

# PLEURODESIS IN MALIGNANT PLEURAL EFFUSION WITH SPECIAL EMPHASIS ON TETRACYCLINE AS THE SCLEROSING AGENT

K. Viskum. Department of Pulmonary Medicine. Bispebjerg Hospital. Copenhagen. Denmark.

## INTRODUCTION

Treatment intended to obliterate the pleural space has been in use since introduced in the operative treatment of tuberculosis by Bethume in 1935<sup>(1)</sup>. It has since been used Observation widely in the treatment of pneumothorax and pleural effusion due to malignant disease.

Repeated thoracocentesis is unpleasant and cumbersome. Therefore other therapeutic procedures have been popular, but in general they are not very effective (Table I). Pleurodesis Chemotherapy is one of the most effective and it has become a frequent procedure in recent years. In developed countries approximately 40% of pleural effusions are now due to a malignancy, the most frequent cause being lung cancer, followed by cancer of the breast<sup>(3)</sup>.

**TABLE I**

| Treatment of recurrent malignant pleural effusion |  |
|---|--|
| Observation                                       | if no symptoms   |
| Thoracocentesis                                   | relief of symptoms in end stage patients                         |
| Chemotherapy                                      | SCCL<br>breast cancer<br>lymphoma<br>seminoma<br>cancer of ovary |
| Radiotherapy                                      | little usefull   |
| Chest tube drainage alone                         | 60% success?   |
| Chest tube drainage + sclerosing agent            | 86% success?   |
| Pleurectomy                                       | 100 % success?   |

Adapted after Sahn<sup>2</sup>

**TABLE II**

| Agents used to create pleurodesis in patients with malignant pleural effusion |                         |
|---|-------------------------|
| Nitrogen mustard  | Glucose 50%             |
| Thiotepa  | Talc                    |
| 5-fluor-uracil  | Tetracycline            |
| Bleomycine  | Fibrin glue             |
| 198 <sub>Au</sub>   | Chorynebacterium Parvum |
| 32P   |                         |
| 90Y   | Cisplatin               |

During the years many treatments have been used in pleural effusion connected with malignant disease in order to obtain pleurodesis (Table II). Tetracycline has since it was first introduced in an animal study<sup>(4)</sup> and in man 1972<sup>(5)</sup> been increasingly popular in the treatment of as well pneumothorax as malignant effusion<sup>(6)</sup>.

In the following the role of Tetracycline as a sclerosing agent in malignant pleural effusion is emphasised, but a number of controlled randomized studies dealing with other sclerosing agents will be mentioned.

A statement like: Tetracycline is currently considered as the optimal sclerosing agent due to its high efficacy, good patient tolerance, simple and repeatable application and low cost of treatment<sup>(6)</sup>, is probably endorsed by many clinicians. I shall try to find from the literature the evidence to justify this popular statement - if available.

## MODE OF ACTION

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Tetracycline was believed to create pleurisy leading to pleurodesis because of the low pH. It is not as simple as that. Three different concentrations of Tetracycline with the same pH were given intrapleurally to rabbits. Only 35 mg/kg. created a pleural fibrosis and symphysis, whereas 7 and 20 mg/kg. did not. There seems to be a dose response curve<sup>(7)</sup>.

In a randomized study in patients this observation was confirmed. The occurrence of pleurodesis did not depend on pH in the instilled substance but on the presence of Tetracycline<sup>(8)</sup>.

The mode of action is not known for sure, but fibroblasts growth seems to be stimulated<sup>(9)</sup> probably by a factor released by mesothelial cells<sup>(10)</sup>.

## PROCEDURE

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Before attempting pleurodesis it is essential to make sure the lung can expand.

The procedure can be performed in local anaesthesia.

Preoperative medication is necessary. It is well known, that the instillation of Tetracycline hurts and the patient is often scared of the situation. Many different drugs have been used. We have for a long time used Levopromazine, which at the same time is tranquilizer and a pain-killer<sup>(11)</sup>, but many drugs are used with good results. The local anesthesia for inserting the tube drainage has to be sufficient, as complications can occur if attention is not paid to this detail<sup>(12)</sup>.

Administration has mainly been through an indwelling tube drainage or a small bore catheter, which is clamped for 2-3 hours after administration.

Often a local anaesthetic is administered intrapleurally right before the Tetracycline is given. If Lidocain is used a dosis of less than 3 mg/kg. is recommended<sup>(13)</sup>, as this will not give blood levels that are toxic. Higher dosages, 250 mg as standard, have, however, been used without problems<sup>(14)</sup> and other local anaesthetics have been used as well.

By giving Tetracycline 20 mg/kg. intrapleurally therapeutic blood levels were found in 80% of the patients after 1 1/2 hour<sup>(13)</sup>. 20 mg/kg is more than usually given. Most often a standard dose of 500 mg of Tetracycline is used<sup>(5)</sup>.

The size of the tube does not seem essential for the result. Repeated instillation of Tetracycline has been advocated. In a prospective, randomized study of one or two doses of 20 mg/ kg. Tetracycline intrapleurally no difference was observed between the groups, and thus just one dosis can be recommended<sup>(15)</sup>.

There has been a tradition for shifting the patient into various positions in order to obtain a uniform distribution of the drug. Isotope studies seem to indicate that this distribution will take place in all events<sup>(16)</sup>. It is essential, that all fluid is drained from the cavity and the drain is therefore left in situ until only a minimal amount of fluid is drained during 24 hours, usually no more than 100 ml.

## INDICATION AND CONTRAINDICATIONS FOR PLEURODESIS IN MALIGNANCY

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The diagnosis of a malignancy must be certain and the tumour type not sensitive to chemotherapy. The pleural fluid should be present in such an amount, that symptoms arise (shortness of breath), and it recurs after evacuation. The lung must not be trapped. This should be tested by expanding the lung before an irritant is instilled.

The general condition of the patient should be good and the life expectancy is at least 3 months. This last is a difficult clinical evaluation. Some help may be gained by studies of pH and glucose levels in the pleural fluid<sup>(17)</sup>. Very old patients tolerate the procedure less well. It is a trauma to have tetracycline or other sclerosing substances instilled in the pleura and in a weak patient this might be sufficient to hasten deterioration considerably.

## COMPLICATIONS AND UNWANTED SIDE EFFECTS

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Most patients experience some pain when Tetracycline is instilled in the pleural cavity. Pain is difficult to measure, but the pain seems to be stronger in patients with pneumothorax than in patients with malignant pleural changes.

The pain is ameliorated by proper premedication, by local anaesthesia in the pleural cavity and by a proper preoperative explanation and psychic conditioning of the patient. Still it hurts some. The pain can provoke a vasovagal attack with severe bradycardia and should for this reason too be minimised.

On the evening of the pleurodesis and on the following 23 days a rise in temperature is usual. Initial temperatures up to 39-40 degrees centigrade are seen. This is not a sign of an infection but of a non-specific inflammation. If the temperature elevation persists the possibility of a bacterial infection should be taken into consideration. This is a rare complication, but empyemas are seen, as is local wound infection. The frequency of these complications obviously depend on the sterile technique and on the number of days the tube drainage is left in situ. The last statement is an assumption as no evidence from the literature is available. .

Spread of the neoplasm through the incision wound is known to occur after thoracoscopy, especially in mesothelioma<sup>(18)</sup>. Some will give prophylactic irradiation to prevent this complication<sup>(18)</sup>.

Subcutaneous emphysema is a very common finding but in the vast majority of cases it is unimportant, not giving symptoms and will disappear by itself.

Respiratory insufficiency. If a pleurodesis is made in a patient with a severely reduced lung function the following pain may immobilise the chest and later the sedation may suppress the respiration. If patients are properly selected respiratory insufficiency is no problem.

Pleural haemorrhage. If thrombocyte count is above 40.000 and prothrombin time over 40% haemorrhagic complications of importance are rare. Patients receiving chemotherapy or on dialysis may give unexpected problems.

Trapped lung. The ability of the lung to expand after evacuation of fluid should be tested before pleurodesis. If this is not done or if an inability to expand is ignored, the result will be a pleural cavity with a sterile inflammation, which will make a possible later decortication even more difficult.

A search of the literature for complications to pleurodesis has been made. This did not prove productive. In the very few prospective randomised studies no difference was found between talc and Tetracycline pleurodesis<sup>(19)</sup>. No significant difference was observed as far as complications were concerned between simple drainage and drainage + talc. These results were substantiated in a study of patients treated with simple drainage, drainage + talc or drainage

+ Tetracycline for pneumothora<sup>(20)</sup>. In a prospective comparison of corynebacterium parvum versus tetracycline fever and pain was significantly less pronounced in the latter treatment<sup>(21)</sup>.

Long term sequelae. From treatment of patients with pneumothorax with Tetracycline we know, that a few continue to have an occasional stabbing pain in the chest<sup>(20)</sup>.

As most patients with pleural effusion due to malignancy have a rather short survival, long term sequelae can be ignored.

Effectiveness. As mentioned, the number of agents and procedures used during the years in order create a pleurodesis has been considerable. Most of them have been published as effective, the success rate varying between 25 and 100% (Table III). In most Studies neoplasms originating in the lung and the breast dominate, but this of course does not make the results of the studies comparable. We know that success rate with talc, Quinacrine and Tetracycline are high whereas lower success rate have been found using other substances. Still we are not sure that the difference are real, as controlled prospective randomised studies are very few.

In our department at Bispebjerg Hospital, two studies have been performed. In one study simple repeated thoracocentesis was compared with repeated thoracocentesis + Thiotepa and repeated thoracocentesis + Quinacrine<sup>(23)</sup>. The Quinacrine treatment was significantly better than thoracocentesis alone.

In a later study from the department<sup>(11)</sup> simple drainage was compared to drainage + talc. Simple drainage was followed by pleurodesis in approximately 60%, significantly lower than in the group in which talc was added, but still higher than in reports on some sclerosing agents.

The number of non-evaluable patients is high, 7 died early, in 2 the lung could not be expanded and one got an empyema, which illustrates the difficulties in these studies.

A randomized study of patients with breast cancer receiving either drainage alone or drainage+ 32 P showed no significant difference between the groups. Again the response to drainage alone was approximately 60%<sup>(24)</sup>.

The effect of corynebacterium parvum has been compared to Bleomycine in both conditions without drainage. The success rate was highly in favour of corynebacterium parvum<sup>(25)</sup>.

Corynebacterium parvum and Tetracycline have been compared. The study<sup>(21)</sup> is from two centers and techniques were not uniform, but it seems that there was no significant difference in the success rate.

A comparison of tube drainage + Quinacrine or Tetracycline showed the treatments equally effective<sup>(26)</sup>.

Doxycycline + tube drainage compared with talc + drainage gave no difference of significance between the two treatments<sup>(19)</sup>. Fibrine glue + drain and Tetracycline + drain has been compared in a prospective study. There seems to be no difference between the treatment<sup>(27)</sup>.

TABLE III

| Sclerosing agents for intrapleural applications in malignant pleural effusion |                      |                 |                |          |
|---|----------------------|-----------------|----------------|----------|
| Sclerosing agent  | Number of references | Number of cases | Success rate % | Range    |
| Radioisotope  | 25                   | 980             | 55             | 25 - 100 |
| Talc  | 8                    | 105             | 92             | 76 - 100 |
| Nitrogen mustard  | 10                   | 338             | 52             | 28 - 87  |
| Thiotepa  | 3                    | 39              | 46             | 30 - 63  |
| S-Fluorouracil  | 1                    | 35              | 66             | —        |
| Bleomycine  | 1                    | 19              | 90             | —        |
| Quinacrine  | 9                    | 128             | 80             | 57 - 100 |
| Tetracycline  | 3                    | 31              | 87             | 83 - 100 |

After Austin, Flye 1981<sup>22</sup> and Frank et al. 1989<sup>6</sup>

## STAY IN HOSPITAL, LENGTH OF DRAINAGE, COMPLICATIONS

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Comparable data are available to a very limited extent. No difference was found between Tetracycline and talc treatment in the study by Muir et al. 19. In the study by Bayly et al.<sup>(26)</sup> fever and pain was significantly less pronounced in the Tetracycline than in the Quinacrine group. No significant difference was found between patients with spontaneous pneumothorax, but this group is hardly comparable to the cancer group<sup>(20)</sup>.

## PROGNOSIS

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As the obliteration of the pleural space is only a palliative procedure little influence on the survival can be expected. No study is available to give exact information on this topic.

It seems that the survival of patient eligible for pleurodesis can be predicted by the pH and glucose level. This should be used in the evaluation of patients for pleurodesis<sup>(28)</sup>.

Low glucose and pH levels in the pleural fluid are predictors of a lower success rate in pleurodesis treatment<sup>(28)</sup>. The results are, however, not so much poorer that the treatment should not be attempted.

## CONCLUSION

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Following the established indications and procedures Tetracycline is an acceptable sclerosing agent in patients with malignant pleural effusion. The results and side effects seem to be comparable to the results obtained with talc and Quinacrine.

## LITERATURE

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