



*Original Contribution*

## EFFECTIVENESS OF TALC SLURRY IN PRODUCING PLEURODESIS: A STUDY IN RABBITS

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### ABSTRACT

Pleurodesis is routinely used for the treatment of malignant pleural effusions. Talc is probably the most efficacious pleural sclerosant agent. It has been used for this purpose as poudrage or as slurry. Our aim was to evaluate whether talc in slurry is an effective pleural sclerosant. An experimental rabbit model was used to examine the pleural changes that occur following talc slurry pleurodesis. Gross pathology on 28th day of talc instillation has shown no uniform distribution in the pleural space, with low grade of pleurodesis. Histologically, we established two forms of talc distribution: individual particles and massive aggregates in the structure of foreign body granulomas. It was visible that individual talc particles damaged the mesothelium and caused pleural fibrosis. Fibrous strands and adhesions between pleural surfaces were established as a result of pleural fibrosis. Foreign body granulomas did not cause pleural fibrosis; that was why they were the cause of pleurodesis.

We have concluded that talc in slurry has no uniform distribution in the pleural space, with predominantly pleural accumulation as massive aggregates. Talc slurry is not considered an effective method of pleurodesis.

**Key words:** talc slurry, pleurodesis, pleural fibrosis, pleural effusion

### INTRODUCTION

Pleurodesis, from the Greek *pleura* and *desis*(binding together) is intended to achieve a symphysis between parietal and visceral pleura. Pleurodesis is routinely used for the treatment of malignant pleural effusions. The mechanism of pleurodesis is based on pleural irritation to create an inflammatory reaction leading to fibrogenesis. One of the methods of pleurodesis includes intrapleural instillation of a sclerosant agent. Talc ( $Mg_3SiO_{10}[OH]_2$ ) is known as a highly effective pleurodesis agent. It has been used for this purpose since 1935. Talc poudrage at the time of thoracoscopy is the most common method of administration. Another method of talc administration is via slurry through chest tube.

Talc slurry is used in patients who do not require a diagnostic thoracoscopy or who are unable to tolerate thoracoscopy. Using talc as slurry permits its bedside administration in extremely weak patients.

The aim of the present study was to

evaluate whether talc in slurry is an effective pleural sclerosant. We used an experimental rabbit model to examine the pleural changes that occur following talc slurry pleurodesis.

### MATERIALS AND METHODS

Six normal New Zealand white rabbits weighing 2.5 to 3.5 kg were used for this study.

#### Talc slurry preparation

Talc was dry heated and sterilized at 165<sup>0</sup> for 6 h. Rabbits received intrapleural 400 mg/kg of talc, each mixed in a total volume of 2 ml of normal saline solution. The slurry was prepared and placed into sterile syringe of 5 ml. The talc slurry was gently shaken immediately before intrapleural injection.

#### Experimental procedure

The animals were lightly anesthetized with 25mg/kg intramuscular ketamine hydrochloride (*Kalipsol*). The right chest wall was shaved, scrubbed with Betadine and then a 2.0 cm skin incision was made midway between the spine and scapular tip. The

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muscles of the thoracic wall were bluntly dissected to allow exposition of the parietal pleura. A specially prepared multi-perforated catheter (from the 22-G angiocatheter) was then introduced into the pleural space. The end of the catheter was removed so that the right lung could collapse. After that the slurry was injected into the right pleural cavity through the catheter. Immediately after talc instillation, all air was aspirated from the pleural space and the catheter was removed. The muscles and skin were sutured. Finally, animals were turned over for one minute to ensure a homogeneous intrapleural distribution of talc.

### Gross pathology

After talc instillation on 28th day the animals were killed with 50 mg/kg of thiopental injected into the marginal ear vein. The sternum and the median portions of the ribs were removed so the two hemithoraces could be evaluated macroscopically. The left hemithorax served as a control. The degree of pleurodesis was graded according to the following scheme: 0-normal pleural space; 1-less than three adhesions; 2-more than three adhesions; 3-generalized adhesions; 4-completely obliteration of pleural space by the adhesions than three adhesions.

### Tissue specimen preparation

Tissue specimens of the parietal pleura and thoracic wall, visceral pleura and lung from the right hemithorax were obtained. The specimens were placed in a 10% formalin solution for 2 days. After that, they were fixed in paraffin. Histologic sections were prepared from the tissue specimens and were stained with hematoxylin and eosin. The microscopic slides were evaluated by light field microscopy.

### Animal care

In this study we adhered to the "Guide of the Care and Use of Experimental Animal Care"<sup>1</sup>

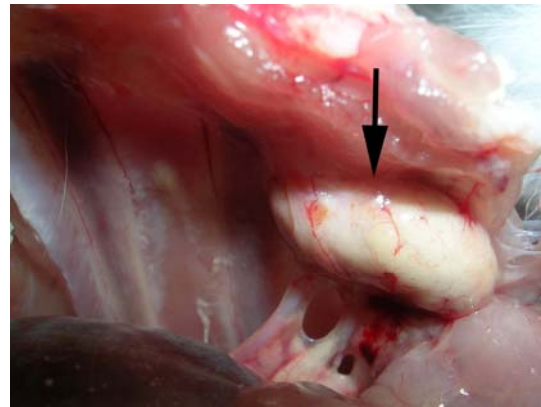
### Statistical analysis

The degree of pleurodesis, assessed grossly, was estimated by variable analysis using computer software. Data are expressed as the mean  $\pm$  SEM.

## RESULTS

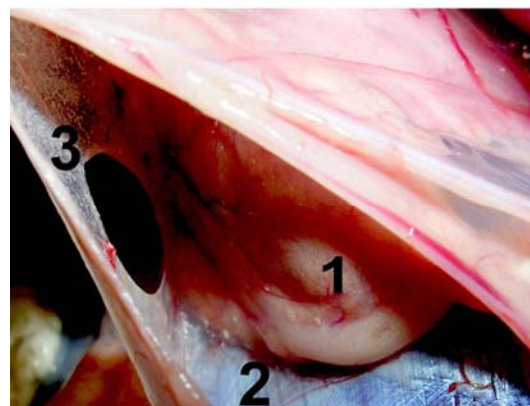
### Gross pathology

None of the rabbits died during the 28 days after the intrapleural instillation of talc. No rabbits had pleural effusion or haemothorax at the time of autopsy. Collections of talc were visible on parietal and visceral pleural surfaces in the right hemithorax. Large collections were noted more frequently. They presented as foreign body granulomas, which were localized predominantly on the parietal pleural surface (**Figure 1**).



**Figure 1.** Large collection of talc onto the parietal pleural surface as a foreign body granuloma. The arrow has showed the foreign body granuloma. (Digital photography on the right hemithorax, on 28<sup>th</sup> day after talc instillation)

The small collections of talc were mainly incorporated into the fibrous strands. These strands, connecting visceral and parietal pleural surfaces were localized predominantly in the ventral areas. (**Figure 2**).



**Figure 2:** Fibrous strands between pleural surfaces, in the right hemihorax. [1- right inferior lung lobe; 2- diaphragm; 3- fibrous strands with small talc collections]

We established mean value of gross pleurodesis score of  $1.33 \pm 0.21$  in the right pleural space. None of the rabbits had visible severe atelectasis of the underlying lung.

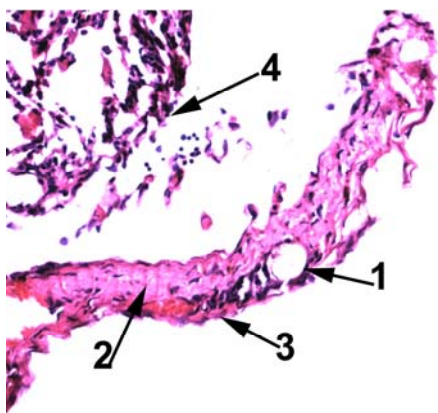
There were no established collections of talc in the left pleural space. The degree of pleurodesis on the left was 0 in all rabbits.

## Histology

### *Pleural talc distribution*

Two forms of pleural talc particles distribution were established: individual particles and massive aggregates.

Individual talc particles were incorporated into the thickened pleural connective tissue (**Figure 3**).



**Figure 3.** Pleural and subpleural lung changes at 28<sup>th</sup> day after talc slurry instillation (haematoxylin-eosin; x200). 1: Talc particle, incorporated into the fibrous visceral pleura; 2: Visceral pleural fibrosis: collagen fibers and fibrocytes; 3: Denudement of mesothelial cells in the area of fibrotic remodelling of the pleura; 4: Subpleural mononuclear infiltration.

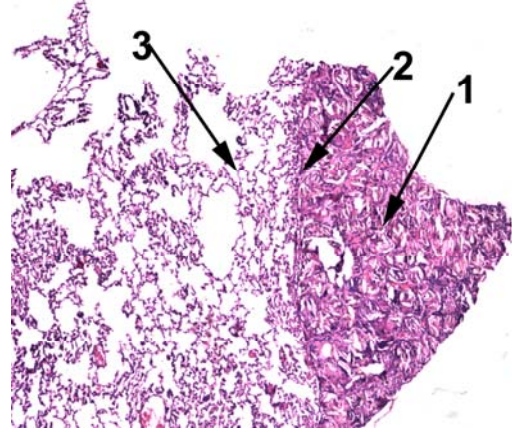
Talc aggregates were results of focal talc depositions, incorporated in the structure of foreign body granulomas. By light microscopy, granulomas were visible on the pleural surfaces (**Figure 4**).

The following structures of granulomas were established: a large number of talc particles surrounding connective tissue stroma; mononuclear inflammatory cells and multinucleate giant cells, infiltrated tissue stroma (**Figure 5**).

### **Pleural changes**

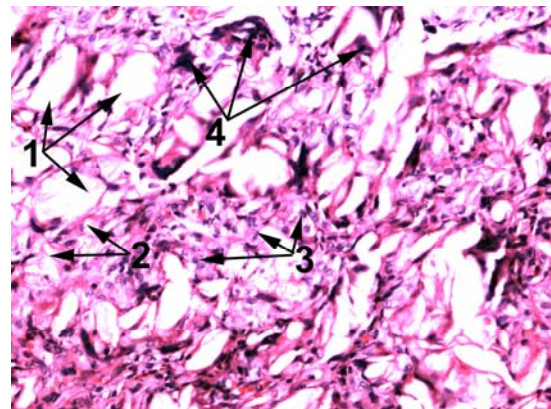
Visceral and parietal pleura were focally changed, in association with individual talc particles. Talc particles had provoked focal fibrotic response. In these areas pleura was thickened, with layers replaced by connective tissue-collagen fibres and fibrocytes.

Collagen matrix contained talc particles. Histological specimens demonstrated denudement of mesothelial cells in the areas of fibrotic remodelling of the pleura (**Figure 3**).



**Figure 4.** Foreign body granuloma onto the visceral pleural surface (haematoxylin-eosin; x100).

1: Foreign body granuloma, with many incorporated talc particles; 2: preserved mesothelial layer, without pleural fibrosis; 3: atelectasis of subpleural lung parenchyma.



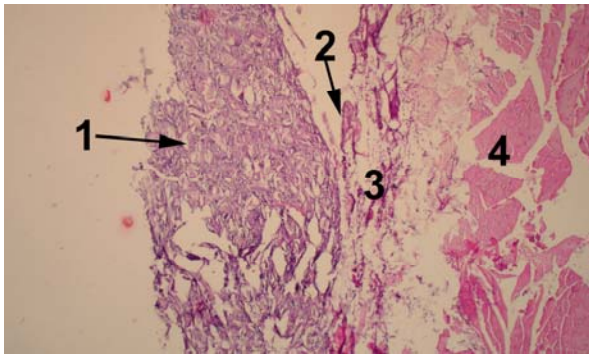
**Figure 5:** The structure of foreign body granuloma (haematoxylin-eosin; x200). 1: talc particles; 2- connective tissue stroma; 3: mononuclear infiltration; 4: multinucleate giant cells.

Mesothelial layer was preserved and pleura had no fibrotic change in the areas with foreign body granulomas on its surface (**Figure 4**).

### **Lung and thoracic wall changes**

Light atelectasis of the subpleural parenchyma was established in the areas of talc distribution-as individual particles and as well as foreign body granulomas. The subpleural interstitial connective tissue and peripheral airspaces were infiltrated with mononuclear cells. There was no observed talc deposition in the lung (**Figure 3**, **Figure 4**).

Similar reaction was seen on the thoracic wall. Mononuclear infiltrates were demonstrated between the parietal pleura and intercostal muscles (**Figure 6**). There was no talc deposition on the thoracic wall tissues.



**Figure 6.** Thoracic wall changes at 28<sup>th</sup> day after talc slurry instillation (haematoxylin-eosin; x100). 1: talc collection as a foreign body granuloma; 2: preserved parietal mesothelial layer; 3: subpleural connective tissue with light mononuclear infiltration; 4: thoracic wall muscles.

## DISCUSSION

Clinical studies have suggested that talc is probably the most efficacious sclerosant for malignant pleural effusions. Walker et al. in a review of the literature reported that talc completely controlled the pleural effusions in 95% of patients (2). As a pleural sclerosant agent, talc could be insufflated in the pleural cavity in the form of poudrage or as slurry. In our practice, talc has been used in malignant pleural effusions as a poudrage in the time of thoracoscopy. We have not used talc as slurry. There are studies, which have demonstrated effectiveness of talc as slurry in the treatment of malignant pleural effusions (3). There has been some criticism on the method of administration for pleurodesis because of no uniform distribution in the pleural space (4).

This experimental study was our first attempt at studying the effectiveness of talc as a pleural sclerosing agent. We have investigated not only the effectiveness of talc as a slurry but we have made the first step in understanding the mechanism of talc pleurodesis.

There are reported results of experimental studies of pleural talc instillation. As a poudrage talc has been used in dogs and cats, with high effectiveness in producing pleurodesis (4). Talc has been used as slurry predominantly in rabbits (5, 6, 7, 8, 9). With regard to published data, we have used the highest published dose of talc slurry in rabbits-400mg/kg. 28 days after talc

administration was considered adequate time for producing pleurodesis. We confirmed the finding of the other authors at autopsy of the rabbits – intrapleural administration of talc led to pleurodesis without development of pleural effusion, haemothorax and fibrothorax (10). Our finding at autopsy was a low grade gross pleurodesis score ( $1.33 \pm 0.21$ ), despite high dose of talc administration. Pleural adhesions were caused only by talc, distributed as small collections. Foreign body talc granulomas did not lead to pleurodesis.

Pleural changes were caused by individual talc particles. Talc particles have caused denudement of the mesothelium. Denudement of mesothelium is a trigger for pleural inflammatory reaction (11, 12, 13). The final result is a fibrotic remodelling of the pleura in the areas of its damage (without mesothelium). Talc particles have been incorporated into the collagen fibres. We considered pleural fibrosis as a final result of protective pleural reaction against talc particles. On the other hand pleural fibrosis has led to formed fibrous strands and adhesions between pleural surfaces (pleurodesis).

Massive talc aggregates were ineffective in producing pleural fibrosis. As a protective reaction against massive aggregates, pleura have formed foreign body granulomas on its surface. Talc aggregates were incorporated into the structure of foreign body granulomas. In the areas of granulomas the mesothelial layer was preserved and pleural fibrosis did not develop. That is why in these areas there were no fibrous strands and pleural adhesions – lack of pleurodesis.

J. Ferrer has described three types of talc deposition in the lung: 1. no talc particles in the lung parenchyma, 2. individual talc particles in parenchyma and 3. deposition of talc aggregates (9). We have established lack of talc in the lung parenchyma with minimal tissue reaction, expressed in subpleural mononuclear cells infiltration. The same cell reaction was established in the subpleural tissue of the thoracic wall. This is a protective reaction from the lung and thoracic wall tissues to this pleural sclerosant.

## CONCLUSION

1. In summary, talc has caused pleurodesis by process of pleural fibrosis, which is activated by denudement of mesothelium.
2. Only individual talc particles have led to pleurodesis.
3. Talc slurry has no uniform distribution in the pleural space, with predominantly

pleural accumulation as massive aggregates. We have considered talc slurry as not an effective method of pleurodesis.

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