treatment elsewhere), one for renal tuberculosis in the 54th month, and the remaining one for sputum-positive pulmonary tuberculosis in the 52nd month after admission. One patient in the 6R series died due to tuberculosis in the 7th month after the start of treatment, following surgery for acute abdomen, and 8 (6 6R, 2 12E) patients died due to causes other than tuberculosis; one of squamous cell carcinoma, 2 of hepato-renal syndrome, one of cerebral haemorrhage, one due to anaphylactic shock following surgery, one of hepatic failure, one due to alcoholic cirrhosis of the liver and the remaining one in a road accident. One patient in the 12E series was lost to follow-up from the 11th month onwards; she was asymptomatic at the time. One patient in the 6R series was clinically stable when examined at the 48th month but subsequently defaulted. None of the remaining 129 (68 6R, 61 12E) patients had relapse of abdominal tuberculosis, and they are being followed up to 120 months after admission.

ADVERSE REACTIONS TO DRUGS: Patients were not questioned about symptoms of drug toxicity, but any spontaneous complaint made was recorded after careful questioning. All the 193 patients admitted to the study were considered for analysis (Table 6). The overall incidence of adverse reactions was 26 (27% ) in the 6R series and 10 (10%) in the 12E series. The difference is statistically significant (P < 0.01).

HEPATOTOXICITY: Hepatitis occurred in 16 (17%) of 96 patients in the rifampicin series and 4 (4%) of 97 patients in the non-rifampicin series (P < 0.01). Of these, 12 (9 6R, 3 12E) patients had clinical jaundice. The onset of jaundice was within 2 months in the 6R series but after 6 months in the 12E series. R, H and Z in the rifampicin series and H in the non-rifampicin series were withheld for 7 to 58 days, and substituted with daily S and E in the rifampicin series and S in the non-rifampicin series. Treatment was resumed in all uneventfully after recovery from jaundice.

PERIPHERAL NEURITIS: In the 6R series 2 patients and 1 in 12E series developed peripheral neuritis in the 1st, 4th and 5th months of treatment. The dosages of isoniazid they received were 8.0, 9.4 and 8.5 mg/kg body weight respectively. Isoniazid was terminated and substituted with pyrazinamide. All recovered subsequently.

VISUAL: Two patients, both in the 12E series, developed dimness of vision by the seventh month of treatment. Ethambutol was terminated for constriction of visual fields and substituted with pyrazinamide. The field of vision became normal.

CUTANEOUS: One patient in the 6R series developed pruritus in the 1st week and the drugs were continued along with antihistamines for 6 months. One other patient in the 12E series developed fixed drug eruptions on the 76th day of treatment; isoniazid was terminated and substituted with pyrazinamide. The drug eruptions completely subsided.

ARTHRALGIA: In the 6R series, 7 (7%) of 96 patients in the first 6 to 8 weeks developed arthralgia. All responded to analgesics.

VERTIGO: Two (2%) of 97 patients in the 12E
series developed mild giddiness on the 3rd and 12th day of treatment and were managed symptomatically.

DISCUSSION

The results of our study clearly indicate that abdominal tuberculosis can be successfully treated with short-course chemotherapy of 6 months’ duration alone, without recourse to surgery.

The majority of our patients (74%) had presented with abdominal pain in association with one or more of the following: tenderness of abdomen, alteration of bowel habits, distention of abdomen or increased borborygmi. Sharp et al. had reported that abdominal pain, night sweats and weight loss were observed in more than half of the 72 patients in East Birmingham. However, in Hamdani’s series, it was reported that the most frequent clinical form of peritoneal tuberculosis was painful febrile ascitis in 70% of patients. In Taiwan 79% of 121 patients had abdominal pain and 53% had fever. Thus the symptoms and signs vary depending on the site of lesions and no single symptom or sign was pathognomonic of the disease. This view has been expressed by many others in the literature. The same is true for the site of lesion as well. Intestinal tuberculosis was the commonest manifestation (70%) in our series; but in Wells’ series, collected over a period of 18 years, 5 (17%) of 30 patients in the UK had intestinal tuberculosis. Thus the site of involvement is also highly variable.

Cheest radiograph was suggestive of pulmonary tuberculosis (sputum cultures were positive in 20%) in 48% of 193 patients in our series. Coexisting pulmonary tuberculosis has been observed by others as well; 69% in Chang’s series in Taiwan, 78% in black patients in Maharaj’s series and in 62% of 82 patients in South Africa. These findings indicate that presence of associated pulmonary tuberculosis adds weight to the diagnosis of all forms of abdominal tuberculosis.

It was possible to establish the diagnosis in 138 (72%) of 193 patients in our series, by undertaking culture examination of the biopsy specimens and ascitic fluid, in multiple liquid and solid media. The proportions are higher than in Chang’s series (32%) and in Maharaj’s series (59%). This finding highlights the advantages of culturing the specimens in multiple liquid and solid media to improve the sensitivity of diagnosis.

Considering the overall efficacy of the regimens, the incidence of chemotherapy modifications and tuberculous deaths was higher in the 12-month regimen than in the 6-month regimen; however the difference was not statistically significant. Successful outcome was also not related to the type of disease, nor presentation, nor chemotherapeutic agents. These findings suggest that the 6-month regimen is as effective as the 12-month regimen, and appears to be adequate in all forms of abdominal tuberculosis. But, in the literature published so far, standard chemotherapy of 9 to 12 months has been recommended by Palmer et al., Galloway et al. and Marshall for abdominal tuberculosis.

It is worth pointing out that all 37 patients who had only radiological proof of tuberculosis showed radiological resolution of the lesions at the end of treatment. Similarly, all 8 patients who were diagnosed only on the basis of clinical features showed remarkable clinical improvement at the end of treatment. Hence it appears unlikely that these patients were suffering from other inflammatory or neoplastic diseases of the gastro-intestinal tract which mimic tuberculosis.

Regarding the role of surgery, only two of our patients in the 12E series during the chemotherapy phase required surgical intervention for obstruction. However, in patients with intestinal tuberculosis radical surgery such as right hemicolectomy was advocated by Banerjee and Bansal, although Joshi recommended conservative surgery like resection anastomosis.

Nevertheless our study has shown that there is no role for routine surgery in the treatment of abdominal tuberculosis. In the follow-up phase, 2 (2%) of 85 in the 6-month series underwent surgical procedures for suspected obstruction, which is probably a sequelae to tuberculous lesion in the intestine. But in British studies of abdominal tuberculosis, respectively 32% and 33% needed surgical intervention for confirmation of diagnosis, as it needs to be differentiated from the more prevalent Crohn’s disease in Britain. Similarly, in Taiwan, 79% of 121 patients underwent surgical procedures either for confirmation of diagnosis or for complications.

With reference to mortality, 3 (2%) of 193 patients died due to complications of tuberculosis in our series; but in a report by Lingenfelser et al. from South Africa, 6 (7%) of 82 patients died in hospital due to tuberculosis.

During the follow-up of 5 years, none of the 147 patients developed relapse of abdominal tuberculosis. This finding suggests that the two regimens employed in our study are very effective.

In conclusion, the five year follow-up results have shown that:

- the 6-month short-course chemotherapy regimen is adequate in all forms of abdominal tuberculosis;
- surgery is indicated only for the management of complications like perforation or obstruction;
- the 6-month rifampin regimen was significantly more hepatotoxic than the 12-month non-rifampicin regimen, but this problem could be managed with temporary interruption of the drugs during the period of jaundice and the same drugs could be resumed after recovery from jaundice;
- none relapsed during the five-year period of follow-up.
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References


RESUMEN

OBJETIVOS: Evaluar y comparar la eficacia de un esquema de quimioterapia de corta duración de 6 meses (QCD) con un esquema estándar de 12 meses en el tratamiento de la tuberculosis abdominal.

MÉTODO Y SUJETOS: Un total de 193 pacientes con tuberculosis abdominal fueron asignados en forma aleatoria en uno de dos esquemas cotidianos: 1) QCD con rifampicina másisoniacida más pirazinamida por un periodo de 2 meses, seguido por rifampicina eisoniacida durante 4 meses adicionales (serie 6R), y 2) el esquema
estándar de 12 meses con etambutol e isoniazida por 12 meses con un suplemento inicial de estreptomicina durante 2 semanas (serie 12E). La cirugía se efectuó solamente en los pacientes con sospecha de obstrucción o perforación.

**RESULTADOS**: En análisis de eficacia se efectuó en 163 pacientes (85 serie 6R, 78 serie 12E), 30 fueron excluidos. Al final del tratamiento, el estado clínico fue considerado normal en 84 (99%) pacientes de la serie 6R y en 73 (94%) de la serie 12E. De estos, 147 pacientes fueron seguidos durante 5 años; ninguno había recaído de la tuberculosis abdominal.

**CONCLUSIÓN**: El esquema de 6 meses (QCD) fue tan eficaz como el esquema de 12 meses en el tratamiento de todas las formas de tuberculosis abdominal.