SIX MONTHS VERSUS 9 MONTHS OF ANTI-TB THERAPY FOR ABDOMINAL TUBERCULOSIS: A META ANALYSIS

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ABSTRACT

Significance: Abdominal tuberculosis, which is one of the most prevalent forms of extrapulmonary tuberculosis, is an increasing health problem mainly due to the increasing incidence of AIDS and multidrug resistant tuberculosis. In the Philippines, tuberculosis (TB) is the sixth leading cause of morbidity and mortality. A 6-month treatment regimen has been recommended for abdominal tuberculosis based on the 2016 clinical practice guidelines for the diagnosis, prevention and treatment of tuberculosis for adult Filipinos. Many clinicians still extend the treatment to 9 or 12 months. We sought to find out whether 6 months therapy is as effective as 9 months therapy.

Methodology: A comprehensive electronic literature search was carried out for RCTs comparing six versus 9 months therapy for abdominal tuberculosis. Internet database search was done in Cochrane, PubMed, and Google Scholar. Validation was done using the JADAD score. The Cochrane risk of bias tool was used to assess methodological quality. Statistical analysis was done using the software RevMan v5.3. Fixed model Mantel-Haenszel meta-analysis was used.

Results: Two out of four retrieved trials were included. Fixed model meta analysis showed that there was no statistically significant difference between six months treatment versus nine months treatment for abdominal tuberculosis as overall Mean difference was 0.95, 95% CI: 0.53 – 1.71, p-value =0.88. There was no heterogeneity noted.

Conclusion: A six-month treatment for abdominal tuberculosis is as effective as nine months of treatment in terms of achieving complete response to treatment.

Keywords: Abdominal tuberculosis, treatment duration, six months versus 9 months

INTRODUCTION

Abdominal tuberculosis is the sixth most frequent site of extrapulmonary tuberculosis involvement and can involve any part of the gastrointestinal tract[10]. Both the incidence and severity of abdominal tuberculosis are expected to increase with increasing incidence of HIV infection. Tuberculous bacilli reach the gastrointestinal tract via haematogenous spread, ingestion of infected sputum, or direct spread from infected contiguous lymph nodes and fallopian tubes. The gross pathology is characterized by transverse ulcers, fibrosis, thickening and stricturing of the bowel wall, enlarged and matted mesenteric lymph nodes, omental thickening, and peritoneal tubercles. The most common site of involvement of the gastrointestinal tuberculosis is the ileocaecal region. Ileocaecal and small bowel tuberculosis present with a palpable mass in the right lower quadrant and/or complications of obstruction, perforation or malabsorption especially in the presence of stricture. Rare clinical presentations include dysphagia, odynophagia and a mid oesophageal ulcer due to oesophageal tuberculosis, dyspepsia and gastric outlet obstruction due to gastroduodenal tuberculosis, lower abdominal pain and haematochezia due to colonic tuberculosis, and annular rectal stricture and multiple perianal fistulae due to rectal and anal involvement[11].

Chest X-rays show evidence of concomitant pulmonary lesions in less than 25 per cent of cases. Useful modalities for investigating a suspected case include small bowel barium meal, barium enema, ultrasonography, computed tomographic scan and colonoscopy. Ascitic fluid examination reveals straw coloured fluid with high protein, serum ascitis albumin gradient less than 1.1 g/dl, predominantly lymphocytic cells, and adenosine deaminase levels above 36 U/l. Laparoscopy is a very useful investigation in doubtful cases[13].

Management is conventionally done with antituberculosis therapy for 9-12 months. The recommended surgical procedures today are conservative and a period of preoperative drug therapy is controversial. The new guidelines from the World Health Organization recommends 6 months duration of therapy.

The evidence regarding the duration of therapy has conflicting results. So, we tried to do a systematic review and meta-analysis to establish whether 6 months therapy is as effective as 9 months therapy.

OBJECTIVES

General Objective:
To evaluate whether 6 months of treatment for patients with abdominal tuberculosis is as effective as a 9-month treatment duration.

Specific Objectives:
Primary: To compare the efficacy of a 6 month treatment regimen versus 9 months of treatment of abdominal tuberculosis in terms of achievement of complete clinical response.

Secondary: To compare the efficacy of a 6 month treatment regimen versus 9 months of treatment of abdominal tuberculosis in terms of disease recurrence after treatment.

METHODOLOGY

Article Search:
A systematic search for clinical trials through the Cochrane library, Pubmed database, and Google Scholar, supplemented by a manual search for other relevant journals was conducted. We came across 4 trials which compared different treatment durations for abdominal tuberculosis. During our search through Cochrane, we found a proposal for a similar meta-analysis on TB duration of therapy. This study was published November of this year. Our meta analysis was completed by September of this year.

Key words:
Abdominal tuberculosis treatment duration, six months versus nine months

Selection:
The criteria for selection of trials for inclusion in the review were:
- A randomized controlled trial comparing 6 months versus 9 months treatment duration for abdominal tuberculosis
- Human studies
- The criteria for exclusion were:
- Studies done on animals
- Treatment durations other than 6 or 9 months
- Patients with other significant co-morbid medical conditions such as HIV/AIDS, and malignancy

Selection and Validity Assessment of trials:
From the total 4 trials, two trials were excluded because they used a different treatment duration for comparison to 6 months (Balasubramanian, et al) and included HIV/AIDS patients in the study population (Swaminathan, et al). The remaining 2 studies were both randomized controlled trials comparing 6 months versus 9 months treatment duration for abdominal tuberculosis. The included studies involved 287 participants. The studies were validated using the JADAD scoring system. Cochrane risk of bias tool. Both trials did not use blinding.

Table 1: Summary of the Validity of the trials:

	Park 2009	Makharia 2015
Randomized	1	1
Method of Randomization	1	1
Double Blinded	0	?
Method of Blinding	0	?
Handling of Dropouts and withdrawal	1	1

Data extraction and management:
Two review authors (DE, KS) screened search results for eligible trials and finalized the 2 trials for inclusion. The 2 excluded trials were listed with reasons for exclusion as explained earlier. Two review authors (KS and DE) independently reviewed the search results and selected the trials. In case of conflict, disagreements between reviewers were resolved by consensus. Data on baseline participant characteristics, methodology of trial, risk of bias, and the result needed for review were gathered from the included trials.

Quantitative Data Synthesis:
The statistical analysis in this meta-analysis was done using RevMan software version 5.3. The studies used had the same outcome. A meta-analysis of intention-to-treat data was performed using the fixed model Mantel-Haenszel method. P values <0.05 were considered significant. The extent of statistical heterogeneity was calculated using I^2 index.
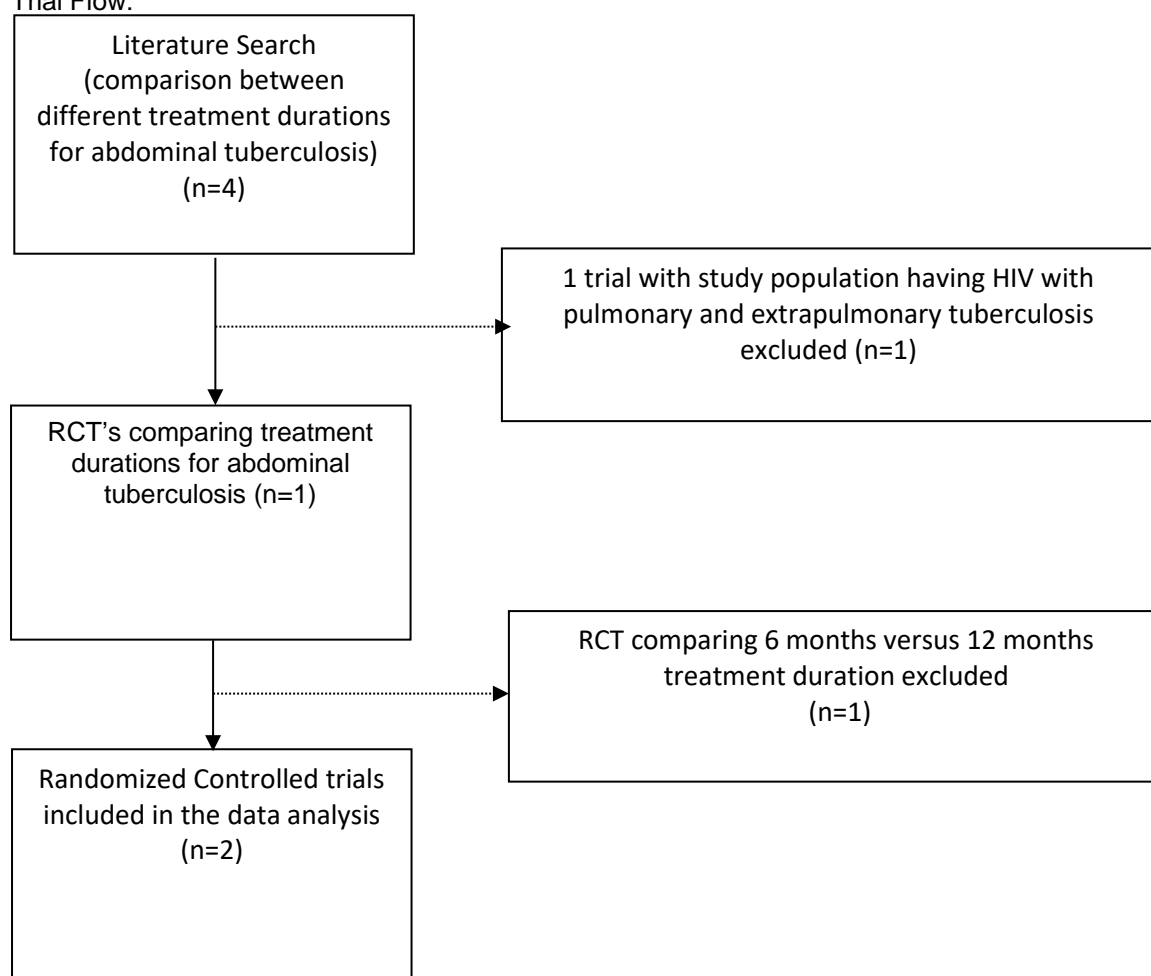
Trial Flow:

Literature Search
(comparison between different treatment durations for abdominal tuberculosis)
(n=4)

1 trial with study population having HIV with pulmonary and extrapulmonary tuberculosis excluded (n=1)

RCT's comparing treatment durations for abdominal tuberculosis (n=1)

RCT comparing 6 months versus 12 months treatment duration excluded
(n=1)

Randomized Controlled trials included in the data analysis
(n=2)

Diagram A. Flow of RCT inclusion in the systematic review

Trial Characteristics:
The first study done in Korea by Park et al in 2009 randomized 90 patients definitely diagnosed with intestinal TB into 6-month and 9 –month treatment groups. The primary endpoint was complete response. Relapse was also assessed 1 year after therapy. Baseline characteristics of the study population were similar.

The second trial was a multicenter study in India done by Makharia et al. The study randomized 197 patients with abdominal tuberculosis to receive either 6 months or 9 months of antituberculosis therapy

using intermittent directly observed therapy. Evaluation was done for the primary endpoint which was complete clinical response. Patients were followed up 1 year after therapy to assess recurrence. Baseline characteristics were similar between the two randomized groups. Table 1 shows the methodological and clinical details for each trial.

Table 2: Summary of the Studies:

Study	Methods	Participants	Intervention	Endpoints
1.Park et al. 2009	Randomized controlled trial	90 (19 to 74 years old) definitely diagnosed with intestinal TB	45 patients received 6-month Z2H6R6E6 treatment and 45 patients received 9-month treatment with Z2H9R9E9	Primary: Complete response Secondary: Relapse 1 year after the end of therapy
2. Makharia et al. 2015	Randomized controlled trial	197 (15 to 65 years old) newly diagnosed patients with abdominal tuberculosis	HRZE x 2 months + HR x 4 months (6-month group: 104 patients) HR x 7 months (9-month group: 93 patients)	Primary: Complete clinical response, partial response, and no response Secondary: Recurrence of the disease at the end of 1 year of follow up

RESULTS: Primary Analysis

In both studies, data for efficacy at end of treatment were provided, randomizing 287 patients. In the pooled analysis, there was no significant difference in the efficacy of 6 months treatment duration versus that of 9 months duration. (OR=0.95, 95% CI 0.53-1.71, P=0.88). There was no evidence of heterogeneity (I^2=0%)
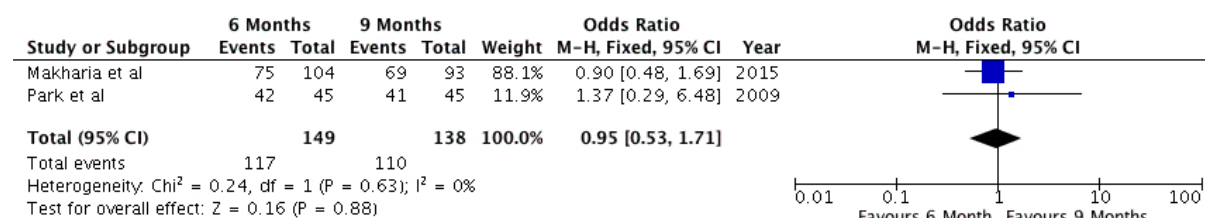

Both studies also compared the risk of relapse within 1 year after the end of treatment between the 6-month and 9-month treatment durations. Analysis showed no significant difference between the two (OR=2.86, 95% CI 0.29-27.97, P=0.37). For both studies, 1 patient had a relapse of abdominal tuberculosis in the 6-month treatment duration group and none had a relapse in the 9-month treatment duration group.
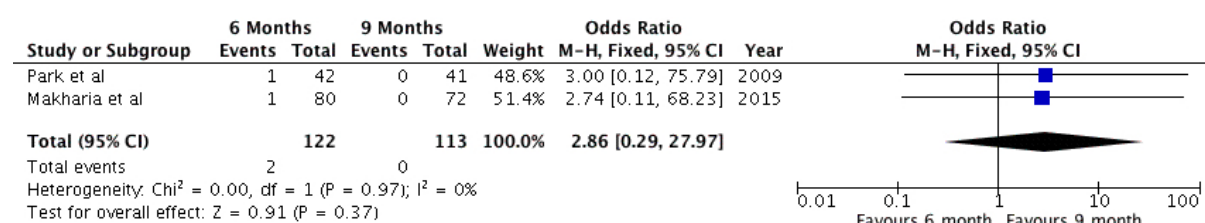
Publication Bias
The Funnel plot was used to detect any evidence of publication bias. Since all studies fall inside the funnel line, the publication bias in the studies was negligible.
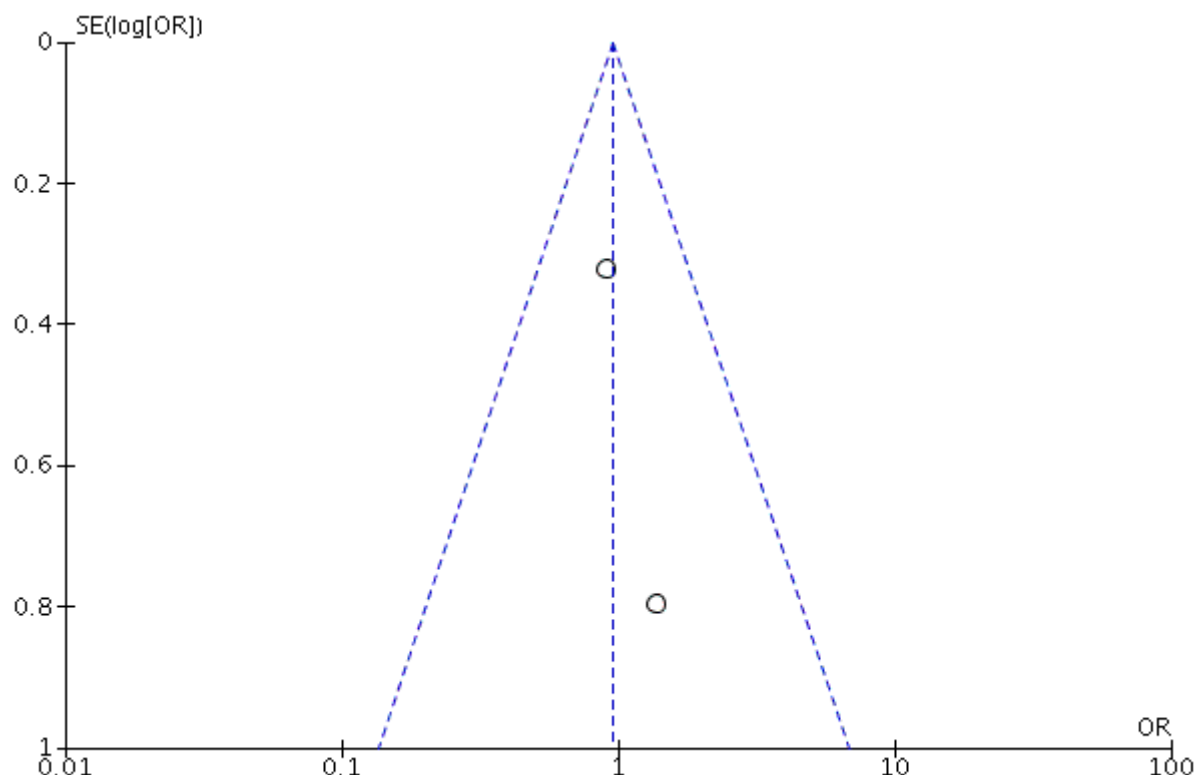
Assessment of Heterogeneity

For the primary outcome of complete response to treatment, the studies were homogenous (P=0.63, I^2=0%). For the secondary outcome of relapse 1 year after treatment, both studies were also homogenous (P=0.97, I^2=0%).

RESULTS AND DISCUSSION

Tuberculosis (TB) is a life threatening disease which can virtually affect any organ system. TB can disseminate to other parts of the body from the lung, which is usually the primary site. Extra-pulmonary organ involvement of Tuberculosis is estimated as 10%-15% of patients not infected with HIV whereas the frequency is about 50%-70% in patients infected with HIV. It is an increasing health problem mainly due to the increasing incidence of AIDS and multidrug resistant tuberculosis. Especially in third world countires, the spread of the disease is further aided by poverty, overcrowding, and drug resistance[12].

Abdominal TB has non-specific clinical and radiological presentations. A high degree of suspicion is needed for diagnosis. Abdominal TB usually occurs in four forms: tuberculous lymphadenopathy, peritoneal tuberculosis, gastrointestinal (GI) tuberculosis and visceral tuberculosis involving the solid organs. Usually a combination of these findings occurs in any individual patient. Abdominal tuberculosis is responsive to medical management. Early diagnosis followed by prompt initiation of treatment is therefore very important for prevention of unnecessary surgical intervention. As recommended by the 2016 Philippine clinical practice guidelines for the diagnosis, treatment, prevention and control of tuberculosis in adult Filipinos, a 6-month treatment regimen for abdominal tuberculosis is enough to achieve complete response to treatment. However, many clinicians extend treatment duration to 9 or 12 months.

Only a few studies have been conducted comparing 6 months versus a longer treatment duration for abdominal TB. This meta-analysis only used trials comparing 6 months versus 9 months treatment duration. Analysis of the pooled data for the 2 studies used showed no significant difference between 6 months versus 9 months treatment regimen in terms of efficacy at the end of treatment and risk of

relapse within 1 year after the end of treatment. This finding is especially relevant in the Philippine setting where TB is endemic, and duration plus cost of treatment plays a big role in patient compliance.

CONCLUSIONS

A six-month treatment for abdominal tuberculosis is as effective as nine months of treatment in terms of achieving complete response to treatment. Further studies on a larger population could be done to draw more significant conclusions.

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