Review Article

Thoracoscopic pleurodesis using talc poudrage versus cytotoxic drug in malignant pleural effusion: narrative review

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Abstract: Malignant pleural effusion (MPE) indicates incurable cancer with a variable prognosis, from 4 to 12 months. Definitive control of effusion with pleurodesis should be undertaken in all patients with an expandable lung who are likely to require frequent drainages and with an expected survival greater than 3 months. Presently, talc is the most commonly used pleurodesis agent. It is inexpensive and readily available worldwide. Its superiority over alternative compounds has been suggested by more than one meta-analysis; thus, it is the agent of choice in the international guidelines. Talc is highly effective, with success rates from 80% to 95%, relative to the dose, number of administrations and patient's metabolic and nutritional conditions, with acceptable side effects and risks in a patient with a modest life expectancy. Other substances used are tetracyclines (doxycycline, minocycline), bleomycin, nitrogen mustards, quinacrine, *Corynebacterium parvum*, interferon (IFN), methylprednisolone, doxorubicin, cisplatin, cytarabine, etoposide, fluorouracil, mitomycin C, gold- and phosphorus-radioactive isotopes, alcohol, povidone-iodine and silver nitrate. Talc remains the most effective sclerosant available for pleurodesis. There are no comparative studies showing the superiority of other substances to talc. Talc poudrage is highly effective, at least equivalent to talc slurry, with possible increased efficacy in certain disease subgroups. The lack of comparative randomized trials, different eligibility criteria and heterogeneity of the study populations do not help scientists determine the standards concerning the type of substance to be used, indications, and methods.

Keywords: Malignant pleural effusion (MPE); pleurodesis; thoracoscopy; talc (poudrage); sclerosing agents

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Background

Relapsing pleural effusion is a frequent occurrence in primary and secondary malignancies of the pleura and lung. Malignant pleural effusion (MPE) indicates incurable cancer with a variable prognosis, from a median survival of 4 months for lung carcinoma to 12 months for mesothelioma (1-3).

No pleural intervention is curative for MPE; thus, the management remains palliative (4-23).

The therapeutic goal is not only fluid removal but also symptom relief (particularly breathlessness), improvement in the quality of life (QoL), and maximization of the time outside of the hospital (24).

All pleural drainage procedures are associated with the risks of complications (e.g., pain, pneumothorax,

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infection, vagal reflexes, hypotension, and pulmonary edema). Compared with chest tube insertion, thoracentesis has a lower complication rate, but it exposes patients to cumulative risks because it is repeatedly performed. Pleurodesis and indwelling pleural catheter (IPC) placement are effective treatments for recurrent MPE, with improvements in dyspnea and QoL with both treatments (1,25,26).

Thus, definitive control of MPE using pleurodesis or IPC placement should be undertaken in all patients who are likely to require ongoing and frequent drainages.

Chemical pleurodesis comprises the instillation of a sclerosing agent in the pleural cavity to cause an inflammatory pleural reaction, with consequent adhesion and fibrosis of the pleura. Thus, the obliteration of the pleural space will prevent the recurrence of pleural effusion.

This article represents a narrative review of the characteristics of pleurodesic substances, the main roles of talc poudrage, and its comparison with other treatment choices. We searched on PubMed database, systematic reviews, and clinical trials, edited in English from 1906 to 2020. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jxym-20-67).

History of pleurodesis

The term "pleurodesis" comes from the Greek pleura (pleura) and desmos (bond).

The history of "chemical" pleurodesis began in 1901, when Dr. Lucius Spengler, a Swiss surgeon, instilled a hypertonic glucose solution in the pleural cavity to produce pleural adhesions. The attempt was unsuccessful; thus, he proposed using silver nitrate solution (27-29).

In 1934, the Canadian Dr. Henry Norman Bethune first insufflated talc in the pleural space (30). As a world-renowned surgeon, Dr. Bethune was considered an innovator regarding his numerous scientific contributions and a social activist for the welfare of the poor and reform of the health care system. Bethune used talc to anchor pulmonary lobes so that they remained in position during the resection of other lobes (31). To do so, he used a Jacobeus thoracoscope and a return-air pleural powder blower, similar to what is still currently used for talc poudrage.

The use of talc for the palliative treatment of MPE was introduced in 1958 by Dr. John Chamber.

In the last 50 years, the palliative treatment of MPE has comprised the endocavitary administration of various substances to seal the pleural space and prevent subsequent reaccumulation of fluid.

Tetracyclines and bleomycin have shown high efficacy, not only for the antiblastic or cancerocidal effect but also for the irritative activity on the pleura. These drugs quickly build up pleural adhesion bridges that determine the obliteration of the pleural cavity and control of pleural effusion recurrence. This treatment was considered effective, safe and cheap for these patients with advanced pathology.

A medical powder containing sterile talc, purified from contaminants, but asbestos-free, became widely available on the market at a very low cost. Talc has a high pleurodesic activity and no antiblastic effects.

Talc use has been implicated in contributing to certain types of disease, mainly cancers of the ovaries and lungs. Talc-containing asbestos is classified as a group 1 agent (carcinogenic to humans), talc use in the perineal region is classified as a group 2B agent (possibly carcinogenic to humans) and talc-less asbestos is classified as group 3 (unclassifiable as to carcinogenicity in humans).

Indications

Asymptomatic effusion does not require intervention, as demonstrated by a large multinational series, in which only 51% of patients with MPE required/opted for definitive treatment (3,26,32).

Patients with symptomatic MPE and an expected median survival of more than 3 months should be offered definitive palliative intervention, which may include chemical pleurodesis and/or the insertion of an IPC (5,26).

Currently, guidelines regarding how to choose between pleurodesis and IPC in a naïve situation are lacking, but ATS/STS/STR (American Thoracic Society, Society of Thoracic Surgeons, and Society of Thoracic Radiology) guidelines advise using IPC instead of chemical pleurodesis in patients with non-expandable lung or failed pleurodesis. Approximately 50% of IPC patients develop spontaneous pleurodesis without chemical instillation (1,25,33), but recent studies are addressing the possibility of performing pleurodesis using IPCs (4).

Pleurodesis is considered effective when the effusion does not relapse in the subsequent 30 days.

Some prerequisites must be met for successful pleurodesis:

- An expandable lung;

- ❖ Sclerosing substance administration must be uniformly realized for most of the pleural surface;
- ❖ The patient must not have reached the condition of terminal illness, with a reduced life expectancy; the clinical conditions must be acceptable and ensure metabolic support for tissue repair processes to form;
- ❖ The patient is not being treated with antiblastic and/or cortisone drugs, and the nutritional status is acceptable; a significant capacity for tissue regeneration must be present.

Pleurodesis success is associated with several factors, including pleural fluid pH, pleural fluid glucose, extent of pleural involvement and tumor type (34,35).

A contraindication to pleurodesis is the presence of neoplastic forms that are decidedly responsive to systemic chemotherapy treatments. This type of effusion is related to neoplastic diseases waiting to be treated and can regress once an adequate therapy has been set (e.g., lymphomas and SCLC).

It is not advisable to obliterate the pleural cavity in subjects who could be submitted to invasive procedures aimed at restaging and/or histological redefinition of the tumor.

Regarding the timing of pleurodesis, most clinicians perform it only when the drain output is reduced to <150 mL over 24 h. Once the pleurodesic substance has been instilled, the consensus opinion suggests clamping for 1 h (36) with radiological evidence of lung expansion.

The traditional practice of rotating the patient during tube clamping is no longer advocated (37).

Regarding the dose of talc to be used, it varies from 2 to 8 g; the most frequently used is 4–5 g (38).

The duration of chest drainage following pleurodesis has been studied in two RCTs (39,40).

In the first study, earlier (24 hours, versus 72 hours) drain removal was not associated with a higher recurrence rate, opening new horizons toward the outpatient management of these patients (39); however, the results need to be confirmed in larger studies.

Pleurodesis substances

Talc is, to our best knowledge, the most commonly used pleurodesing agent (41). It is inexpensive and readily available worldwide. Its superiority over alternative compounds has been suggested by more than one meta-analysis; thus, it is the agent of choice in the international guidelines (36,42,43).

Its medical use is preceded by its transformation into a sterile product. Talc comprises magnesium hydrosilicate crystals. The different varieties of talc differ in the presence of replacement elements in the crystalline structure. In medical talc, aluminum replaces silicon; aluminum, iron and manganese replace magnesium; calcite, magnesite, dolomite, chlorite, serpentine, and quartz can be contaminants. The size of the talc particles depends on the size of the mineral filter pores in the production phase (200, 325, or 400 mesh) (44).

Talc is highly effective, with success rates from 80% to 95%, relative to the dose, number of administrations and patient's metabolic and nutritional conditions, with acceptable side effects and risks in a patient with a modest life expectancy.

In the RCT presented by Dresler *et al.* in 2005, the success rate of talc pleurodesis was approximately 75% at 1 month but progressively decreased to approximately 50% at 6 months (45).

Talc can be instilled as a slurry via an intercostal catheter or by dry-powder poudrage during thoracoscopy. Talc administration is better performed thoracoscopically and the positioning of the pleural drainage must be guaranteed to ensure complete cleansing of the pleural cavity, acceptable parenchymal re-expansion, escape of pleural fluid newly formed for the exudative pleurisy generated by talc and close monitoring of procedure effectiveness.

Other substances used are tetracyclines (doxycycline and minocycline), bleomycin, nitrogen mustards, quinacrine, *Corynebacterium parvum*, interferon (IFN), methylprednisolone, doxorubicin, cisplatin, cytarabine, etoposide, fluorouracil, mitomycin C, gold- and phosphorus-radioactive isotopes, alcohol, povidone-iodine and silver nitrate (5,46).

Tetracyclines are broad-spectrum antibiotic compounds that have a common basic structure and are either isolated directly from several species of Streptomyces bacteria or produced semi synthetically from those isolated compounds (47). Parenteral tetracyclines are no longer available for this indication in many countries because its production has ceased.

Doxycycline is a semi-synthetic tetracycline available as an inexpensive drug.

Minocycline is another tetracycline, generally less preferred than doxycycline.

Bleomycin is an antiblastic agent. Its main toxicity consists of the induction of pulmonary fibrosis due to

a higher sensitivity to oxygen toxicity mediated by a proinflammatory cytokine cascade.

Nitrogen mustards are cytotoxic organic compounds defined as "nonspecific DNA alkylating agents" (48). Although originally produced as chemical warfare agents (49,50), they were the first chemotherapeutic agents for cancer (51) and lymphoma. They are powerful and persistent blister agents.Their production and use are therefore strongly restricted (52).

Quinacrine is a medication with several uses (antiprotozoal, antirheumatic and intrapleural sclerosing agent) related to chloroquine and mefloquine.

Corynebacterium parvum is an anaerobic diphtheroid, likely acting not only as a sclerosant but also as an immunostimulant (53-56).

IFNs are a group of cytokine proteins that are released by cells in response to the presence of several viruses to trigger the protective defenses of the immune system. They activate immune cells, such as natural killer cells and macrophages and increase host defenses by upregulating antigen presentation by major histocompatibility complex (MHC). There are over twenty distinct IFN proteins. IFN-β (46) and IFN-α2b (57) have been used for pleurodesis.

Doxorubicin, cisplatin, cytarabine, etoposide, fluorouracil, and mitomycin C are chemotherapeutic agents.

Alcohol is utilized because of its irritant nature. It is diluted in a normal saline solution (generally 40 mL of alcohol in 100 mL of normal saline solution), and the irritant solution is sprayed with a device that allows it to reach the entire pleural surface. In a retrospective study, Brega-Massone *et al.* reported no direct complications regarding the use of alcohol for pleurodesis but described a statistically significant difference between talc and alcohol for the therapeutic success of pleurodesis and pleural effusion relapse, favoring talc. The study concluded that talc remains the most commonly utilized fibrosing substance because of its ease of use, good tolerability, reasonable rate of success, and low cost (58).

Povidone-iodine, also known as iodopovidone, is an antiseptic used for skin disinfection before and after surgery, available from 1955.

Its side effects include skin irritation. In large doses, it can cause renal failure, alterations of the serum sodium levels, deranged liver enzymes and metabolic acidosis. It is contraindicated in pregnant women and patients under lithium treatment or affected by thyreopathy (9% to 12% of available iodine). It can cause confusion and visual loss (59-62).

Silver nitrate is used in medicine as an antiseptic and cauterizing agent. It can cause acute kidney injury and acute respiratory distress syndrome (ARDS) (4).

Comparative studies: talc versus other substances

There are no comparative studies showing the superiority of other substances to talc.

In a retrospective, nonrandomized study, Sayir *et al.* utilized sterile talc in 45 cases (75%), liquid tetracycline in 9 patients (14%), and bleomycin in 6 cases (9.8%). Insufflation and homogeneous dispersion of these chemical agents in all the pleural areas were provided by the thoracoscope. Respiratory failure developed in one patient due to the administered chemical agent (liquid tetracycline). This patient recovered following 3 days of mechanical ventilation treatment. Apart from the side effects due to chemical pleurodesis, pain was described, particularly in all the patients treated with tetracycline. The success rate was 91.1% for talc, 66% for tetracycline and 66% for bleomycin. They concluded that talc powdering by video-assisted thoracoscopic surgery (VATS) is a safe and inexpensive procedure with a low morbidity rate (63).

At least two meta-analyses found that nonrecurrence of effusion was more likely with talc than other sclerosants, suggesting little advantage of using other agents over large-particle talc (6,43).

In particular, a meta-analysis of 36 randomized controlled trials (RCTs) (43) stated that the use of sclerosants (mitoxantrone, talc and tetracycline) compared with control (isotonic saline) was associated with an increased efficacy of pleurodesis. Using sclerosants, the RR of the nonrecurrence of MPE is 1.20. This value increases to 1.34 using talc compared with bleomycin, tetracycline, mustine and tube drainage alone. Only one procedure-related death was reported.

The authors concluded that successful pleurodesis required chemical sclerosants, talc is the agent of choice, and the thoracoscopic technique is preferred regarding pleurodesis efficacy. Talc was deemed a safe agent, with no evidence of increasing mortality after talc pleurodesis.

A MEDLINE search conducted by Walker-Renard in 1994 concluded that the success rate of the pleurodesis agents varied from 0% with etoposide to 93% with talc. *Corynebacterium parvum*, tetracyclines, and bleomycin had success rates of 76%, 67%, and 54%, respectively (46).

Many studies aim to evaluate the comparison of talc with individual alternative agents. For example, compared with

bleomycin, talc appears to be the better option (43,64).

Only doxycycline has success and complication rates comparable to those of talc (65).

Terra *et al.* recently reported the safety profile of three different doses of silver nitrate used for pleurodesis in MPE (66). They described complications such as acute kidney injury, ARDS and confusion. Four patients died during this study, with one death possibly related to the agent. Silver nitrate solution may be an effective pleurodesis agent after failed thoracoscopic talc poudrage (67,68).

Mohsen *et al.* performed an RCT of VATS vs. povidone-iodine pleurodesis via a chest tube in 42 patients with metastatic breast cancer. Neither group demonstrated superiority in terms of the length of stay or pleurodesis failure rate (69).

Agarwal *et al.* (61) published a systematic review to update a previously reported meta-analysis on the efficacy and safety of iodopovidone pleurodesis. The success rates varied from 70% to 100% in different studies and were not affected by the method (tube thoracostomy vs. thoracoscopy). The only significant complication reported was chest pain of varying degree. Systemic hypotension was reported in six patients across the studies. No deaths were associated with iodopovidone pleurodesis. They concluded that iodopovidone might be considered a safe and effective agent for chemical pleurodesis in patients with pleural effusions and recurrent pneumothoraces because it does not persist in biological tissues. Statistical heterogeneity and publication bias were found. Moreover, the literature described other side effects already listed above that cannot be ignored, suggesting the need for further studies.

Many of the remaining studies in the literature comparing talc with other substances were retrospective; in these studies, the choice of the pleurodesis substance was not randomized but dependent on local availability.

Furthermore, the available studies include all types of patients and all tumor departure organs, with percentages differing from center to another, depending on geographical organization of the health care system. This results in nonhomogeneous samples and non-comparable outcomes.

Talc poudrage versus talc slurry

Talc poudrage (the insufflation of talc into the pleural cavity under a thoracoscopic guide) is preferred to pleurodesis with talc through a drainage tube (talc slurry) because the poudrage ensures a more uniform distribution of talc in the pleural cavity. Furthermore, thoracoscopy allows the surgeon to do the following: explore the pleural cavity using direct visualization; perform pleural biopsies for histological determination, oncological staging and hormonal or molecular biology characterization; and attempt to partially free a trapped lung (adhesiolysis), although it increases operative risks and time (70).

However, bedside instillation of talc slurry (or alternative agent) via a chest tube is reserved for patients with a low performance status.

Compared with bedside talc slurry, thoracoscopic talc insufflation was associated with reduced recurrence in a systematic review edited by Tan *et al.* (42).

Several randomized trials, however, showed no differences in the success rates of the two techniques. Therefore, the 2018 ATS/STS/STR Clinical Practice Guideline recommends using either talc poudrage or talc slurry for chemical pleurodesis.

For example, Dresler et al., in the largest (n=482) RCT of VATS in MPE to date, assigned patients to either VATS or talc slurry pleurodesis (45).

No difference was observed between the study arms in the percentage of patients with successful 30-day outcomes (poudrage, 78%; slurry, 71%). However, post-hoc analyses suggest a possible benefit of VATS in primary lung and breast cancer patients (82% *vs.* 67%). Poudrage revealed its superiority also in terms of quality-of-life measurement (less fatigue and patient ratings of comfort and safety).

A recent meta-analysis including twenty trials and involving 1,525 patients with MPE found talc poudrage to be superior to talc slurry in pleurodesis success. Thoracoscopic talc poudrage was more effective than bedside talc slurry (relative risk, 1.12; 95% confidence interval, 1.01–1.23; P=0.026) (71).

The Evaluating the Efficacy of Thoracoscopy and Talc Poudrage Versus Pleurodesis Using Talc Slurry (TAPPS) trial is a multicenter, open-label, randomized, controlled trial designed to compare the pleurodesis success rate of talc poudrage with talc slurry (72).

The phase 3 trial reported in *JAMA* showed comparable outcomes regardless of how talc was delivered (73).

Yim *et al.* randomized 53 patients to VATS talc poudrage or bedside talc slurry pleurodesis and found no significant difference in the hospital stay, chest tube drainage duration, analgesic requirement, or recurrence rates of effusion (74).

Regarding complications, VATS talc poudrage appears to be more invasive and resource consuming. Postoperative pneumonia and respiratory failure were more frequent after talc poudrage (45).

Respiratory complications were more common following poudrage than slurry (14% *vs*. 6%). Respiratory failure was observed in 4% of slurry patients and 8% of poudrage patients (45).

VATS-related complications such as bleeding and prolonged air leak have been reported in up to 15% of patients and persistent pain or discomfort at 3 months for over a third of patients (75,76).

The current evidence suggests that talc poudrage is a highly effective method of pleurodesis that is at least equivalent to talc slurry with possibly increased efficacy in certain disease subgroups. Further targeted studies in these subgroups are needed (77).

Complications and side effects of talc administration

When the pleural cavity instillation of substances aimed at pleurodesis is carried out, the side effects can vary in relation to the type and severity. First, thoracic pain requires the simultaneous administration of local anesthetics and analgesics parenterally to control the symptom. Fever is frequent up to 38–38.5 ℃ (38) and is usually interpreted by the operators as an expression of treatment effectiveness.

Coughing may also occur. Infection at the drain insertion site is more frequent than empyema. An exuberant fibro adhesive reaction can develop in the long term.

Bronchospasm, allergic reaction, arrhythmias, pulmonary edema, pneumonia, respiratory failure and ARDS (approximately 5–6% of cases) are also possible side effects. Concerning ARDS, the action of talc or contaminants (e.g., dolomite, quartz, kaolinite, calcite, and chlorite) has been advocated. Systemic absorption, with the release of inflammation mediators, plays a key role in the onset of ARDS (4).

Recent studies have demonstrated that ARDS results from the systemic absorption of small-sized talc particles (78).

Although the complication is probably related to the size of the talc particles, individual variations occur in the diameter of the pleuro-lymphatic communications that underlie the distribution pattern of the particles.

An observational study of 550 patients undergoing thoracoscopic poudrage with large-particle-size talc showed no cases of ARDS; nonetheless, oxygenation deteriorated in the first few days after pleurodesis (68).

Talc is present in the BAL of subjects affected by ARDS after pleurodesis (Campos *et al.*) (78).

Talc was present at the autopsy in the lungs, brain, liver, kidneys, heart and skeletal muscles of a subject who died of the complication (78).

In rabbits sacrificed after pleural talc, the mineral was present in various organs (79,80).

Dose reduction would avoid the onset of complications (4 cases of Milanez Campos case series occurred after talc administration with only 2 g) (78).

Talc can cause tenacious pleural symphysis because it is an inert substance, not metabolized, and responsible for the inflammatory stimulus persistence over time.

Other critical aspects of talc are an inconsistent uniform distribution, particle migration in different districts, and the carcinogenicity potential.

Discussion

Patients with MPE are a heterogeneous group of different underlying tumors, staging, and comorbidity and thus a variable prognosis. Therefore, every study or evaluation must match the clinical subtype of patient with the prognosis.

The clinical weight of MPE is variable, depending on the symptoms (dyspnea is the main one) caused by the effusion itself. Some patients will derive a great benefit from the evacuation of fluid and definitive treatment; in other patients, symptoms such as breathlessness are not attributable to the effusion. If the disease is responsive to chemotherapy, pleurodesis is not required because the effusion will not relapse after drainage. Some other patients will lose their weak balance after drainage and pleurodesis.

The critical aspect of the management of MPE and skill of the professional lies in intercepting the patient before prognosis reaches a point of no return. Indeed, in patients with a shorter survival, fewer drainage procedures, such as thoracentesis, may be indicated. The loss of fluids, nutrients, electrolytes, leukocytes and more from drainage, together with the administration of drugs or irritants in the pleural cavity, can cause irreversible deterioration and death if pleurodesis is performed in an improper phase.

The patient's needs and preferences, tumor type, prognosis, clinical conditions and pre-existing QoL will impact the success of any intervention offered.

Beyond subjective clinical expertise, studies are needed to assess the prognosis of patients with MPE and likelihood of the recurrence of fluid to guide treatment. A recent study has identified the LENT score (which comprises the pleural fluid LDH, ECOG performance status, neutrophil-to-lymphocyte ratio in peripheral blood, and tumor type) as a useful algorithm (2).

Although the choice between talc and other agents has been long debated, high-quality, incontrovertible data are not yet available to date. The main topics on the management of MPE mainly rely on consensus opinions.

Thus, talc is likely the only substance with an adequate benefit/risk ratio, the most used agent worldwide, with a standardized practice that guarantees the right safety and efficacy standards. The timing of pleurodesis will respect the rule of fluid quantity of less than 150 mL in the last 24 hours. The choice between talc slurry or poudrage will depend on the patient's clinical conditions, with both methods being equally efficacious. Talc pleurodesis will be followed by tube clamping for 1 hour, and tube removal usually occurs within 48 hours.

However, an individualized approach, rather than anyone specific modality, must be considered to state the best treatment choice for that patient.

Conclusions

To date, despite many substances and studies, no ideal sclerosing agent exists.

The lack of comparative randomized trials, different eligibility criteria and heterogeneity of the study populations do not help scientists to determine the standards concerning the type of substance to be used and methods.

Talc remains the most effective sclerosant available for pleurodesis.

Graded talc should always be used instead of ungraded talc to reduce the risk of respiratory failure and ARDS. Talc poudrage is highly effective, at least equivalent to talc slurry, with possibly increased efficacy in certain disease subgroups.

Bleomycin is considered an alternative sclerosant with a modest efficacy rate. Chest pain and fever are the most common side effects of chemical pleurodesis.

In the future, enhanced recovery strategies, including the less invasive practices of pleural drainage and pleurodesis, combined with exercise, diet, medical supportive therapy and outpatient management, will increase the global benefits of treatment.

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