STEROIDS FOR TUBERCULOUS PLEURISY

A Systematic Review and Meta-analysis of clinical trials

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Dissertation submitted in partial fulfilment of the requirements for the Masters in Public Health degree at the University of Cape Town, School of Public Health and Family Medicine

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DECLARATION

I, Mark Engel hereby declare that the work contained herein is my original work except where acknowledgements indicate otherwise, and that neither the whole work nor any part thereof has been, or is to be submitted for another degree in this or any other university.

Signed by candidate

Signature Removed

December 2004

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Hayden, my dear son, who remains my inspiration to succeed.

Ad maiorem dei gloriam

SYNOPSIS

Tuberculous pleurisy results from tuberculous infection of the pleura, the membrane surrounding the lungs. This results in a build up of fluid around the lung which impairs breathing and may also lead to long term effects permanently restricting lung function.

Some clinicians believe that steroids used in combination with anti-tuberculous drugs can help to prevent these complications. Concern also exists regarding the potential adverse effects of steroids, especially in HIV positive patients. However, high quality evidence on the benefits and harms associated with steroid use is limited.

This review finds no clear evidence on which to base decisions regarding the use of steroids in patients with tuberculous pleurisy. Trials that are large enough to assess important outcomes such as lung function and death are needed. Future research should, in particular, evaluate the balance between benefit and harm in people infected with HIV.

ABSTRACT

Background: Corticosteroids used in addition to anti-tuberculous therapy have been reported to benefit people with tuberculous pleurisy. However, research findings are not consistent, raising doubt as to whether such treatment is worthwhile. Concern also exists regarding the potential adverse effects of steroids, especially in HIV positive patients. An earlier Cochrane review summarized the existing evidence on the effects of steroids in people with tuberculous pleurisy. This review updates the evidence and, for the first time sheds light on the effects of steroids in patients with tuberculous pleurisy co-infected with HIV.

Objectives: To examine the evidence from randomised controlled trials concerning the effect of steroids in patients with tuberculosis of the pleura.

Search strategy: The following databases were searched: Cochrane Infectious Diseases Group specialized trials register (October 2003), The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2003), MEDLINE (1966 to October 2003), EMBASE (1980 to October 2003), LILACS (October 2003), U.S. NIH ClinicalTrials.gov (October 2003), and Current Controlled Trials (October 2003). In addition, Lists of references from review articles and primary studies were scanned for further studies

Selection criteria: Randomised and quasi-randomised trials evaluating the effects of adjunctive corticosteroids in patients diagnosed with TB pleurisy were sought.

Data collection & analysis: Two authors independently applied inclusion criteria,

assessed trial quality and extracted relevant information. We analyzed data using Review Manager (Version 4.2) and pooled estimates of effect using relative risks for binary data.

Main results: Four trials with 433 participants met the inclusion criteria; only one study included patients with HIV infection.

Compared to placebo, steroid use was associated with less residual pleural fluid at both 4 weeks (2 trials, 311 participants: relative risk (RR) 0.67, 95% confidence interval (CI) 0.50 to 0.90) and 8 weeks (2 trials, 234 patients: RR 0.53, 95% CI 0.37 to 0.77). However, we found no evidence of an effect of steroids on respiratory function, mortality, pleural thickening or pleural adhesions.

Although discontinuation of treatment due to adverse effects was more frequent in patients receiving steroids than placebo, (3 trials, 304 participants: RR = 2.67, 95% CI 1.03 to 6.96) the effects were generally mild. It is possible that the risk of Kaposi sarcoma is increased in HIV positive patients receiving steroids (1 trial, 194 participants: RR = 13.00, 95% CI 0.74 to 227.63).

Conclusions: There are currently insufficient data to support evidence-based recommendations regarding the use of adjunctive steroids in patients with tuberculous pleurisy. Randomised trials that are sufficiently powered to evaluate both morbidity and mortality are needed. In people co-infected with HIV the effects of steroids on HIV-related complications, such as Kaposi sarcoma, should be assessed.

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1. BACKGROUND

Extrapulmonary tuberculosis including tuberculous lymphadenitis, pericarditis, meningitis and pleural effusion has become more frequent in recent years (Harries 1990) and this increase is believed to be attributable to co-infection with HIV (Song 2003; Yang 2004).

1.1 Definition and Incidence

Tuberculous pleural effusion (TPE) arises from abnormal accumulation of fluid in the pleural space between the lungs and chest wall. It is thought to be a delayed hypersensitivity reaction following a recent mycobacterial infection of the pleura, a semi-permeable membrane covering the lungs (Rossi 1987). TPE is the most frequent extrapulmonary manifestation of TB (Mehta 1991) and is relatively common in areas where TB occurs. In one series of 1700 TB patients, 70 cases of TPE were identified (Seibert 1991). A higher prevalence of TPE has been reported in HIV infected participants than in those not infected with the virus (Elliott 1990; Frye 1997). Possible explanations for this association include a higher burden of microorganisms due to impaired host response (Relkin 1994) and detection bias resulting from more opportunity for diagnosis of TPE in HIV positive individuals (Frye 1997).

1.2 Prognosis

The clinical manifestation of TPE is acute with symptoms including cough, fever, chest pain and dyspnoea (Morehead 1998). Although TPE can resolve spontaneously within a few weeks or months, medical treatment is believed to speed resolution of the effusion and reduce long-term complications such as fibrosis and thickening of the pleura which can further restrict lung function. Therapeutic options for pleural space infections include intravenous antibiotics, chest tube drainage, intrapleural administration of a fibrinolytic

agent to dissolve fibrous adhesions, thoracotomy to remove fibrinous and infected tissue and steroid therapy (Chapman 2004). The theoretical basis for using steroids in patients with TPE is that they suppress the inflammatory response, which is believed to be responsible for the condition. Prednisone or prednisolone is recommended at a daily dose of about 1 mg/kg gradually reducing after one to two weeks with a total treatment course sometimes being as long as three months (Lemaistre 1951; Mathur 1960; Morehead 1998; Blumberg 2003).

1.3 Debates

Studies of adjunctive steroids for the treatment of TPE show conflicting results. Non-randomised studies done in the pre-HIV era found that steroids led to more rapid resolution of the effusion and reduced likelihood of residual pleural thickening and pleural adhesions (Menon 1964; Singh 1965). Recently, an observational study of HIV positive participants with TPE found that compared with those not treated, prednisolone was associated with faster resolution of lymphadenopathy, [relative risk (RR) = 2.28, 95% CI = 1.27; 4.10] and cough [RR = 2.15, (1.21; 3.84)] (Elliott 1992).

In contrast, a critical appraisal of published studies demonstrated beneficial effects of steroids on acute symptoms, but found no benefit for chronic endpoints such as fibrosis, irrespective of dose (Dooley 1997). The authors noted that many of the studies however, lacked rigour and clinical correlations. Furthermore, a previous Cochrane review encompassing three randomised trials (total participants n=236) concluded that there was insufficient evidence for the effectiveness of adjunctive steroids verses placebo on mortality or morbidity as measured by incidence of pleural adhesions, RR = 0.30, [95% CI: 0.03;2.66]; residual pleural thickening at the end of treatment, RR = 0.75,

[0.44;1.28]; residual fluid at the end of treatments, RR = 0.29 [0.06;1.35] and acute clinical symptoms, RR = 0.07 [0.00;1.16]. No HIV-related data were available at the time.

In addition to the uncertainty about benefits of steroid therapy there is also concern about potential risks. In immunocompromised patients, such as those infected with HIV, steroids may further constrain the immune system leading to an increased frequency of opportunistic infections and tumours such as Kaposi sarcoma, a vascular tumour accompanied by numerous unconnected lesions of the skin which is thought to be associated with human herpes virus-8 infection (Ensoli 2001). More generally, adverse effects of steroids such as fluid retention and gastrointestinal disturbances have also been documented in people with TB (Anonymous 1983).

1.4 Aim of study

The aim of the study was to appraise the existing evidence on the benefits and harms of steroids regardless of individuals' HIV status. The study hypothesis was that in patients with TB pleurisy, there was no difference in the effects of steroid therapy and placebo on either mortality or morbidity.

2. METHODS

2.1 Objective

To examine the evidence from randomised controlled trials concerning the effects of steroids in people with tuberculosis of the pleura.

2.2 Inclusion criteria for studies in this review

2.2.1 Types of studies

Randomised and quasi-randomised trials[1]

2.2.2 Types of participants

Persons diagnosed with TB pleurisy by chest X-ray (as defined by authors) in addition to any one of the following: pleural biopsy for histology, Ziehl-Neelsen staining and/or culture of sputum, pleural fluid or pleural biopsy.

2.2.3 Types of interventions

Intervention: Any corticosteroid used in combination with anti-tuberculosis treatment (ATT)

Control: Any of the following in combination with ATT: no treatment, placebo, other active treatment

[1] *A trial using a quasi-random method, such as alternation, for the allocation of participants*

2.2.4 Types of outcome measures

PRIMARY

- Mortality from any cause
- Improvement in respiratory function

SECONDARY

- Reabsorption of pleural effusion (as defined by authors)
- Presence of pleural thickening
- Improvement in clinical symptoms and signs
- Adverse events due to treatment
- HIV-associated events

2.3 Search strategy for identification of studies

An attempt was made to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

The following search terms were used for all trial registers and databases (For detailed strategy, see appendix 7.1 "*Detailed Search Strategy*")

- *steroids*
- *corticosteroids*
- *dexamethasone*
- *hydrocortisone*
- *prednisolone*
- *prednisone*

in conjunction with '*tuberculosis or TB*'.

Databases searched:

a. The Cochrane Infectious Diseases Group specialised trials register for relevant trials (up to October 2003). Full details of the Cochrane Infectious Diseases Group methods and the journals hand searched are published in The Cochrane Library in the section on Collaborative Review Groups.

b. The Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* issue 4, 2003.

c. Electronic databases searched using the above search terms in combination with the search strategy developed by The Cochrane Collaboration and detailed in the Cochrane Reviewers' Handbook (Clarke 2003):

(1) MEDLINE (January 1966 to October 2003);

(2) EMBASE (January 1980 to October 2003);

(3) LILACS (La Literatura Latinoamericana y del Caribe de Informacion en Ciencias de Salud) www.bireme.br; accessed October 2003;

(4) U.S. National Institutes of Health. ClinicalTrials.gov <http://www.clinicaltrials.gov> accessed October 2003; and

(5) Current Controlled Trials. <http://www.controlled-trials.com/> accessed October 2003.

We also scanned references from review articles and primary studies and contacted experts in the field of tuberculosis to identify any additional unpublished and ongoing trials.

2.4 Study selection

The results of the search were screened to select potentially relevant studies. Two reviewers (ME, author and JV, supervisor) independently applied eligibility criteria, based on the study design, type of participant and interventions assessed. Differences in opinion were resolved through discussion. Where the abstracts were unclear or if there was any other reason for uncertainty, we obtained the full article before making a decision on study eligibility. When abstracts were not available in English we obtained the assistance of translators.

2.5 Assessment of methodological quality of trials

The quality of included trials was independently assessed using the following criteria:

(1) Generation of allocation sequence: judged as 'adequate' if methods such as table of random numbers, computer generated random numbers, or coin tossing were used.

(2) Concealment of allocation: judged as 'adequate' if methods such as central randomisation, sequentially numbered, sealed, opaque envelopes were used.

(3) Blinding: we reported whether investigators, participants, or assessors were blinded.

(4) Completeness to follow up: we recorded the percentage of randomised participants included in the analysis in each study.

2.6 Data extraction

Using a specially designed data extraction form (see Appendix 1), the following information was extracted for each trial with JV independently cross checking the data:

(1) Trial characteristics

- Method of randomisation
- Allocation concealment
- Blinding
- Type, frequency and duration of follow up
- Duration of trial
- Diagnostic criteria used, noting specifically whether participants were culture negative or positive
- Morbidity and mortality outcomes
- Adverse effects

(2) Intervention characteristics

- Type of treatment
- Dose of treatment
- Administration route of treatment

(3) Participant characteristics

- Number
- Age
- Gender
- HIV status

Differences in the extracted data were resolved by referring to the original articles and through discussion.

2.7 Analysis

Data were analysed using Review Manager (Version 4.2). We pooled estimates of effect using relative risks for binary data. We assessed heterogeneity by visually examining the forest plot and by the statistical Chi-square test for heterogeneity using a 10% level of significance. In the absence of homogeneity of treatment effects, we planned to use a random effects model. We planned to investigate clinical heterogeneity based on participants' HIV status. We also planned to conduct a sensitivity analysis based on study quality using adequacy of allocation of concealment as an indicator of the quality.

3. RESULTS

3.1 Description of studies

Forty-two studies were assessed of which 1 unpublished and 16 published trials were identified for possible inclusion into the review.

3.1.1 Included Trials

Four trials with 433 participants (Lee 1988, Galarza 1995, Wyser 1996, Elliott 2003) met our inclusion criteria. Included trials were conducted in Taiwan (Lee 1988), Spain (Galarza 1995), South Africa (Wyser 1996) and Uganda (Elliott 2003) with sample sizes being 45, 117, 74 and 197 respectively. All studies included participants of both sexes. Participants were adults except in one study (Galarza 1995) which included children from 11 years of age. One trial (Elliott 2003) comprised only HIV-positive participants, two (Galarza 1995, Wyser 1996) excluded HIV positive participants, while in the remaining study (Lee 1988), HIV status was not determined. All participants with pleural effusion had TB confirmed by a laboratory diagnosis except for Galarza (1995), where only 63% of participants had a confirmatory pathological or micro-biological diagnosis. Trials considered in this review are described in 'Table 1: Characteristics of included studies'.

Three trials were published in languages other than English and are awaiting translation and further assessment. The reasons for excluding studies, initially considered relevant, are provided in 'Table 2: Characteristics of excluded studies'.

Table 1: Characteristics of included studies

Study	Methods	Participants	Interventions
Elliott 2003	Computer generated random numbers. Concealment adequate. Placebo-controlled. 1.5% excluded from analysis.	Men and women, mean age 34 years, admitted to a single hospital in Uganda with tuberculous pleural effusion. Diagnosis confirmed by microbiological culture and/or histopathology on pleural biopsy, pleural fluid or sputum.	Experimental = ATT plus prednisolone. Control = ATT plus placebo. ATT consisted of: INH 5mg/kg/d (max. 300mg/d), Rifampicin 10mg/kg/d (max 600 mg/d), pyrazinamide 18-26 mg/kg/d, ethambutol 14-21mg/kg/d , for 2 months followed by 4 months of INH and Rifampicin. Prednisolone was given as a single oral dose of 50mg/d for 14 days, 40mg/d for 14 days, 25mg/d for 14 days, 15mg/d for 14 days.
Galarza 1995	Random allocation. Concealment unclear. Placebo-controlled. No loss to follow up. Intention to treat analysis done. None excluded from analysis.	Men and women aged 11 to 53 years admitted to a single hospital in Spain with tuberculous pleural effusion. Definite microbiological or pathological diagnosis in 63% of patients.	Experimental = ATT plus prednisone Control = ATT plus placebo ATT consisted of: INH 5mg/kg/d (max. 300mg/d) and Rifampicin 10mg/kg/d (max 600 mg/d) once daily as a combination tablet for 6 months. Prednisone was given as a single oral dose of 1mg/kg/d for 15 days tapering off over the next 15 days
Lee 1988	Random allocation. Concealment unclear. Placebo-controlled. 11% excluded from analysis.	Men and women aged 18 to 45 years admitted to a single hospital in Taiwan with tuberculous pleural effusion. Diagnosis confirmed on pleural biopsy reported as "tuberculosis or chronic granulomatous inflammation".	Experimental = ATT plus prednisolone Control = ATT plus placebo ATT consisted of: Ethambutol 20mg/kg/d for 3 months; INH 300mg/d and Rifampicin 450mg/d for 9-12 months. Prednisolone was given as an oral dose of 0.75mg/kg/d initially and tapered gradually over 2-3 months once radiological improvement was seen.
Wyser 1996	Random allocation. Concealment unclear. Placebo-controlled. 5% excluded from analysis.	Men and women, mean age 33 years admitted to a single hospital in South Africa with tuberculous pleurisy. Diagnosis confirmed on pleural biopsy showing caseating granulomata +/- acid-fast bacilli on histology and/or positive TB culture.	Experimental = ATT plus prednisone Control = ATT plus placebo. ATT consisted of Rifampicin 10mg/kg/d, INH 8mg/kg/d, and Pyrazinamide 25mg/kg/d as a fixed combination tablet (Rifater) and pyridoxine 25mg/kg/d for 6 months Prednisone was given as an oral dose of 0.75mg/kg/d for 2-4 weeks. After clinical and radiological improvement the dose was tapered by 5mg/d over 2 weeks.

ATT= Antituberculous Therapy

Table 1: Characteristics of included studies (Cont')

Study	Outcomes	Notes	Allocation concealment
Elliott 2003	1. All cause mortality 2. Adverse effects related to steroid use 3. Resolution of tuberculosis 4. HIV-related events	1. HIV-negatives excluded 2. Pleural aspiration and, if possible, biopsy for all patients on admission. 3. Three patients (1.5%) excluded from analysis: 1 died from DVT and pulmonary embolism and reasons are not given for the rest.	A
Galarza 1995	1. Time to normal temperature 2. Lung function assessed by FVC at end of treatment 3. Pleural thickening at baseline and at 1, 6 and 12 months after start of treatment 4. Rate of reabsorption of pleural fluid on Chest X Ray at baseline and at 1, 6 and 12 months after start of treatment 5. Adverse effects	1. Before discharge pleural fluid was drained to one third of hemithorax in all patients 2. HIV positives excluded.	B
Lee 1988	1. Resolution of clinical symptoms and signs 2. Rate of reabsorption of pleural fluid on Chest X Ray 3. Pleural adhesions and thickening 4. Adverse effects	1. Diagnostic thoracocentesis (<50ml) on first day for all patients 2. Five patients (11%) excluded from analysis: 1 developed renal cell carcinoma and 4 did not return for follow-up 3. Duration of follow-up not stated. 4. HIV status of patients not stated.	B
Wyser 1996	1. Resolution of symptoms. Dyspnoea, cough, night sweats, tiredness, appetite, pleuritic chest pain and general well-being were each graded from 0 to 100 using a visual analogue scale and combined index with a maximum score of 700 was calculated. 2. Lung function at end of treatment as assessed by TLC and FVC 3. Recurrence of effusion 4. Residual pleural thickening at 24 weeks 5. Adverse effects.	1. HIV positives excluded 2. Thoracoscopy, bronchoscopy, and complete aspiration of pleural fluid for all patients on admission. 3. Four patients (5%) excluded from analysis: 1 developed oesophageal carcinoma and 3 were not compliant	B

Allocation concealment: A: Adequate; B: Unclear; C: Inadequate; D: Not used

(See Appendix 2 for further explanation)

Table 2: Characteristics of excluded studies

Study	Reason for exclusion
Aspin 1958	No randomisation or pseudorandomisation.
Bilaceroglu 1999	Participants did not have pleurisy - cases of pulmonary TB
Cherednikova 1973	Case series
Cisneros 1996	Review
Damany 1968	Numbers of patients in each arm not clearly stated.
Filler 1963	No randomisation or pseudorandomisation.
Fleishman 1960	Diagnosis of tuberculosis not confirmed.
Grewal 1969	No randomisation or pseudorandomisation.
Manresa 1997	Letter referring to Included trial (Galarza 1995).
Mathur 1960	No randomisation or pseudorandomisation.
Mathur 1965	No randomisation or pseudorandomisation.
Menon 1964	No randomisation or pseudorandomisation.
Paley 1959	No randomisation or pseudorandomisation.
Singh 1965	No randomisation or pseudorandomisation.
Starostenko 1989	No randomisation or pseudorandomisation.
Tani 1964	No randomisation or pseudorandomisation.
Tanzj 1965	No randomisation or pseudorandomisation.

3.1.2 Interventions

Pleural fluid was aspirated prior to randomisation in all but one study (Galarza 1995) where aspiration was conducted prior to patient discharge. In all cases oral steroids or placebo were administered in addition to standard anti-tuberculous therapy (ATT). Prednisolone was administered in two trials (Lee 1988, Elliott 2003) at a daily dose of approximately 0.75mg/kg/day for two weeks while prednisone was administered in the remaining studies (Galarza 1995, Wyser 1996) at a dose ranging from 0.75 to 1.0 mg/kg/day for two weeks. In all cases, the dose was tapered off over a further two-week period. Rifampicin and isoniazid were included in the ATT regimen in all studies.

3.1.3 Follow-up

The period of follow-up varied across studies, ranging from 24 weeks (Wyser 1996) to 46 months (Galarza 1995). Lee et al (1988) did not mention how long participants had been followed, but reported at least one outcome 395 days post-treatment.

3.1.4 Outcome measures

The outcome measures reported were mortality, clinical improvement during treatment, reabsorption of pleural effusion, pleural thickening measured by chest X-ray (CXR), respiratory function, improvement in clinical symptoms and signs at the end of treatment, adverse effects and HIV-associated complications.

3.2 Methodological quality of included studies

3.2.1 Generation of allocation sequence

All trials were reported as randomised. Elliott (2003) explicitly stated that random numbers were computer-generated, which we considered as adequate. The other trials did not indicate how the sequence was generated.

3.2.2 Allocation concealment

One trial gave a detailed report of this aspect of study quality, which we considered to be an adequate method; briefly, prednisolone and matching placebo tablets were packaged in identical sequentially numbered plastic bags labelled with the randomisation code by 2 people unrelated to the study (Elliott 2003). The rest did not provide sufficient information to assess this aspect of study quality.

3.2.3 Blinding

All studies were described as double-blind and placebo-controlled. Wyser (1996) and Elliott (2003) specifically mentioned that those assessing outcomes had been blinded.

3.2.4 Inclusion of all randomised participants

Loss to follow up either did not occur (Galarza 1995) or was small: 11% (Lee 1988), 5% (Wyser 1996) and 1.5% (Elliott 2003).

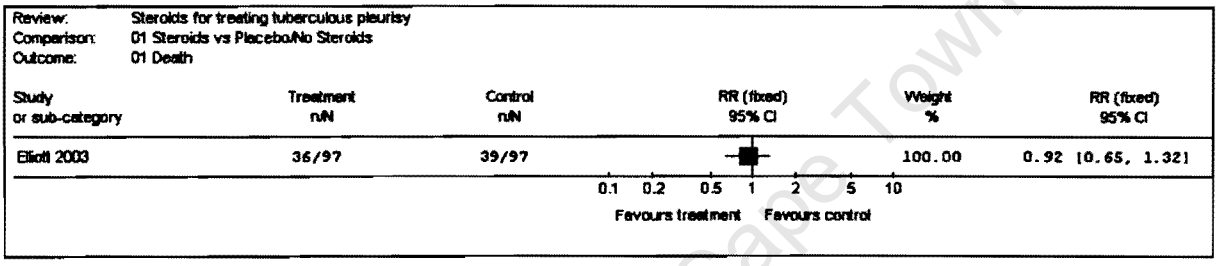
Only Galarza (1995) undertook an intention-to-treat analysis.

3.3 Analysis

3.3.1 Mortality from any cause

Only one trial assessed the risk of death, finding no statistically significant difference between steroids and placebo in the reduction of mortality (Elliott 2003 with 194 participants: relative risk (RR) = 0.92, 95% confidence interval (CI) 0.65 to 1.32), (Figure 1).

Figure 1: Mortality from any cause.



3.3.2 Improvement in respiratory function

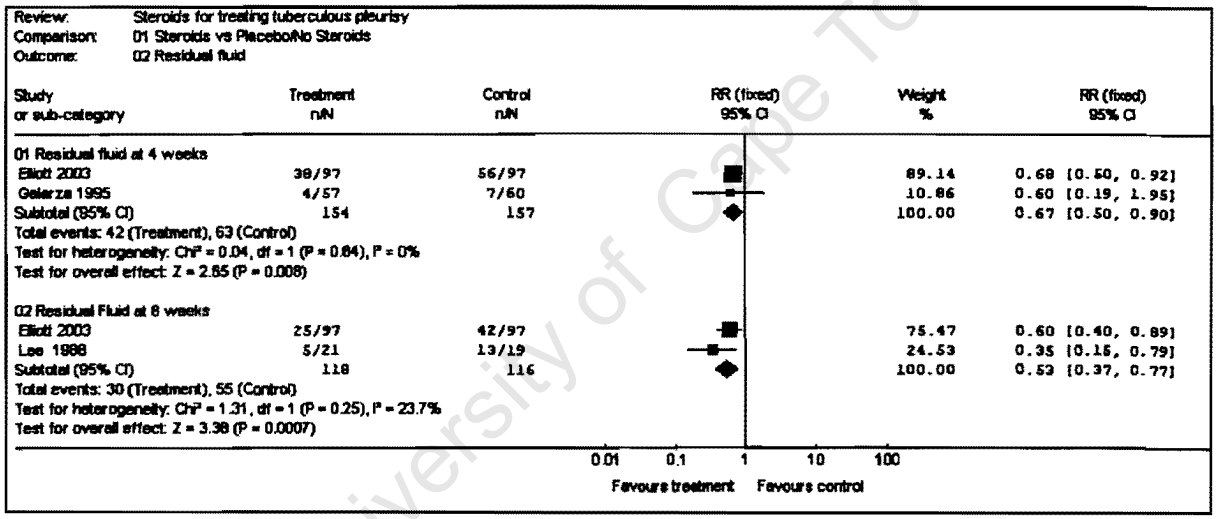
Two trials (Galarza 1995 and Wyser 1996) evaluated improvement in respiratory function finding no difference between steroid and control groups. In Galarza (1995) mean forced vital capacity (FVC) was 95% in both the treatment and control groups at the end of treatment.

Wyser (1996) reported no significant difference in the degree of improvement in pulmonary function between the prednisone and placebo groups, (Total Lung Capacity: p=0.39; FVC: p=0.65) up to six months.

3.3.3 Residual pleural effusion

Steroids reduced residual fluid at 4 weeks (2 trials, Galarza 1995, Elliott 2003 with 311 participants: RR = 0.67, 95% CI 0.50 to 0.90) as well as at 8 weeks (2 trials, Lee 1988, Elliott 2003, with 234 participants: RR = 0.53, 95% CI 0.37 to 0.77), (Figure 2). No statistical heterogeneity was detected for either of these outcomes. In the remaining study (Wyser 1996), complete drainage of pleural fluid was undertaken on admission and effusions did not recur in either group during the course of the study.

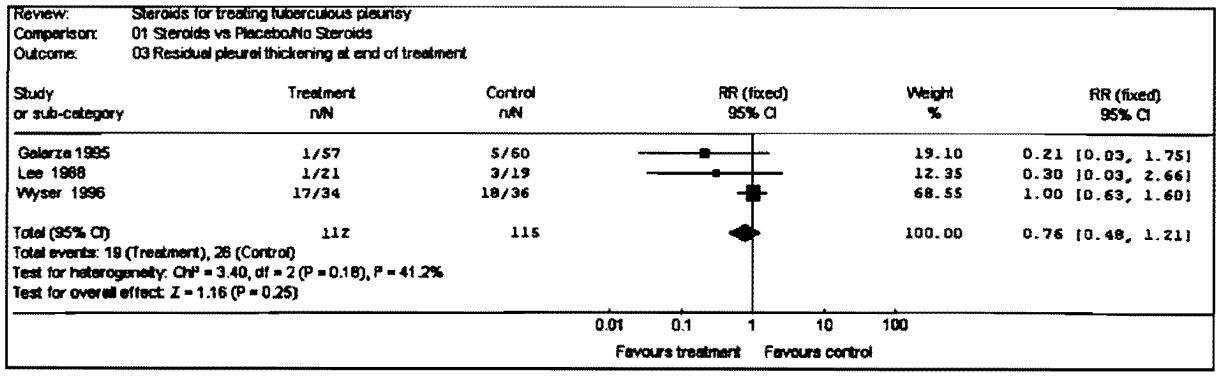
Figure 2: Residual pleural effusion.



3.3.4 Presence of pleural thickening and pleural adhesions

A reduction in the risks of both residual pleural thickening (3 trials, Lee 1988, Galarza 1995, Wyser 1996, with 227 participants: RR = 0.76, 95% CI 0.48 to 1.21) and pleural adhesions 1 trial Lee (1998) with 45 participants RR = 0.30, 95% CI 0.03 to 2.66) were observed but neither of these findings were statistically significant, (Figure 3).

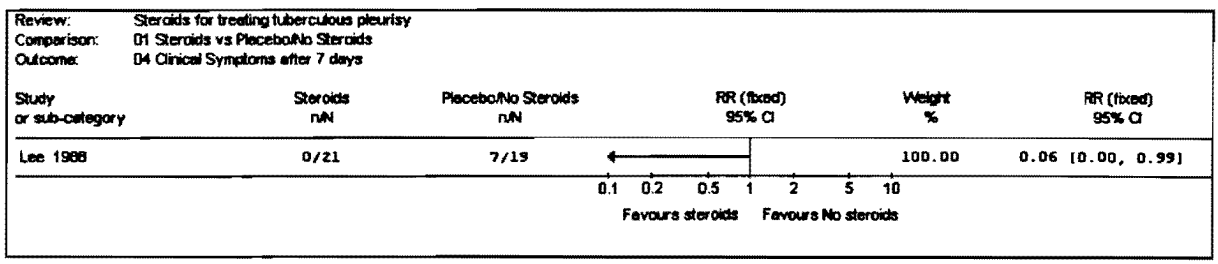
Figure 3: Presence of pleural thickening and pleural adhesions.



3.3.5 Improvement in clinical symptoms and signs

Fever, chest pain and dyspnoea were more likely to be resolved by 7 days post-treatment in one study (Lee 1988) in participants on steroids compared to placebo (RR = 0.06, 95% CI 0.00 to 0.99), (Figure 4). In the same study, steroids reduced the mean number of days to disappearance of acute symptoms ($p<0.05$). All participants, however, were asymptomatic within 14 days. Wyser (1996) reported no differences in the degree of improvement in symptoms (individual or combined Visual Analogue Scores) or in mean weight gain at regular follow-up evaluations over a 24 week period.

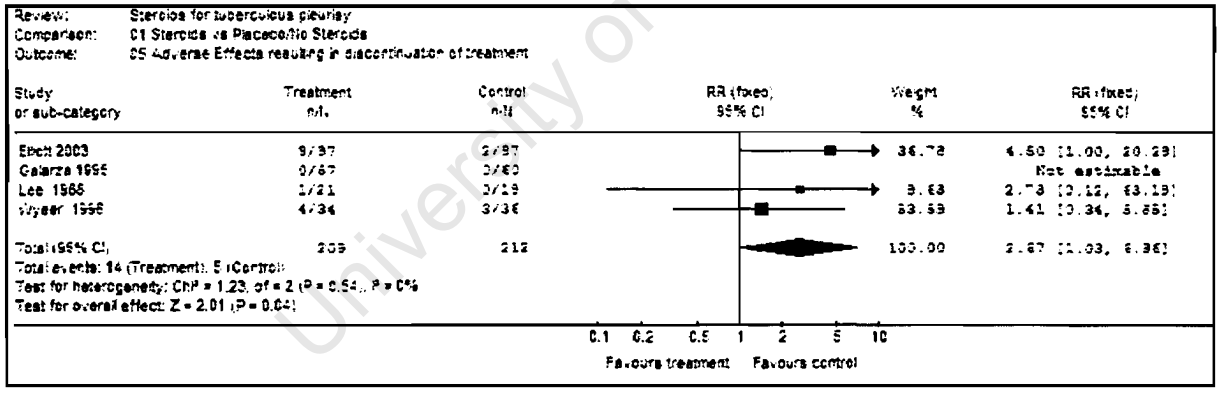
Figure 4: Improvement in clinical symptoms and signs



3.3.6 Adverse events due to treatment

Overall, more people in the steroid group experienced adverse effects leading to the discontinuation of treatment (3 trials, Lee 1988, Wyser 1996, Elliott 2003 with 304 participants: RR = 2.67, 95% CI 1.03 to 6.96), (Figure 5). In Elliott (2003), 9 of 97 participants in the treatment group and 2 of 97 participants in the placebo group required stoppage of treatment due to hyperglycaemia, hypertension, herpes zoster or candida infections. Epigastric pain was reported by Wyser (1996) in 4 of 34 participants on steroid therapy and 3 of 36 on placebo and by Lee (1988) in 1 of 21 participants on steroids and none in the placebo group. The same participant in Lee (1988) developed a 'moon' face and lower limb oedema. Galarza found no adverse effects.

Figure 5: Adverse events due to treatment

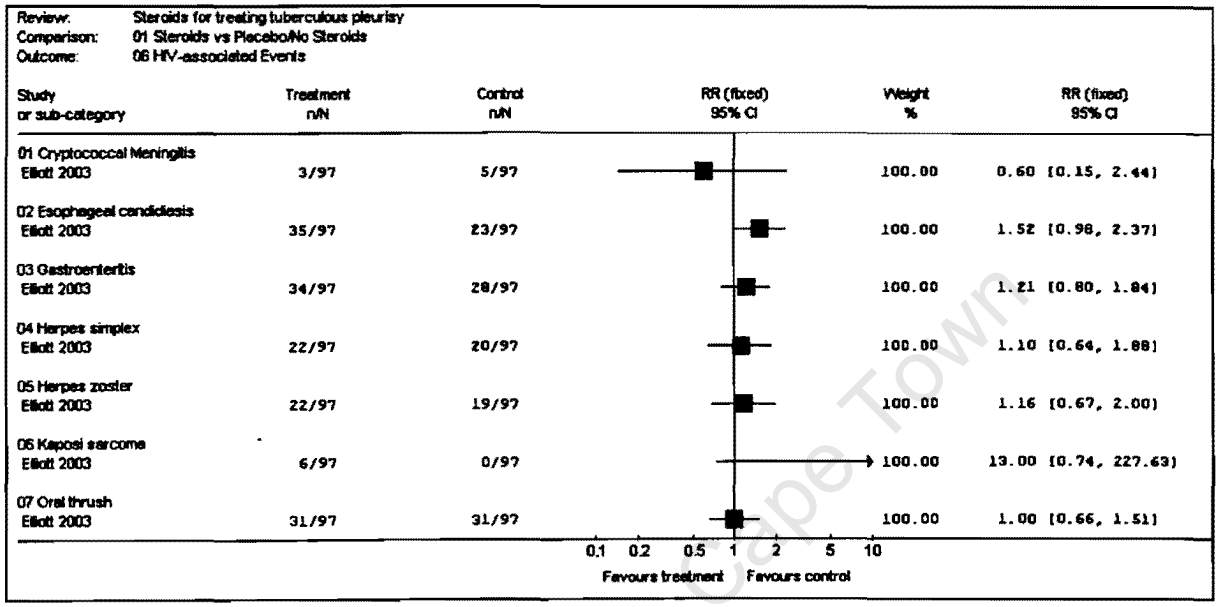


3.3.7 HIV-associated events

One trial comprising only HIV-positive participants reported a trend towards an increase in the incidence of Kaposi's sarcoma in participants receiving steroids (Elliott 2003, with 194 participants: RR = 13.00, 95% CI 0.74 to 227.63), (Figure 6). This trial found no evidence of an effect of steroids on HIV-associated infections including Cryptococcal

meningitidis, esophageal candidiasis, Herpes simplex, Herpes zoster, oral thrush and gastroenteritis.

Figure 6: HIV-associated events



4. DISCUSSION

The evidence base on the effects of corticosteroids administered to people with tuberculous pleurisy remains small, with only four trials evaluating 433 participants.

Only the trial in people infected with HIV evaluated mortality. Due to the small number of events in this study the confidence interval around the effect estimate is wide thus precluding firm conclusions about the effect of steroids on death. The other primary outcome we aimed to assess was improvement in respiratory function. Neither of the two trials focussing on this endpoint provided evidence for benefit of steroids; there was insufficient information to allow us perform a meta-analysis.

Compared to placebo, steroids appear to hasten the resorption of pleural fluid with the pooled results from two trials showing statistically significant reductions of residual fluid at four and eight weeks. The clinical importance of this finding is, however, difficult to interpret. One trial found fewer symptoms at seven days as well as a reduction of the mean number of days to disappearance of symptoms in the steroid arm, while the other found no difference in symptom severity between the comparison groups. There is no evidence that steroids reduce pleural thickening at the end of treatment either from the combined results based on three trials or the biggest of the trials with a relative risk of one.

Adverse events due to treatment were infrequent and mostly mild. There is theoretical concern that corticosteroid-induced immunosuppression may increase the risk of opportunistic infections in HIV-infected participants (Lionakis 2003). Thus the episodes of herpes zoster and esophageal candidiasis, leading to cessation of treatment in Elliott

2003 are noteworthy. There were, however, no statistically significant differences between steroid and placebo arms for any of the opportunistic infections assessed in this trial. In the same trial the risk of Kaposi sarcoma was found to be substantially higher in the steroid group (RR = 13, 95% CI 0.74 to 227.63). This is a potentially important finding which requires confirmation in future trials.

In interpreting the above findings a number of factors need to be kept in mind. Firstly, all 4 trials included in this review were small (sample sizes ranged from 45 to 197), thus increasing the likelihood of both type I and type II error. For example, the single study reporting on mortality will not have been sufficiently powered to assess this outcome. It can be shown that 356 patients per study arm would be required to demonstrate a 10% reduction in mortality from the baseline of 39/97. Secondly, while the methodological quality of the available studies seems reasonably sound, we did not have sufficient information to assess the completeness of allocation concealment in three of the four trials, a factor known to have a substantial influence on internal validity. A third issue concerns the diagnosis of TPE which was not confirmed in one-third of participants in the Galarza 1995 trial; there is no indication as to the distribution of unconfirmed diagnoses in the study arms. Fourthly, the optimal dose of adjunctive steroids is not known. Rifampicin induces the liver metabolism of corticosteroids, thus increasing their plasma clearance (McAllister 1983). It has been suggested that higher doses be used to compensate for the reduced availability of steroids to the tissues (Commerford 1991). Furthermore, the choice of steroid varied across the studies: two trials used prednisolone and the other two, prednisone. Prednisone is a pro-drug that requires metabolism in the liver to prednisolone, the active component.

Finally, three of the trials were carried out in the pre-HIV era and thus the generalisability of the current evidence to most participants with TPE in low and middle income countries who are coinfected with HIV is limited.

5. CONCLUSIONS

5.1 Implications for practice

While evidence from published trials suggests that adjunctive steroid therapy is beneficial for reducing residual pleural fluid, there is currently insufficient data to support evidence-based recommendations regarding the use of steroids on risk of death or improvement in lung function in patients with tuberculous pleural effusion, regardless of HIV status. There is some cause for concern that steroids may increase the risk of Kaposi sarcoma in patients infected with HIV.

5.2 Implications for research

Randomised controlled trials with sufficient statistical power to evaluate the effects of steroids on mortality and key morbidity outcomes are needed. Careful attention should be given to adverse effects particular in patients who are HIV positive.

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7. APPENDIX

7.1 Detailed Search Strategy

Search set	CIDG SR*	CENTRAL	MEDLINE **	EMBASE**	LILACS**
1	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis
2	TB	steroids	tuberculosis	tuberculosis	TB
3	steroids	corticosteroids	TB	TB	1 or 2
4	corticosteroids	glucocorticoids	1 or 2 or 3	1 or 2 or 3	steroids
5	dexamethasone	hydrocortisone	steroid*	steroids	hydrocortisone
6	hydrocortisone	prednisolone	STEROIDS	STEROIDS	dexamethasone
7	prednisolone	dexamethasone	corticosteroids	corticosteroids	prednisolone
8	--	2 or 3 or 4 or 5 or 6 or 7	glucocorticoids	glucocorticoids	4 or 5 or 6 or 7
9	--	1 and 8	hydrocortisone	hydrocortisone	3 and 8
10	--	--	dexamethasone	dexamethasone	--
11	--	--	prednisolone	prednisolone	--
12	--	--	prednisone	methylprednisone	--
13	--	--	methylprednisone	5 or 6 or 7 or 8 or 9 or 10 or 11 or12	--
14	--	--	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	4 and 13	--
15	--	--	4 and 14	Limit 13 to human	--
16	--	--	Limit 15 to human	--	--
	*Cochrane Infectious Diseases Group Specialized Register	**Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Alderson 2005; Upper case: MeSH or EMTREE heading; Lower case: free text term			

7.2 Data extraction form

Data Extraction Form ***Corticosteroids for TB Pleurisy***

ID NUMBER: _____
Authors: _____
Journal / yr / vol / iss / pg: _____
Title: _____

Reviewer
MEE
JAV

Notes:

_____
_____
_____
_____

METHODS:
Randomisation method:

_____
_____
_____

Allocation concealment:

Clearly adequate	Possibly adequate	Clearly inadequate	Not described

Study design and conduct:

	Yes	No	Unclear
Placebo-controlled			
Provider blinded			
Assessor blinded			
Patient blinded			

Date trial was initiated:
Total duration of trial (treatment plus follow-up):
Duration of follow-up:
Type of follow-up:
Frequency of follow-up:

Loss to follow-up:

	Total	Intervention	Control
Total number randomised			
Number available to follow-up			
Loss to follow-up			

% of total number randomised included in analysis?_____

PARTICIPANTS:
Country and setting:

Numbers of persons in trial:

	Total	Intervention	Control
Number			
% of total	100%		

Gender of persons in trial:

	Total		Intervention		Control	
	N	%	N	%	N	%
Male						
Female						
TOTAL		100%		100%		100%

Age of persons in trial:

	Total		Intervention		Control	
Mean age						
Age range						
	N	%	N	%	N	%
=< 13 year						
> 13 year						

Diagnosis of TB pleural effusion:	Yes	No	Unclear
Chest X-Ray			
Pleural biopsy for histology			
Positive Ziel-Neelsen stain			
Positive Microbiological culture of sputum/pleural fluid/pleural biopsy			

INTERVENTION:

Regular ATT:

Description				
Dosage				
Frequency				
Duration				

Corticosteroid:

	Intervention	Control
Description		
Dosage		
Frequency		
Duration		

Outcomes and Results:

	Intervention	Control	Significant	Not reported
Death				
Improvement in respiratory function				
Improvement in clinical symptoms				
Reabsorption of pleural effusion				
Worsening of parenchymal disease (pos AAFB sputum at end of treatment)				
Presence of pleural thickening				

Adverse effects:

	Intervention (N)	**Controls (N)**
Fatal		
Life threatening or requiring hospitalisation		
Other		

COMORBID CONDITIONS:

HIV:

	Yes	No
HIV-positive participants		

If "yes":

	Intervention		Controls	
	Males	Females	Males	Females
HIV positive				
HIV negative				
HIV unknown				

Information outstanding, to be requested:

Comments on ethics of study:

7.3 Allocation concealment (*RevMan Manual*)

Adequate methods of allocation concealment include:

- centralised randomisation schemes;
- randomisation schemes controlled by a pharmacy;
- numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially;
- on-site computer systems, where allocations are in a locked unreadable file;
- sequentially numbered opaque, sealed envelopes.

Rated as *A: Adequate; B: Unclear; C: Inadequate; D: Not used*