

Review

The evidence on the effectiveness of management for malignant pleural effusion: a systematic review

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Summary

The aim of this study was to review systematically the available evidence on pleurodesis for malignant effusion, focusing on the choice of the agents, route of delivery and other strategies to improve outcomes. Four electronic databases (MEDLINE, EMBASE, Web of Science and Cochrane Controlled Trials Register) were searched, reference lists checked and letters requesting details of unpublished trials and data sent to authors of previous trials. Studies of malignant pleural effusion in humans were selected with no language restrictions applied. Criteria for randomised clinical trial (RCT) eligibility were random allocation of patients and non-concurrent use of another experimental medication or device. Methodological quality evaluation of the trials was based on randomisation, blinding, allocation concealment and intention to treat analysis. A random effect model was used to combine the relative risk estimates of the treatment effects whenever pooling for an overall effect was considered appropriate. Forty-six RCTs with a total of 2053 patients with malignant pleural effusions were reviewed for effectiveness of pleurodesis. Talc tended to be associated with fewer recurrences when compared to bleomycin (RR, 0.64; 95% CI, 0.34–1.20) and, with more uncertainty, to tetracycline (RR, 0.50; 95% CI, 0.06–4.42). Tetracycline (or doxycycline) was not superior to bleomycin (RR, 0.92; 95% CI, 0.61–1.38). When compared with bedside talc slurry, thoracoscopic talc insufflation was associated with a reduction in recurrence (RR, 0.21; 95% CI, 0.05–0.93). Strategies such as rolling the patient after instillation of the sclerosing agent, protracted drainage of the effusion and use of larger chest tubes were not found to have any substantial advantages. Talc appears to be effective and should be the agent of choice for pleurodesis. Thoracoscopic talc insufflation is associated with fewer recurrences of effusions compared with bedside talc slurry, but this is based on two small studies. Where thoracoscopy is unavailable bedside talc pleurodesis has a high success rate and is the next best option. Crown Copyright © 2005 Published by Elsevier B.V. All rights reserved.

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1. Introduction

Cancer is one of the most common causes of death and pleural effusion is a frequent feature of disseminated or advanced disease. The sum total of the burden of breathlessness and immobility experienced in the last months of life in cancer sufferers is enormous. Prompt, well-judged and skilled management of the effusion can alleviate breathlessness and improve quality of life.

Pleurodesis, using an intrapleural chemical agent, is widely practiced to obliterate the pleural space, prevent fluid accumulation and improve breathing. Insufflation of a pleural agent can be achieved by video-assisted thoracoscopic surgery (VATS) or at the bedside through a chest tube. Agents used include talc, tetracycline, bleomycin and other anti-neoplastic agents, *Corynebacterium parvum*, and any number of other irritants and pro-inflammatory drugs. There are some nuances concerning the therapeutic intent: most strategies aim at simply creating inflammation to induce adhesion while others include chemotherapeutic agents to kill intrapleural cancer. There are various practices for duration of drainage, drain size and management of the drain.

The subject was reviewed in 1994 [1]. There has been a recent Cochrane systematic review which is confined to the effectiveness of specified chemical agents and the surgical versus medical approaches [2]. The British Thoracic Society guidelines [3,4] lack a systematic review of the evidence base. Without a clear review of the evidence we are unable

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to make clear recommendations to colleagues, or even to plan research studies. As the thoracic surgeon members of cancer multidisciplinary teams, we are the last port of call in the management of these patients. It is our perception (and without evidence it can be no more) that opportunities for symptomatic relief are being lost. On the other hand, pleurodesis may fail or result in infection. For the patient under- or over-use may translate into irretrievable loss of quality in the last months of life. It is in that spirit we undertook this systematic review. Compared with the Cochrane review our work has a much wider scope to provide clinical guidance on the use of pleurodesis, choice of the agents, route of delivery and other strategies to improve outcomes.

We addressed the following questions:

1. Is instilling an intrapleural agent necessary to produce pleurodesis?
2. If so, which is the best intrapleural agent?
3. Which is the best way of introducing the intrapleural agent?
4. Are there any ways of improving the technique?
 - a. Rotation after instillation of agent,
 - b. Duration of drainage,
 - c. Size of chest tube.
5. Are other measures such as pleurectomy or decortication and the use of shunts effective in the management of malignant pleural effusion?

2. Method

2.1. Search and identification of trials

Randomised clinical trials (RCTs) were identified by searching the MEDLINE, EMBASE, Web of Science and Cochrane Controlled Trials Register from 1980 to 2003. The initial search strategy was conservative to retain any likely contributing studies. We used various combinations of MeSH terms and text words that might be related to the treatment of malignant pleural effusion. No language restrictions were applied. The RCT filter designed by the Cochrane Collaboration for identifying RCTs and clinical trials was used for MEDLINE and EMBASE. In addition, we searched the reference lists of trials and reviews to look for additional studies.

Criteria for RCT eligibility were random allocation of patients and non-concurrent use of another experimental medication or device. Discrepancies were resolved with participation of four authors (C.T., A.S., S.S., T.T.).

2.2. Study variables

For each RCT, two authors (C.T., A.S.) abstracted data on (1) the number of patients randomised, (2) publication date, (3) demographics, (4) details of intervention and comparison groups, (5) primary outcome (primary failure/recurrence of the condition) and (6) secondary outcomes (side effects: fever, pain and complications).

2.3. Methodological quality

Methodological quality of RCTs was evaluated based on modified Jadad et al.'s [5] criteria that were as follows:

1. Randomisation and its description.
2. Blinding and its description.
3. Allocation concealment.
4. Intention to treat analysis.

2.4. Statistical analysis

Where sufficient data were available, meta-analysis was performed (A.S.), and relative risks (RR) with 95% confidence intervals (CI) were calculated. The assumption of homogeneity among the trials was tested using the χ^2 statistic formed by summing the weighted difference between each individual estimate and the pooled estimate. In addition I^2 values were evaluated to assess heterogeneity. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. To be conservative, a value greater than 40% was considered as indicative of substantial heterogeneity. Moreover, a random effect method was used to combine the relative risk estimates as a more conservative strategy. Using this method, the variance for each individual study is the sum of within- and between-study components of the variance. The combined RR estimate was based on the weighted average of the individual log RR estimates. The weights correspond to the inverse of the total variance (within plus between) for each study. The 95% CIs were based on the asymptotic normality of the combined estimates. In addition, if substantial heterogeneity was observed, estimates from individual studies were not combined and results were interpreted separately. RevMan 4.2 developed by the Cochrane Collaboration was used in all analyses.

3. Results

After an initial independent search by two authors (C.T., S.S.), 561 potentially relevant papers were identified (Fig. 1). Titles and abstracts were reviewed by three researchers (C.T., S.S., T.T.). All RCTs addressing the above questions were included. In the areas where RCT evidence was lacking, non-randomised studies were considered. This left us with 55 papers of which 46 were RCTs. The data are presented in as logical a sequence as we could devise.

3.1. Is instilling an intrapleural agent necessary to produce pleurodesis?

We found seven RCTs reporting the effectiveness of seven different intrapleural agents compared with various drainage strategies in preventing recurrence. In two, randomisation was described [6,7] and in five, there was intention to treat analysis [6–10]. Due to significant heterogeneity among the trials a quantitative synthesis was not performed. One study compared two different agents separately (mepacrine and triethylenethiophosphoramidate) with saline [11], and talc was the agent under test in two studies [6,12]. The comparison groups were very varied, with three studies in which saline was instilled through the chest tube [8,9,11], one with multivitamin solution [10], two with chest drain alone [6,12] and one with protracted pleural

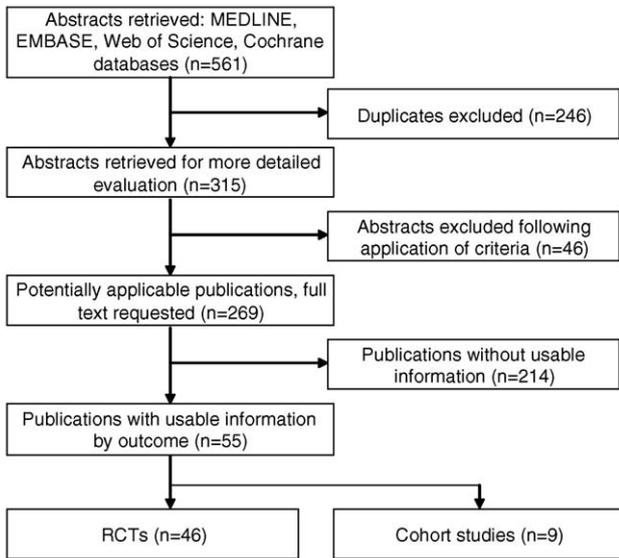


Fig. 1. Search strategy.

drainage [7]. In this last study, it was the long-term ambulatory drainage that was the method under investigation. The results are given in Fig. 2.

3.2. Which is the best agent for pleurodesis?

We found 31 RCTs where intrapleural agents were compared with each other for the prevention of recurrence. In 12, the randomisation process was described and in 26 the analysis was on intention to treat. There was a range of doses

and techniques. The studies are sufficiently homogeneous to allow meta-analysis and are summarised in a series of forest plots. These show comparisons of various agents with talc (Fig. 3) [13–21], tetracycline (Fig. 4) [14,22–33], bleomycin (Fig. 5) [34–38] and intrapleural chemotherapy and immunotherapy (Fig. 6) [39–42]. Talc was compared with other agents in nine studies that included 341 patients. A non-significant reduction in recurrence was found in comparison with bleomycin (RR, 0.64; 95% CI, 0.34–1.20). Similar results were observed when talc was compared to tetracycline (RR, 0.50; 95% CI, 0.06–4.42), but there was larger uncertainty due to wide confidence intervals. There was no significant difference in recurrence when tetracycline (or doxycycline) was compared to bleomycin (RR, 0.92; 95% CI, 0.61–1.38).

In the RCTs where intrapleural chemotherapy or immunotherapy was used, one study used systemic and intraperitoneal treatments in addition to the intrapleural route [40]. Combinations of various agents and doses were included in these studies. Combination therapy (chemotherapy plus immunotherapy) appeared to be superior to either alone (Fig. 6). The final study was a comparison of two different chemotherapy agents (mitoxantrone and mepacrine) and was the only trial we found using these agents [43]. Their figures were therefore not pooled or represented in Fig. 6. There was no significant difference in recurrence of the effusion in the two comparison groups.

3.3. Which is the best way of introducing the intrapleural agent: thoracoscopy or at the bedside?

We found three RCTs covering a total of 141 patients which compared the insufflation of a pleurodesis agent by

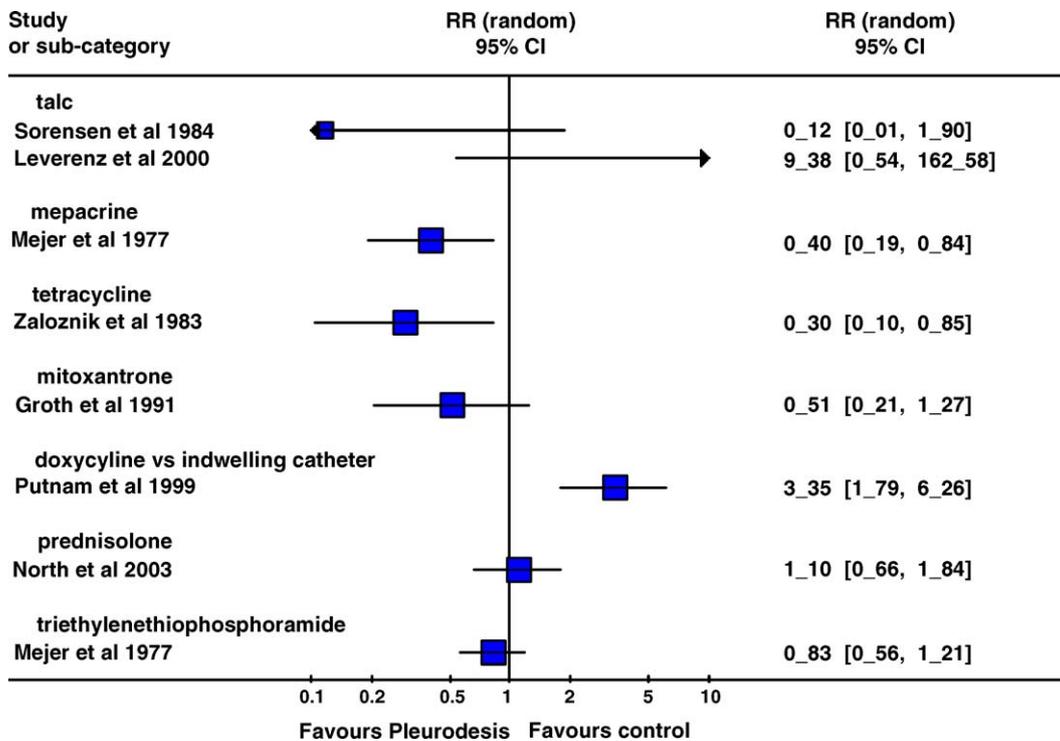


Fig. 2. Intrapleural agents versus drainage without a sclerosing agent. Studies were not combined due to substantial heterogeneity. Each comparison is presented separately.

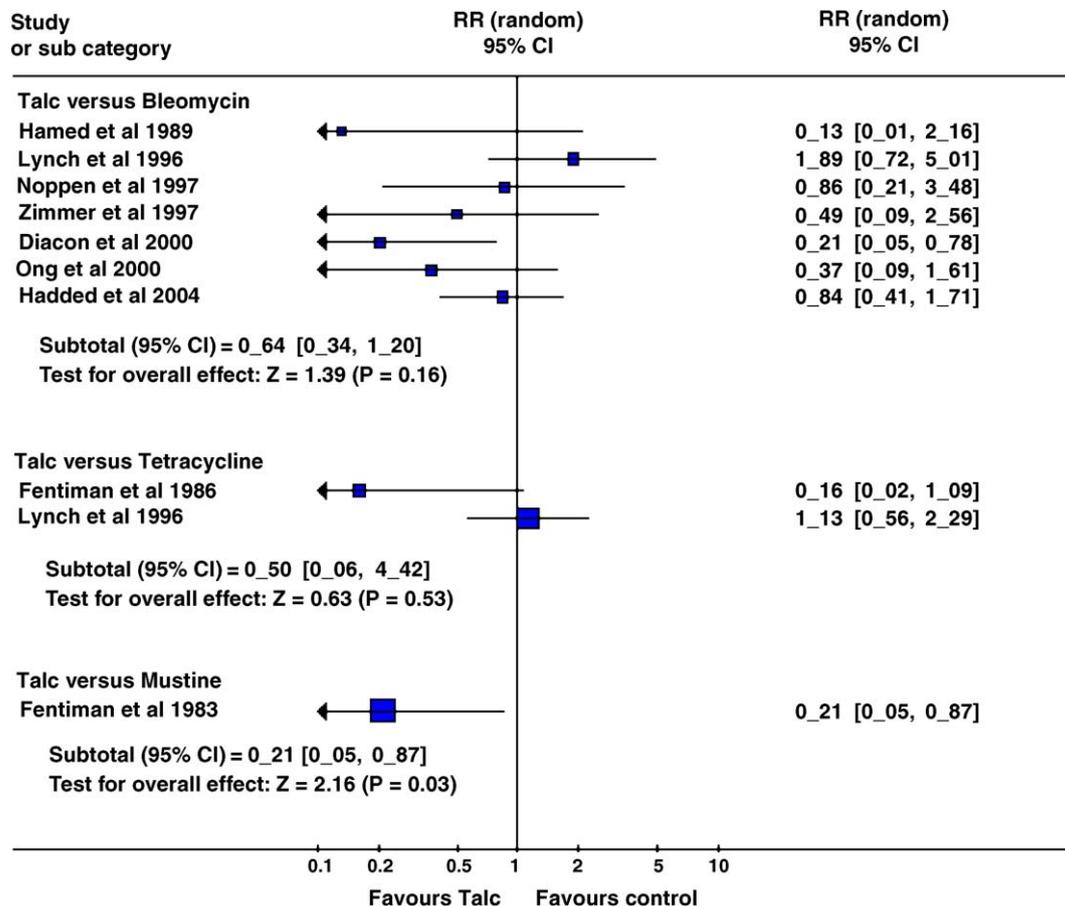


Fig. 3. Talc versus other agents. The overall combined estimate of the effect is calculated for the first two comparisons and is presented only numerically (under subtotals 95% CI).

either VATS or a bedside tube [44–46]. Blinding was not possible in these studies, and an intention to treat approach was used in all analyses. Two employed talc [44,45] and one tetracycline [46]. Talc instillation at thoracoscopy was associated with a reduction in recurrence (RR, 0.21; 95% CI, 0.05–0.93) (Fig. 7) but this is only based on 13 events in a total of 112 patients. In the single RCT that compared VATS with bedside instillation of tetracycline, no significant difference was found (RR, 1.05; 95% CI, 0.57–1.94) [46].

3.4. Are there any ways of improving the technique?

The RCTs addressing technique are summarised in Table 1.

3.4.1. Following instillation of sclerosant, is rotation of the patient beneficial?

Where a sclerosant is introduced through a chest tube at the bedside it has been the custom to roll and tip the patient from time to time to ensure dispersion. Two RCTs have addressed this, one using macrolides (tetracycline or doxycycline) [47] and the other talc [48]. Neither study showed a difference in recurrence conferred by rotation. Within the study by Mager et al. [48] they observed the distribution of talc using ^{99m}Tc -sestamibi-labelled talc suspension and showed that rotation did not influence talc dispersion.

3.4.2. Does shorter chest drain duration affect outcome?

Two RCTs in a total of 52 patients looked at duration of chest drainage following bedside pleurodesis [49,50]. Villanueva et al. [49] compared two drainage strategies, one following the standard protocol of draining to dryness before tube removal, and the other following the shorter protocol of removing the tube after 24 h. The rate of recurrence after tetracycline installation was similar. The second RCT, presented only in abstract form, also showed no difference [50].

3.4.3. Does the size of chest tube affect outcome?

There are no RCTs of large versus small chest tubes using the same method of tube insertion. There is one RCT of 18 patients comparing large chest tube placed during thoracoscopy with small catheters which were percutaneously inserted [51]. Tetracycline was instilled following tube or catheter placement. The recurrence rates were similar (three and two out of nine in each group), but the larger tubes caused more discomfort.

3.5. Are other measures such as pleurectomy or decortication and the use of shunts effective in the management of malignant pleural effusion?

3.5.1. Pleurectomy or decortication

There were no randomised trials reporting on the effectiveness of pleurectomy or decortication for malignant

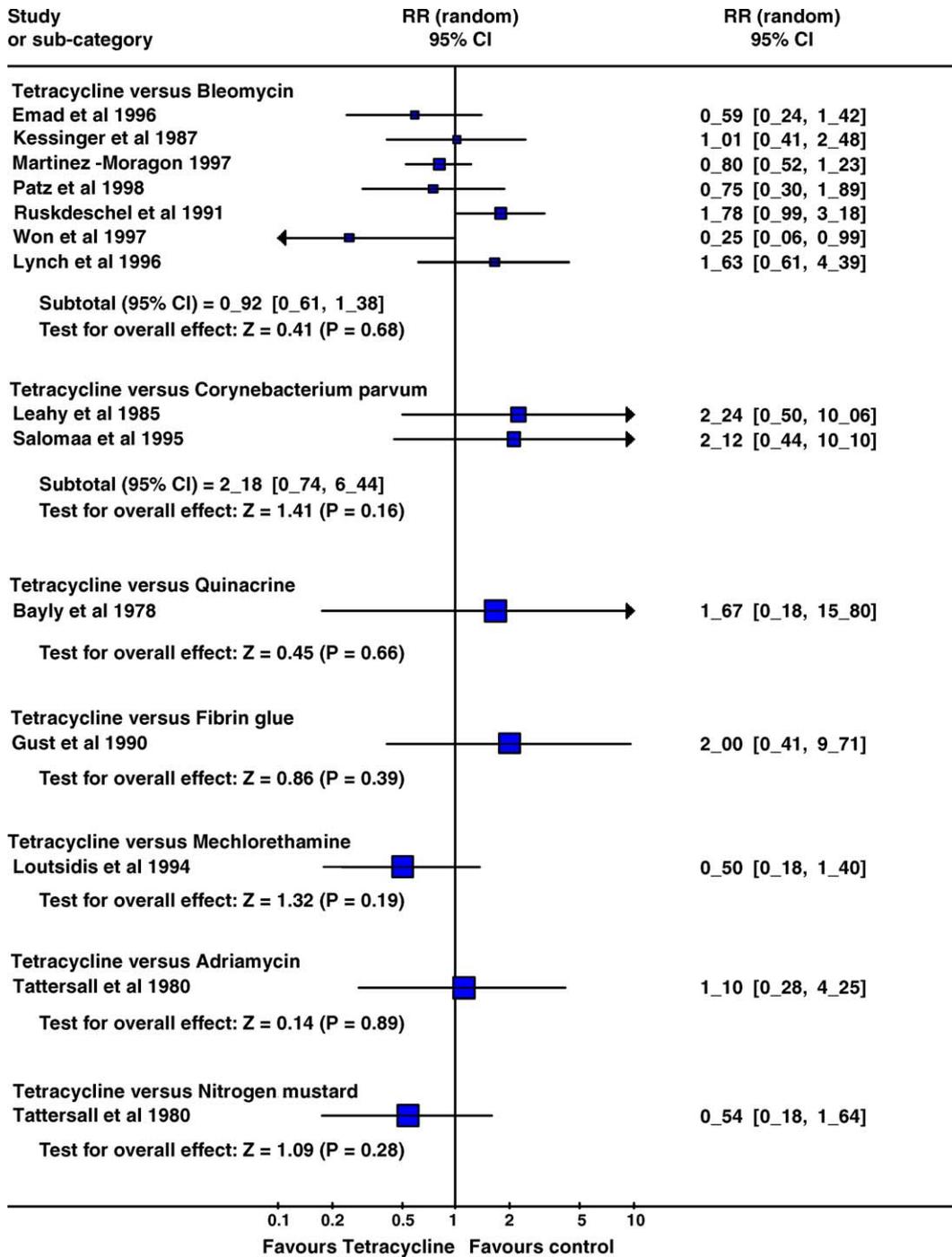


Fig. 4. Tetracycline versus other agents. The overall combined estimate of the effect is calculated for the first two comparisons and is presented only numerically (under subtotals 95% CI).

pleural effusion. We found five case series covering 260 patients [52–56], including a series of mesothelioma [56] and other malignant disease patients in which tumour debulking and decortication were part of the procedure. Some patients had parietal pleurectomy for recurrence after attempted pleurodesis. In others, decortication was performed when the lung was seen to be ‘trapped’ by tumour and/or an accumulation of fibrin on the visceral pleura [52,54,56]. Perioperative mortality of up to 12.5% was reported [52], and

there appears to be a high incidence of prolonged air leak postoperatively, 10–20%.

3.5.2. The use of shunts

There were no randomised trials on the use of shunts in the palliation of malignant pleural effusions. We found four case series covering 250 patients of pleuroperitoneal shunts [57–60]. In all four reports, the main indication for inserting the shunt was the presence of trapped lung, where

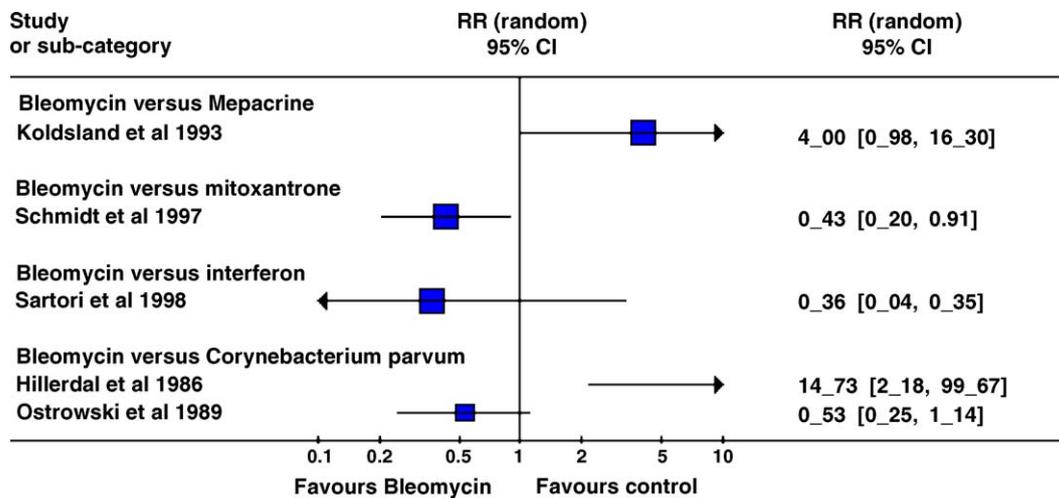


Fig. 5. Bleomycin versus other agents. Studies were not combined in the comparison of bleomycin versus *Corynebacterium parvum* due to large heterogeneity. Each comparison is presented separately.

it was felt that failure of the pleural surfaces to appose would not result in pleurodesis with chemical sclerotherapy. In these groups of patients, effective palliation was reported between 73 and 100%. However, there was a high incidence of shunt complication with shunt occlusion as high as 25% within a median time of 2.5 months [59].

4. Discussion

The studies reviewed are predominantly small and there are few significant results. This reflects the variable

aetiology of the patients studied, their poor prognosis and the difficulty in mounting large comparative studies. This is disappointing for what is a common problem.

On the face of it the evidence in Fig. 2 might suggest that there is no effect of instilling a sclerosing agent. It should be noted however that in the study with the strongest negative effect the drains were left indefinitely which is not a strategy of pleurodesis but a quite different means of coping [7]. Protracted ambulatory drainage alone prevents 'recurrence' in that it cannot be evident. In one study, reported in abstract form and available on <http://meeting.chestjournal.org/cgi/content/abstract/126/4/726S>, 61% of patients had a chest

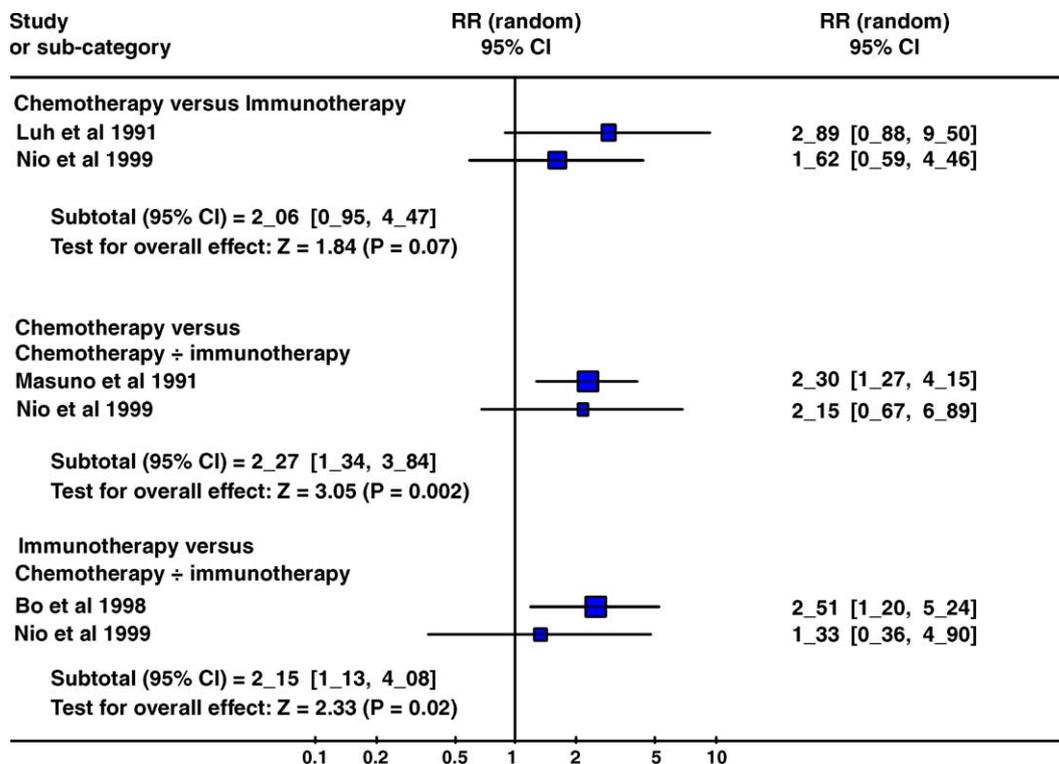


Fig. 6. Other comparisons. The overall combined estimate of the effect is calculated for all three comparisons and is presented only numerically (under subtotals 95% CI).

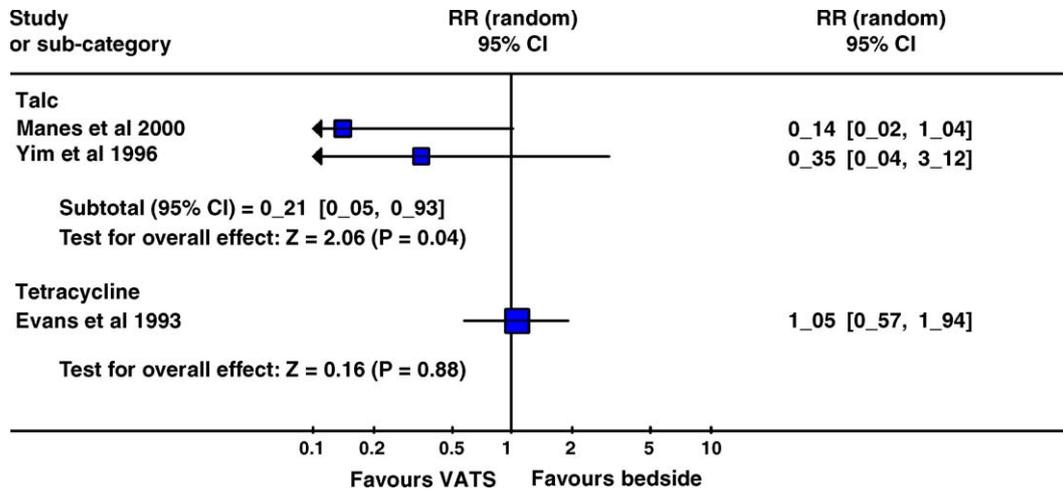


Fig. 7. RCTs comparing bedside and VATS techniques. The overall combined estimate of the effect is calculated for the first comparison and is presented only numerically (under subtotals 95% CI).

drain until death with an average of 105 days and the longest 315 days. The instillation of an agent is intended to leave the patient with an intact integument, free of impediments. That the fluid is coped with by leaving a tube draining until death is not evidence against the efficacy of the agent. This is a trade-off of strategies which would be better compared on the basis of quality of life. Sclerosing agents are widely used and the practice appears more evidence based.

We found no conclusive evidence supporting the use of a particular sclerosing agent over another, but the trend tends to favour talc (Fig. 3). Talc is widely used at present and this evidence suggests no basis for changing current practice.

Talc can be administered either at video-assisted surgery (VATS) or at the bedside. On the basis of the evidence

available here and in the Cochrane review [2], VATS talc insufflation may be associated with fewer recurrences of effusions compared with bedside talc slurry (Fig. 7). This is based on only two randomised trials so a strong recommendation of VATS over the bedside technique cannot be made. However, the high success rate of bedside talc pleurodesis in these studies was associated with a specific protocol within a formal study. If bedside talc slurry is to be employed, the standard of administration would have to be maintained to trial standards and not delegated to less experienced hands if the results are to be reproducible.

When there is a need for tissue (pleural biopsy) to make a diagnosis in addition to palliating the effusion, the clinician may choose VATS over bedside pleurodesis because

Table 1
RCTs which address strategies to improve the outcome of pleurodesis

Study	Description of randomisation	% ♀	Age	Longest F/U	Agent	Comparison groups	N	Recurrence/ no success	Pain	Fever	Other complications
Dryzer et al. [47] ^a	Hospital number	35	63	12 months	Tetracycline, minocycline or doxycycline	Rotation	19	5	NR	NR	NR
						No rotation	21	7	NR	NR	NR
Mager et al. [48] ^a	Not described	35	67	1 month	Radiolabelled talc	Rotation	10	2	NR	NR	NR
						No rotation	10	1	NR	NR	NR
Villanueva et al. [49] ^b	Computer	64	69	30 days	Tetracycline	Standard drain protocol	15	3	NR	NR	NR
						Short-term drain protocol (24 h)	9	2	NR	NR	NR
Davies et al. [50] ^b	Not described	46	72	3 months	Talc	Drain removal after 24 h	13	1	NR	NR	NR
						Drain removal after 72 h	15	2	NR	NR	NR
Clements et al. [51] ^c	Lottery	50	68	9 weeks	Tetracycline	Large bore (at thoracoscopy LA)	9	3	NR	NR	More discomfort with large tube
						Small percutaneous catheter	9	2	NR	NR	

NR: not recorded, LA: local anaesthesia.

^a RCTs of rotation versus no rotation following bedside pleurodesis.

^b RCTs of shorter drainage duration versus 'standard' duration following bedside pleurodesis.

^c RCT of large versus small bore chest tubes.

it allows for full thickness and visually targeted biopsies. The risks of surgery have to be considered but the perioperative mortality is under 1% (UK Thoracic Surgical Register, <http://www.scts.org/>). In a patient with only weeks to live, a quicker bedside procedure may be more acceptable, particularly if it is likely to get the patient home sooner.

Reservations about talc usage are related to the reports of pneumonitis following intrapleural talc instillation. This is believed to be due to variability in particle size [61] and it has been postulated that it might be the cause of the variable clinical reporting of pneumonitis. We found 36 reported cases of pneumonitis following talc pleurodesis in the literature, with none recorded in any of the experimental protocols. Where graded talc is used and small particles thus avoided, this complication has not been seen. When the number of patients undergoing this procedure is considered (likely to be tens of thousands in the US and UK alone) this adverse event should be considered very rare. The overwhelming weight of evidence is that talc is safe and that its safety profile is superior to all other agents.

Amongst the received wisdom on performing pleurodesis are the beliefs that the patient should be tipped and rolled, the tube should be left in for a long time and it must be big. Mager et al. [48], investigating the effect of rolling, combined a study of mechanism (dispersal of radio labelled talc) and outcome. They found no difference, refuting the belief and simplifying practice. Shorter drainage duration is as effective as protracted drainage and although the evidence is limited to two studies, a protocol that shortens or obviates the need for hospital admission would be preferred. Increasingly we are managing drains out of hospital and the two considerations, 'need to be in hospital' and 'need to have a drain', can be separated. Finally, there was no evidence on the benefits of larger chest tube sizes. In one study, results indicate that there may be no difference between large and small tubes [51]. This is supported by evidence found in non-randomised studies [62–70]. These studies included patients in whom the tube was placed under image guidance and/or outpatient drain management protocols were employed. Sclerosant practice varied. The outcomes with the use of smaller drains were found to be similar to larger sizes.

Trapped lung is recognised by an air/fluid level after drainage and a lung that will not re-expand. It can defeat pleurodesis simply due to the mechanical difficulty of getting the pleural surfaces to appose. Options for management under these circumstances include pleurectomy/decortication, a pleuroperitoneal shunt and long-term drainage which we have already addressed. Two retrospective studies have looked at the consequences and outcome of trapped lung and suggest that in itself, it may be well tolerated by some patients [71,72], so we found no strong evidence for an intervention. The focus in these patients should be on the extent to which breathlessness is a limiting symptom, and if it can be reliably relieved. In the case of trapped lung there may be arguments for accepting the situation. Unavailing surgical interventions impose a further burden on the patient with the additional substantial risk of introducing infection.

Note Added in Proof

Since completing the search an RCT in 482 patients has been published, comparing chest tube talc slurry versus thorascopic poudrage [73]. It showed similar effectiveness and does not substantially alter our conclusions.

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