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Talc powder vs doxycycline in the control of malignant pleural effusion: a prospective, randomized trial

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Summary

Background:

Malignant pleural effusion is a common problem in advanced cancers, contributing to the poor quality of life in this group of patients. The aim of the study was to assess the efficiency of talc powder and doxycycline in pleurodesis in patients with malignant pleural effusion in comparable conditions.

Material/Methods:

Of 52 patients screened, 33 entered the trial. They were randomized to the talc group (n=18) and the doxycycline group (n=15). Both groups were comparable with regard to age, sex and the most important variables influencing effectiveness of the procedure, i.e. primary malignancy and stage of metastatic involvement of the pleura. Efficiency of pleurodesis was prospectively assessed.

Results:

The analysis of short-term effectiveness of pleurodesis in the first 33 patients has shown a highly significant difference in favor of talc powder (p=0.009); this difference was the reason for terminating the randomization. Further observation has revealed in the doxycycline group an increasing number of patients with fluid reaccumulation, as time went by; this was not observed in the talc group. A statistical analysis of the long-term effectiveness of both agents studied has shown a more significant difference in favor of the talc powder (p=0.00003).

Conclusions:

Talc powder is superior to doxycycline in achieving pleurodesis in patients with malignant pleural effusion, in both short- and long-term observations.

key words:

malignant pleural effusion • pleurodesis • talc • doxycycline • videothoracoscopy

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BACKGROUND

Malignant pleural effusion is a common problem in advanced cancers, contributing to the poor quality of life in this group of patients. The palliative treatment of choice is obliteration of the pleural space to prevent fluid accumulation (pleurodesis). There is a large body of evidence, that talc and doxycycline are two of the most effective sclerosing agents in treatment of malignant pleural effusions [1–13]. Most trials suggest slightly better effectiveness of talc (76–94.5%) [1–9] over doxycycline (79–88%) [10–13], but the differences are not significant, and the route of administration of the agent varies in most publications. In fact, talc powder was usually administered during thoracoscopy, and doxycycline via a chest tube. Instillation of doxycycline via a chest tube implies an inability to assess the degree of involvement of the pleura. As the advancement of the metastatic process on the surface of the pleura is associated with an increased risk of failure of pleurodesis, [14] the comparison of the effectiveness of talc and doxycycline may be biased by incomparability of the groups studied.

To assess the efficiency of talc powder and doxycycline in comparable conditions we designed a prospective, randomized study using videothoracoscopy.

MATERIAL AND METHODS

We screened all patients admitted to the Division of Interventional Pulmonology of the University Hospital in Cracow with pleural effusion and clinical suspicion of malignant origin. The excluding criteria were as follows:

- 1) failure to confirm malignancy in the pleura by macroscopic assessment in videothoracoscopy and histological examination of parietal pleura specimens;
- 2) establishing the diagnosis of the malignant pleural mesothelioma;
- 3) inability to achieve full re-expansion of the lung.

From October 1998 to December 2000, a group of 52 patients was examined for the study. In this group, 19 patients met at least one of the excluding criteria: in 3 the metastatic disease to the pleura was not confirmed, in 14 the diagnosis of malignant pleural mesothelioma was made, and in 2 we were unable to achieve full re-expansion of the lung. The study was terminated before including the planned number of 100 patients, because the initial analysis had shown a statistically highly significant difference of effectiveness in favor of talc powder. Further randomization would therefore be ethically unacceptable. Thus the data of 33 patients were finally analyzed.

The patients included were randomly assigned to one of the two groups: in the first group, 10 g of talc powder was insufflated on the whole surface of the pleura with a hand insufflator, and in the second group 500 mg doxycycline in 25 ml solution was instilled to the pleural cavity. Videothoracoscopy was used to assess the stage of metastatic involvement of the pleura and to take biopsy specimens allowing for a histopathological diagnosis.

Previous experience at our institution indicates that there is a constant pattern of involvement of the pleura in the metastatic process. Nodular metastatic foci appear always in the same sequence: first, on the lower part of the parietal pleura, then on the upper, and in the more advanced cases on the visceral pleura. We found no exceptions to this rule in 110 patients in whom we had previously performed videothoracoscopy. However, in 5 cases the spreading of cancer had another pattern: in contrast to nodular dissemination, we observed a wide, flat infiltration of great areas of parietal and visceral pleura, with lung entrapment and multilocular fluid collection formation. In this later group, the macroscopic view mimics parapneumonic effusion and the cancer spreads aggressively, leading in a short time to the patient's death.

On the basis of the experience described above, we developed an abbreviated system of staging metastatic involvement of the pleura (table 1).

Videothoracoscopy was performed under general anesthesia. The patients were intubated with a Robertshaw-type tracheal tube allowing separate ventilation of one lung; they were placed in lateral decubitus position with a roll under the flank and the upper arm abducted. We used a rigid 10 mm thoracoscope. The placement of the first port was selected after analysis of chest X-ray and/or CT scans, usually in the 5th intercostal space in the midaxillary line. After needle aspiration to confirm the presence of fluid, the first port was introduced and initial inspection of the pleural cavity was performed. Under visual control we introduced the second (5 mm) port to remove all the fluid by suction (the fluid was collected for cytological examination). After the fluid had been removed, we performed detailed inspection of the pleura, including all its recesses. With a shell-type biopsy forceps, specimens for histological examination were taken from apparently malignant or suspect lesions. If no suspicious lesions were found, multiple parietal biopsies were taken. Finally, the sclerosant agent was given, according to randomization. To prevent rapid evacuation of the agent in the doxycycline group, we suspended the connecting tube 30 cm above the level of the patient's chest; this technique allows evacuation of air from the pleural cavity and lung re-expansion, which is, in our opinion, safer than clamping the chest tube.

The patients were extubated in the OR and transferred to the postoperative unit. Blood oxygen saturation, EKG, blood pressure, temperature and volume of the fluid drained were monitored, and the position of the patient was changed every 15–20 minutes. We used the standard criteria for chest tube removal: full lung reexpansion, no air leak, and volume of the fluid drained ≤ 150 ml/24 h. In the doxycycline group, if the volume of drainage exceeded 150 ml/24 h, we administered the next 500 mg dose, for a total amount of 3 doses, according to the protocol described by Robinson et al [13]. A control chest X-ray was performed the next day after videothoracoscopy, before chest tube removal and on the next day, before discharge of the patient and according to any special indications. All complications were recorded.

Table 1. Staging of metastatic involvement of the pleura.

Stage	Type of involvement
I	Nodular metastases limited to the lower part of parietal pleura
II	Nodular metastases occupying all the parietal pleura
III	Nodular metastases occupying parietal and visceral pleura
IV	Wide infiltration of parietal and visceral pleura, with lung entrapment and multilocular fluid collections

In the patients with advanced malignancy, all parameters, both objective and subjective, deteriorate with time, irrespective of success of pleurodesis. Thus the only reliable criterion for the success of this procedure is the absence of reaccumulation of pleural effusion. A description of pleurodesis effects is shown in table 2.

The short-term and long-term effectiveness of pleurodesis was assessed separately. As a short-term effect we adopted the effectiveness after a single dose of talc powder given during videothoracoscopy or after 1–3 doses of doxycycline. The criterion for long-term effectiveness was no fluid reaccumulation until the death of the patient, or – in the case of those who were still alive at the moment of closing the study – for at least 12 months.

The efficiency of the procedure was analyzed using the Mann-Whitney test, and a p-value of <0.05 was considered significant.

RESULTS

There were 33 patients analyzed: 18 in the talc group and 15 in the doxycycline group. In the talc group there were 4 men and 14 women; the mean age was 63 years (range 47–81). In the doxycycline group there were 2 men and 13 women; the mean age was 61 years (range 44–72).

The most common primary tumor in both groups was breast cancer (16 patients), lung cancer (8 patients), and a group of patients with unknown primary malignancy. In the remaining group there were renal, endometrial, ovarian and prostate carcinomas, lymphoma, myeloma and malignant melanoma, one patient each. For the purpose of statistical analysis they were included in one group.

The analysis showed no statistically significant differences between the talc and doxycycline group with regard to the incidence of primary malignancy ($p=0.14$).

The analysis of advancement of metastatic disease in the above mentioned original scale showed no statistically significant differences between the talc and doxycycline groups ($p=0.55$). Thus, both groups were comparable in regard to age, sex and the most important variables influencing effectiveness of the procedure.

The analysis of short-term effectiveness of pleurodesis showed a highly significant difference in favor of talc

Table 2. Description of pleurodesis outcome.

Effect	Description
Excellent	No fluid reaccumulation
Good	Limited residual fluid, not increasing, no indications for thoracentesis
Poor	Fluid reaccumulation requiring thoracentesis

powder ($p=0.009$) (Figure 1); this difference was the reason for terminating of the randomization.

Further observation revealed that the number of patients with fluid reaccumulation in doxycycline group was increasing with time; this was not observed in the talc group. In the doxycycline group, of 7 patients with excellent response to therapy only in one the effect remained excellent until the end of observation (she died 26 months after pleurodesis); in 3 cases, we observed limited reaccumulation of fluid, not requiring paracentesis (they died after 4, 6 and 17 months) and in 1 patient there was failure of pleurodesis after two weeks. In the remaining 2 patients there were no available long-term data: one of them was lost to follow-up, and the last died 3 days after the VTS due to respiratory and circulatory insufficiency. Two patients in the doxycycline group, in whom the results of pleurodesis were initially good, maintained this effect until the end of observation (one died at 2.5 months and the other was still alive at the moment of final analysis, 15 months after surgery).

In contrast to the increasing rate of pleurodesis failure in the doxycycline group, only in one patient in the talc group we observed limited reaccumulation of fluid in the last month of her life, not requiring thoracentesis (she died 20 months after pleurodesis). A statistical analysis of the long-term effectiveness of both agents studied showed a more significant difference in favor of talc powder ($p=0.00003$) (Figure 2).

Independently of the above analysis, we attempted to achieve talc pleurodesis in 6 patients in the doxycycline group who failed to respond to treatment. One of them died in the postoperative period due to respiratory insufficiency, and in the remaining 5 cases we attempted to achieve pleurodesis with 10 g of talc instilled as a slurry via a chest tube. In 4 of these cases the result was good (three died after 1.3, 5.3 and 10 months, and one was still alive at the moment of final analysis, 21 months after surgery). In the last patient the effect was excellent: he was still alive at the moment of final analysis, 13 months after surgery. Thus, in all patients receiving talc slurry as a second-line treatment, the result was good or excellent.

DISCUSSION

Our results suggest that in patients with malignant pleural effusion the primary sclerosant agent used for pleurodesis should be talc (powder or slurry), because of its highly superior effectiveness.

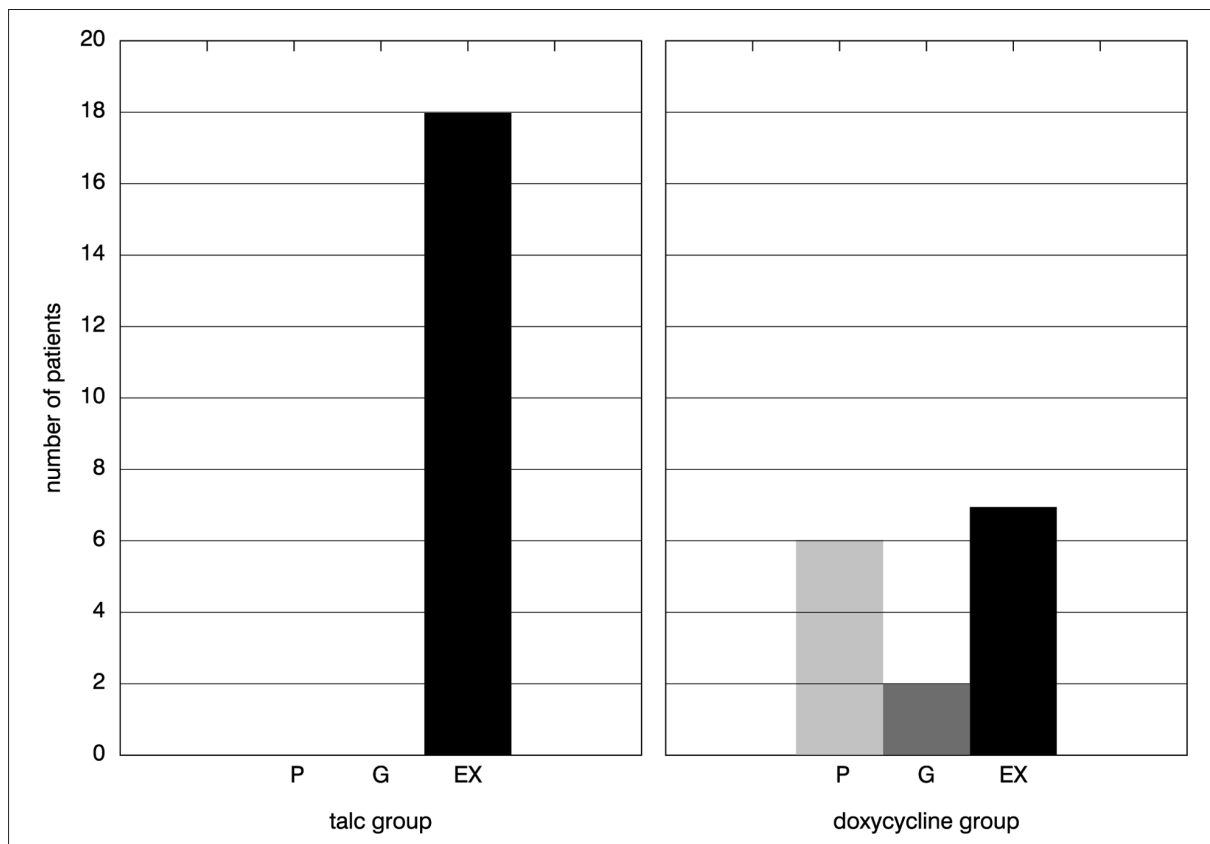


Figure 1. Short-term results of pleurodesis in talc and doxycycline groups. P – poor, G – good, Ex – excellent.

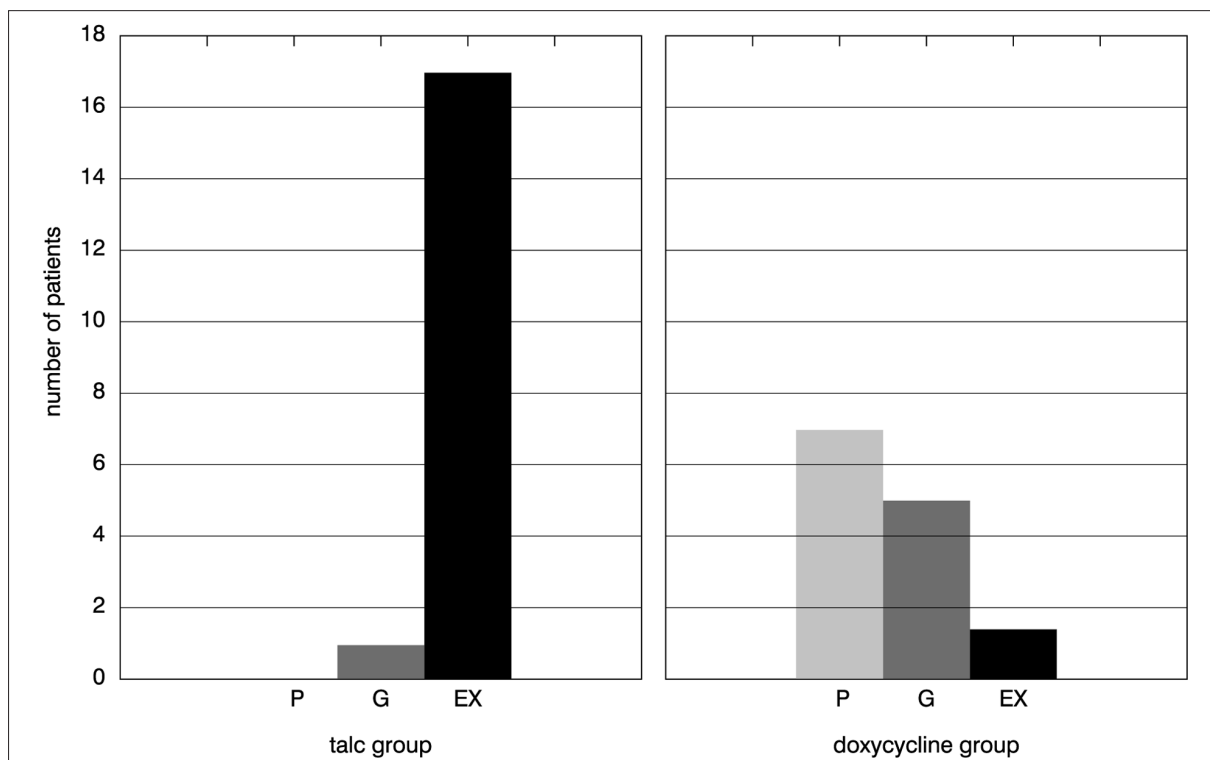


Figure 2. Long-term results of pleurodesis in talc and doxycycline groups. P – poor, G – good, Ex – excellent.

It has been shown that a malignancy is the most common cause of pleural fluid accumulation [15–21], and the estimated number of patients with malignant pleural effusion may be as high as 100/100,000 population [22]. Such a great incidence makes the malignant pleural effusion a serious problem for health-care institutions. Involvement of the pleura in metastatic disease usually makes curative treatment impossible, and therefore the goal in these patients is palliation of symptoms that may significantly worsen the quality of their life. A number of methods have been investigated in the treatment of malignant pleural effusion, including repeated needle aspiration, continuous pleural drainage (also in outpatients, with thin-bore catheter and bag) [23–27], pleurectomy [28,29], irradiation of the chest [30], intrapleural chemotherapy [31,32], chemoimmunotherapy [33], and intrapleural α -2b interferon [34], TNF [35], and interleukin-2 [36]. Although these methods may be indicated in certain clinical conditions, the most commonly used in clinical practice is chemical pleurodesis. This is because of the simplicity, safety and effectiveness of this method. There are many agents used to achieve pleurodesis, including tetracycline, doxycycline, minocycline, bleomycin, cisplatin, doxorubicine, vincristine, etoposide, 5-fluorouracil, interferon, mitomycin C, *Corynebacterium parvum*, methylprednisolone, talc, povidone-iodine, polidocanol, erythromycin, mepacrine, and silver nitrate [1–13]. A great number of papers have been published in the past two decades, showing good effectiveness of talc and doxycycline [32–45], but the differences of methods used make comparison difficult. In most of the studies the stage of involvement of pleura in metastatic disease was not recorded. The increasing popularity of videothoracoscopy makes it possible to specify the stage, giving the opportunity to design a study, assessing the real effectiveness of sclerosing agents in comparable groups of patients.

The shortcoming of our study is undoubtedly the limited number of patients analyzed. This was partly because of the restrictive excluding criteria we adopted. However, the impossibility of re-expansion of the lung makes pleurodesis impossible, and we believe that including patients with malignant pleural mesothelioma would have biased the results. Malignant mesothelioma, being in the pleura localized, not metastatic disease, is characterized by different behavior; in selected patients there is the possibility of curative treatment, consisting of radical surgery and chemoradiotherapy. The significant number of patients with malignant mesothelioma in our group (14 of 52) is due to the activity of an asbestos factory in our region (terminated two years ago).

Despite the smaller than initially planned number of patients analyzed, making the assessment of events like talc complications impossible, the study was able to answer the main clinical question about the relative efficiency of talc powder and doxycycline in achieving pleurodesis in patients with malignant pleural effusion.

CONCLUSION

Talc powder is superior to doxycycline in achieving pleurodesis in patients with malignant pleural effusion,

and the difference is statistically highly significant. Our results suggest that the use of doxycycline for pleurodesis should be abandoned with the exception of non-malignant diseases.

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