

# KARŞIT GÖRÜŞ (PRO-CON): TALC İYİDİR (TALC IS GOOD FOR PLEURODESIS)

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Pleurodesis is a procedure performed to obliterate the pleural space in order to prevent recurrent pleural effusion or recurrent pneumothorax, or to treat recurrent or persistent pneumothorax. Pleurodesis is commonly accomplished by draining the pleural fluid when present, followed by a mechanical procedure (i.e., abrasion, or (partial) pleurotomy) or by instillation of a chemical irritant into the pleural space. Both types of procedures induce inflammation and pleural fibrosis. Talc pleurodesis is a specific form of chemical pleurodesis. Talc instillation (by insufflation and by slurry) causes an intense intrapleural inflammatory process, characterized by the production of cytokines, adhesion molecules, and other mediators of inflammation such as interleukin-8, vascular endothelial growth factor (VEGF), and Tumor Growth Factor- $\beta$  (1). Among other effects, IL-8 causes neutrophil chemotaxis involved in the acute inflammatory response, VEGF causes increased capillary permeability, angiogenesis and lymphogenesis, TGF- $\beta$  presents profibrotic and immunomodulatory properties.

Talc is hydrated magnesium silicate ( $Mg_3Si_4O_{10}(OH)_2$ ), and was first used for pleurodesis in 1935 (2). Since then, talc has increasingly been used by pulmonologists and surgeons, because of its effectiveness, availability and low cost. Talc composition can vary in the amount of calcium, aluminium and iron, according to its origin. Several mineral contaminants may be present, but medicinal talc is asbestos free (3). In clinical practice, however, it is the proportion of talc particles  $<5$  micron in diameter which relates to the severity of local and systemic inflammatory responses, and to safety (4). Since there are currently no standards

for talc production, there is a wide variation in composition and particle size in the various talc preparations used worldwide.

Talc pleurodesis is used to manage recurrent malignant pleural effusions, refractory non-malignant pleural effusions, recurrent and persistent spontaneous primary and secondary pneumothorax.

### Recurrent Malignant Effusion

Chemical pleurodesis was shown in a meta-analysis of 36 randomized, controlled trials including 1499 patients to be more effective than placebo or tube drainage alone in achieving non-recurrence of fluid (relative risk 1.20, CI 1.04 to 1.38) (5). Of all chemical pleurodesis agents, talc has repeatedly been shown to be the most effective agent, i.e., with the lowest recurrence rates of fluid. Most studies report success rates around 90 % (5-8).

### Refractory Non-Malignant Effusion

Chemical, including talc, pleurodesis is less commonly used for the treatment of refractory non-malignant pleural effusions, and its use is controversial (9,10): the major concern being exposure of patients with non-malignant disease to the rare but potentially severe adverse effects, although judicious use of size-calibrated talc is now shown to be safe. Although success rates of talc pleurodesis may vary by disease, and although most studies are too small to draw definitive conclusions, talc pleurodesis can be ef-

fective in managing up to 80 percent of non-malignant effusions, including effusions caused by chronic ambulatory peritoneal dialysis, yellow nail syndrome, chylothorax, nephritic syndrome, lupus, hepatic hydrothorax and congestive heart failure (11).

### Recurrent and Persistent Spontaneous Pneumothorax

Pleurodesis is the cornerstone of recurrence prevention in primary (after the first recurrence) and secondary (after the first occurrence) spontaneous pneumothorax (12). Recurrence rates after talc pleurodesis (without other interventions) vary between 5 and 8 percent (13-15). Controversy exists whether talc should be used as a sclerosant agent in young, otherwise healthy individuals, again because of safety reasons and fear for long-term complications. Recent overviews of the existing literature, including an analysis of 181 papers, eight of which were relevant, confirm however that talc pleurodesis in these patients appears to have only very minimal long-term adverse consequences (4,16). Talc pleurodesis has also been proven to be a safe and effective sclerosant agent in patients suffering from a secondary spontaneous pneumothorax (17-19). Talc pleurodesis does not significantly interfere with ulterior thoracic surgery (20) although it is advised to discuss with your surgical team, e.g. in case of recurrent pneumothorax in cystic fibrosis, LAM or other diseases in which lung transplantation remains a therapeutic option.

Notwithstanding these impressive data on talc efficacy in daily clinical practice, a number of pulmonologists and surgeons today still are reluctant to use talc for pleurodesis, especially in young, otherwise healthy individuals e.g. in case of primary spontaneous pneumothorax. This reluctance is inspired by alarming reports on short-term and long-term complications and side-effects induced by talc. However, short-term complications (which can be severe, but are rare) can be attributed to the use of non size-calibrated talc containing abundantly small talc particles less than five micron in diameter; long-term complications can be considered a hoax in view of the abundant literature on long-term follow-up in thousands of patients. To generalize isolated case reports of massive pleural fibrosis – which are still presented today on world conferences by eminent speakers-can no longer be considered sound scientific reasoning. To these speakers: please present sound scientific evidence!

### Short-Term Safety of Talc

Although some have observed respiratory failure, ARDS, and even death after talc pleurodesis (21,22), others have

not, even in large series (8,23,24). In any case, these serious complications are extremely rare ( 41 cases on 4030 patients in a review by Sahn (25), and they have only been observed in series from the USA, Brasil, and New Zealand, and not , for instance, in Europe or Israel. The occurrence of these serious complications seemed to be independent on the underlying disorder (malignant effusion or pneumothorax), the volume of talc used ( 2 to 10 grams), or the method of administration (slurry or poudrage). An important observation however was that talc dissemination has been observed in virtually all organs when North American or Brazilian talc was used (26,27) ( except when extremely high doses were used (28), whereas no talc dissemination occurred when European, size-calibrated talc was used (29). Lung damage indeed occurs only when small particle size talc is used, and not after exposure to large particle size talc (30). Small particle size talc causes more inflammation and more impaired gas exchange than large particle size talc (31). The observed differences in serious complications within various countries therefore probably can mainly be attributed to differences in talc used, that is, differences in the number or proportion of small size talc (3) particles. This hypothesis is corroborated by the fact that particle size is only mentioned in one paper describing serious complications (diameter of talc particles 5 to 70  $\mu$ ), by the Spanish observation that complications indeed occur more often when small particle size talc is used (cut off : 5  $\mu$ ) ( Rodriguez-Panadero, as yet unpublished results), and, finally, by the results of a large , prospective, observational European study where no case of ARDS has been observed in a cohort of 558 patients treated with talc poudrage (32). Conclusion: talc is safe, if you use size calibrated talc, and at normal dosages.

### Long-Term Safety of Talc

Medical thoracoscopic talc poudrage is not only simple and feasible under local anaesthesia (18,33,34), it is also safe at the long term. A thorough review published in 1979 (!) was unable to show any serious or well-documented side-effects of talc poudrage, even after a long-term observation (35). Lange et al documented in a large series of patients observed for more than 20 years that talc did not provoke pulmonary fibrosis (36). They did see a mild but asymptomatic restrictive impairment in pulmonary function. This has also been observed by others in the early months following the procedure, although pulmonary function improved within one year (18) . Viskum et al re-examined 99 patients 22 to 35 years after talc poudrage for spontaneous pneumothorax and found no serious complications or side-effects (as well as a recurrence rate of only 2.5%) (37).

In summary, talc does not cause cancer or mesothelioma, does not cause pulmonary fibrosis, and does not cause significant impairment in pulmonary function at the long term. Does it cause angry surgeons? In my experience: yes. I therefore refer them to the recent surgical literature: Cardillo et al, for instance, have performed VATS talc poudrage in 861 spontaneous pneumothorax patients. They found no significant short- or long-term complications, and even checked pulmonary function in a subgroup of 29 patients, all remaining normal (38). Other brave surgeons include Pletinckx et al (39) and Luh et al. (40), for instance. Finally, does talc poudrage make later thoracic or thoracoscopic surgery impossible? No ! Doddoli et al. (20) showed that VATS reintervention after previous talc poudrage upto 13 years earlier is feasible in the majority of patients; in 12 out of 39 patients only, a reconversion to (successful) thoracotomy was necessary. More difficult: yes. Impossible ? No.

### Systemic Inflammation

Talc pleurodesis also causes systemic inflammation, which may be linked to safety issues. This systemic inflammation may be linked to the systemic absorption of talc particles (which in turn is linked to talc particle size and to the presence of an access route that facilitates systemic absorption of talc particles, such as multiple parietal pleura biopsy procedures), to the extent, degree and type of intrapleural inflammation (which also is linked to talc particle size, the dosage of talc, and maybe to the presence of talc contaminants) "leaking" into the systemic circulation (again , linked to the access route).

In short , "small particle size talc", with >10% to 50% of particles smaller than 5 to 10 $\mu$ , has been shown to be systemically absorbed, and to cause a more intense pleural, lung and systemic inflammation characterized by fever and increase in serum C reactive protein levels, without increasing the likelihood of successful pleurodesis (3,4,30,31,41,42).

### Conclusion

Talc is the most widely used pleurodetic agent. When patient selection is correct (43), it is the most efficient chemical pleurodesis agent. When the correct talc preparation is used (i.e., size-calibrated talc) at the correct dosage, it is safe. Importantly also, it is widely available and very, very cheap. Although new, "sexy" pleurodesis agents are under research (44), the new "ideal" agent can only to be expected to marginally increase efficacy, and very probably at a much higher cost. It is very unlikely that such new agent will ever find its place into clinical practice.

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