Corticosteroid Treatment of Peritoneal Tuberculosis

Abdulrahman A. Alrajhi, Magid A. Halim, Abdullah Al-Hokail, Fahad Alrabiah, and Kawther Al-Omran

Corticosteroids are beneficial as treatment of certain tuberculosis syndromes. We reviewed all cases of peritoneal tuberculosis diagnosed at our institution over 10 years to evaluate the role of corticosteroid administration combined with antituberculous therapy. Nine patients were treated with steroids plus antituberculosis agents (cases), and 26 received antituberculosis treatment only (controls). The two groups were not significantly different in terms of their basic demographics or disease. Nineteen controls compared with one case had recurrent abdominal pain. Seven controls had 17 emergency department visits because of abdominal pain. Intestinal obstruction was diagnosed for five of these patients, four of whom underwent laparotomy revealing extensive adhesions. Three controls died, and no case died. No case required laparotomy, had a diagnosis of intestinal obstruction, or visited the emergency department because of abdominal pain. These findings suggest that corticosteroid administration combined with antituberculosis treatment reduces the frequency of morbidity and complications in patients with peritoneal tuberculosis.

The recent resurgence of tuberculosis (TB) is global. This increase has been mainly attributed to HIV infection, but TB also affects the HIV-negative population to a lesser extent [1]. The increase in the incidence of extrapulmonary TB over a 5-year period was 20%, compared with an incidence of pulmonary tuberculosis of 3% in the United States [2]. Peritoneal TB accounts for 3.3% of cases of extrapulmonary TB [3]. Most patients with TB do well with antimycobacterial therapy alone. The beneficial role of steroid administration in conjunction with antituberculous chemotherapy was noted for few conditions, notably pericarditis and meningitis [4–12]. Other conditions for which steroid administration may be beneficial are severe debilitation, hypoxia in association with miliary TB, and pleurisy [13–15].

Methods

We reviewed all cases of TB at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) over a 10-year period (1987–1996). Peritoneal TB was defined by at least one of the following two criteria: isolation of Mycobacterium tuberculosis from ascitic fluid or a peritoneal tissue biopsy specimen, or observation of small tubercles in the peritoneum during laparoscopy or laparotomy with biopsy-proven granuloma and a favorable clinical response to antituberculous chemotherapy. Basic demographic and diagnostic data were collected for all the patients meeting the inclusion criteria. Data on follow-up, symptoms and signs, duration of follow-up, emergency department visits and admissions because of abdominal pain, and laparotomy for treatment of intestinal obstruction after therapy were collected before data about treatment and steroid use. Data on treatment (including types and duration of antituberculous therapy and dose and duration of steroids) were collected by a different investigator to reduce
bias. If the patient complained of unexplained abdominal pain during at least three different follow-up visits, recurrent abdominal pain was noted as a late complication of peritoneal TB. Any emergency department visit because of abdominal pain during or after treatment was recorded, as was intestinal obstruction (which was indicated in the patient’s record if supported by radiological evidence of air-fluid levels).

The patients were grouped into two groups: those treated with steroids plus anti-TB therapy (cases) and those treated with anti-TB therapy without steroids (controls). The two groups were compared in terms of their basic demographics, symptoms and signs, duration of symptoms before treatment, diagnostic findings, susceptibility of M. tuberculosis isolates, types and duration of treatment, and follow-up findings.

Data entry and analysis were performed by Epi-Info Version 6.04 (USD, Stone Mountain, GA) and Statistica Version 5.0 (StatSoft, Tulsa, OK). The Student’s t test was used to calculate continuous variables, and the χ² or Fisher’s exact test was used to calculate categorical variables. A P value of <.05 was considered significant.

Results

Forty-one cases met one or both of the inclusion criteria. Six cases could not be included in the analysis: two had a postmortem diagnosis (M. tuberculosis was isolated from ascitic fluid that was drawn during evaluation; these cases never received anti-TB treatment), and four were referred to our institution for laparoscopy and were sent back to their referring hospitals after the procedure (peritoneal TB was confirmed by culture weeks later; no treatment was initiated at our institution, and no follow-up was performed).

Detailed data were available for 35 patients. Nine were treated with steroids and anti-TB therapy (cases), and 26 were treated with anti-TB therapy without steroids (controls). The cases of peritoneal TB in both groups were spread evenly over the 10-year period. There were 17 males and 18 females. All 35 patients were followed up for a mean of 24 months (range, 2–118 months). The cases had a mean follow-up of 23 months (range, 13–32 months; median, 22 months) compared with a mean follow-up of 24 months (range, 2–118 months; median, 16 months) for the controls. The shorter minimal follow-up for the controls resulted from the early death of a patient in this group.

Ascitic fluid specimens from 27 patients were sent for culture for acid-fast bacilli (AFB); M. tuberculosis was isolated from 14 (52%) of these patients. Peritoneal biopsy specimens from 26 patients were sent for AFB culture; M. tuberculosis was isolated from 24 (92%) of these patients. AFB staining of the two culture-negative biopsy specimens was negative, and histopathologic examination of these specimens revealed caseating granulomata. M. tuberculosis was not isolated from ascitic fluid or peritoneal biopsy specimens from one case and three controls. These four patients were included in the analysis on the basis of their laparoscopic and histopathologic findings and their good clinical response to anti-TB medications. There was no significant difference between the patients for whom cultures yielded M. tuberculosis and those for whom cultures did not, in terms of their basic demographic data, duration of symptoms, and results of ascitic fluid analysis. M. tuberculosis was isolated from a mesenteric lymph node specimen from one case, and two cases had chest roentgenograms suggestive of TB. M. tuberculosis was isolated from cecum, adrenal gland, and liver specimens from three controls, and seven controls had chest roentgenograms suggestive of TB.

All patients received isoniazid and rifampin at the initiation of therapy except for one control who received rifampin without isoniazid because of concerns that this patient’s chronic viral hepatitis would worsen. Use of other first-line antituberculous drugs was similar in both groups. Cases were given steroids with antituberculous therapy according to the caring physician’s practice. Cases received a dose of prednisone, 0.5–1.0 mg/(kg·d) for a mean of 6.6 weeks (range, 4–9 weeks). Corticosteroids were given as oral prednisone once daily, and the dose was tapered by 5–10 mg every 10–14 days. Steroids were given at the initiation of anti-TB therapy to six cases and after 3, 4, and 6 days to three cases.

The side effects attributed to steroids in the cases’ records were limited to epigastric discomfort in two cases; the discomfort was treated by antacids in one and ranitidine in the other. A third case’s oral hypoglycemic requirements were increased after 3, 4, and 6 days to three cases. Fourteen cases met one or both of the inclusion criteria.

There was no significant difference between the cases and controls in terms of their mean age, gender distribution, mean duration of symptoms before treatment, duration of treatment, mean highest recorded temperature, results of ascitic fluid analysis, differential blood cell count, types and duration of anti-TB therapy, duration of follow-up, and susceptibility pattern of the isolated organism. These findings are summarized in table 1.

During follow-up, 19 controls (73%) complained repeatedly of abdominal pain compared with one case (11%) (Fisher’s exact test, P = .0019). Seven controls (27%) had recurrent vomiting compared with none of the cases. These seven controls presented to the emergency department 17 times because of abdominal pain and vomiting. Five of these controls were admitted, and intestinal obstruction with radiological evidence of air-fluid levels was diagnosed; four required laparotomy. Extensive adhesions were noted and thought to be the cause of the intestinal obstruction. On the other hand, no case underwent laparotomy or had a diagnosis of intestinal obstruction. None of the cases visited the emergency department because of abdominal pain. These data are summarized in table 2.

One control had secondary infertility requiring in vitro fertilization on two occasions. A subgroup analysis of patients with...
Table 1. Comparison between patients with peritoneal tuberculosis who were treated with antituberculous therapy with (cases) or without (controls) steroids.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Mean age in y (SE)</td>
<td>40 (1.85)</td>
<td>47 (2.8)</td>
<td>.20</td>
</tr>
<tr>
<td>No. (% of females)</td>
<td>5 (56)</td>
<td>13 (50)</td>
<td>.69</td>
</tr>
<tr>
<td>Mean duration of symptoms before treatment in w (SE)</td>
<td>14.2 (2.63)</td>
<td>15.8 (2.70)</td>
<td>.76</td>
</tr>
<tr>
<td>Mean highest temperature in °C (SE)</td>
<td>38.2 (0.22)</td>
<td>37.8 (0.16)</td>
<td>.18</td>
</tr>
<tr>
<td>Mean WBC count in ascitic fluid in /mm³ (SE)</td>
<td>1,385 (553)</td>
<td>1,036 (272)</td>
<td>.53</td>
</tr>
<tr>
<td>Mean lymphocyte percentage in ascitic fluid (SE)</td>
<td>68 (5.68)</td>
<td>78 (4.75)</td>
<td>.21</td>
</tr>
<tr>
<td>Mean total protein level in g/dL (SE)</td>
<td>57 (3.38)</td>
<td>46 (4.82)</td>
<td>.32</td>
</tr>
<tr>
<td>Mean treatment duration in mo (SE)</td>
<td>13 (2.4)</td>
<td>10 (1.0)</td>
<td>.12</td>
</tr>
<tr>
<td>Mean follow-up duration in mo (SE)</td>
<td>23 (2.0)</td>
<td>24 (5.5)</td>
<td>.85</td>
</tr>
</tbody>
</table>

Peritoneal complications compared with patients without complications showed no significant difference in terms of their initial demographics or disease criteria. The duration of symptoms before therapy for patients with complications was 8 weeks longer than that for patients without (mean, 18 weeks vs. 10 weeks) but was not statistically significant (P = .17), probably because of the small numbers.

Three controls died. One of them died after 9 months of treatment, of complications of hepatic cirrhosis and gastrointestinal bleeding related to hepatitis C virus infection. The other two controls died after 8 and 10 weeks of treatment, respectively, of complications related to intestinal obstruction, perforation, and multiorgan failure in one and debilitation, massive ascites, and sepsis in the other. No case died.

Discussion

Corticosteroids have significant antiinflammatory and immunosuppressive effects. They inhibit the production of some cytokines by lymphocytes and mononuclear phagocytes [18]. Steroids also block the effect of cytokines on some target cells [19], reduce the polymorphonuclear inflammatory response, and decrease peripheral blood lymphocytes, monocytes, basophils, and eosinophils. Historically, the immunosuppressive effect of steroids on the progression of TB was noted before the availability of anti-TB chemotherapy [20]. Corticosteroid administration in cases of TB was thought to be contraindicated [21], but subsequently corticosteroids were noted to be associated with no progression of TB if anti-TB chemotherapy was used [22].

It took more than a decade before a comprehensive review of steroid administration in TB cases was reported [23]. Adjuvant steroid therapy has certain benefits in some cases of TB syndromes. Improved survival was noted when corticosteroids were used by some investigators for treatment of tuberculous meningitis [7–11]. There is also good evidence to support the use of concurrent steroids with anti-TB therapy in cases of tuberculous pericarditis as indicated by the Working Group on Steroid Use of the Infectious Diseases Society of America [12]. The antiinflammatory effect of steroids reduces restrictive pericarditis and decreases the morbidity and mortality due to tuberculous pericarditis [6].

On the other hand, for peritoneal TB, no conclusive evidence for or against the combination of steroids plus anti-TB therapy was found [12]. In 1969, Singh et al. [16] reported a nonblinded study where they prospectively gave steroids to alternate patients with peritoneal TB. Of 47 patients, 23 were given 30 mg of prednisone daily for 3 months along with isoniazid and streptomycin. The prednisone dose was tapered over the fourth month to zero. There was no difference between the two groups in terms of the initial symptomatic response. During follow-up, the patients treated with the steroid plus anti-TB therapy had no intestinal obstruction compared with three of the 24 patients treated with anti-TB therapy only who had intestinal obstruction requiring surgical intervention to free adhesive bands. There were no deaths in either groups. To our knowledge, no other study in the English-language literature reported the effect of steroids on the outcome of peritoneal TB.

In three recent reviews of steroid use in TB cases [13, 24, 25], peritoneal TB was not even discussed as a TB condition

Table 2. Outcome variables for patients with peritoneal tuberculosis who were treated with antituberculous therapy with (cases) or without (controls) steroids.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 26)</th>
<th>Cases (n = 9)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% of patients complaining of repeated abdominal pain)</td>
<td>19 (73)</td>
<td>1 (11)</td>
<td>.0019</td>
</tr>
<tr>
<td>No. (% of patients visiting the emergency department because of abdominal pain)</td>
<td>7 (27)</td>
<td>0</td>
<td>.15</td>
</tr>
<tr>
<td>No. (% of patients for whom intestinal obstruction was diagnosed)</td>
<td>5 (19)</td>
<td>0</td>
<td>.29</td>
</tr>
<tr>
<td>No. (% of patients who underwent laparotomy for treatment of intestinal obstruction)</td>
<td>4 (15)</td>
<td>0</td>
<td>.55</td>
</tr>
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</table>

* Fisher’s exact test; values are two-tailed.
that may benefit from steroid treatment. Bastani et al. [26] reported using steroids as therapy for more than one-half of their patients with tuberculous peritonitis but did not mention the effect of this treatment on the patients’ outcomes. Other studies of peritoneal TB retrospectively analyzed the role of adding corticosteroid therapy to anti-TB treatment [27]; of 22 patients, six were given varying doses of prednisone at different times in their disease course. No additional benefit was noted from steroid treatment. The outcome parameters that Piéron et al. [20] evaluated were different from those in our series. In another French report [28] of 20 patients, six received steroid therapy and had more rapid resolution of symptoms than did other patients, but long-term follow-up was not reported. The case definition in these and other series [17] was not clear, and cases of abdominal or intestinal TB were also included.

Bennani et al. [17] prospectively randomized 50 of 100 patients to receive 30 mg of prednisone for the first 8 weeks. Response to treatment was similar in the two groups. Follow-up laparoscopy after 12 or 24 months of therapy showed that 25 of 30 patients in the control group compared with 24 of 28 patients in the steroid group had persistent adhesions. The methodology was not clear, and intervals for evaluation of granulomata were not consistent in both groups. Clinical follow-up data were not reported.

In our series, all patients had confirmed tuberculosis of the peritoneum. The cases and controls were quite comparable in terms of criteria, disease severity, duration, antimicrobial therapy, and microbial susceptibility. Although fewer patients were treated with steroids than with anti-TB therapy alone, only one of the nine cases complained of abdominal pain during follow-up visits. Looking at a more objective outcome, the number of emergency department visits by the controls was 17 (0.7 visit per patient) during the follow-up period. No case visited the emergency department because of abdominal pain or had a diagnosis of intestinal obstruction. Abdominal pain was described in >83% of patients with peritoneal TB in other series [26, 29].

Similar to the findings of Singh et al. [16], intestinal obstruction was diagnosed for five of our controls by clinical and radiological parameters. Four of these patients required laparotomy for treatment of intestinal obstruction. Extensive adhesive bands were noted in the abdomen and thought to be the cause of the obstruction. These adhesions were attributed to previous peritoneal TB and the associated inflammatory fibrotic process. This process was probably modified by concurrent use of steroids, as shown in a randomized, prospective study of TB pericarditis [6]. Khoury et al. [29] described 30 patients with peritoneal TB; 14 presented to the emergency department, of whom five had emergency abdominal surgery and two had bowel resection for treatment of the obstruction. Of the 29 patients who had abdominal surgery, 12 had adhesions, and one underwent another operation 1 month later for division of the adhesions.

In our series, the three deaths of controls cannot be attributed to the lack of steroid use. One patient’s death was related to hepatic cirrhosis and gastrointestinal bleeding complicating viral hepatitis after several months of anti-TB treatment. The two other patients died of complications of peritoneal TB that may not have been prevented by steroid treatment.

Although our study was not prospective, we tried to reduce reviewer bias by first collecting follow-up data and then collecting treatment data (including steroid use) by another investigator. A prospective, randomized, double-blind study would be the investigation to convincingly prove that steroid use reduces morbidity in cases of peritoneal TB. To our knowledge, similar studies have never been performed for other conditions (e.g., tuberculous meningitis); nevertheless, the role of steroids as adjuvant therapy for tuberculous meningitis is not disputed now. Until results of a prospective, randomized, double-blind trial are available, we advocate the use of steroids with anti-TB drugs to reduce the frequency of complications and morbidity in patients with peritoneal TB.

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References